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[¹⁸F]FLT PET Quantification of Bone Marrow Response to Radiation Dose

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Abstract

Purpose—The purpose of this study was to quantify bone marrow response to radiation dose using [¹⁸F]FLT uptake quantified in PET scans.

Methods and Materials—Pre- and post week 1 treatment [¹⁸F]FLT PET images were registered to the CT image used to create the radiation treatment plan. Change in [¹⁸F]FLT uptake was measured using profile data of standardized uptake values (SUVs) and dose along the vertebral bodies located at a field border where a range of radiation doses were present for 10 patients. Data from the profile measurements were grouped into 1 Gy dose bins from 1 – 9 Gy to compare SUV change for all patients. Additionally, the maximum pre-treatment, post week 1 treatment, and dose values located within the C6 - T7 vertebrae that straddled the field edge were measured for all patients.

Results—Both the profile and individual vertebral data showed a strong correlation between SUV change and radiation dose. The relative differences in SUV between bins > 1 Gy and < 7 Gy were statistically significant ($p < 0.01$ 2-sample t-test). The reduction in SUV was approximately linear until it reached a threshold at a 75-80% reduction in SUV for doses greater than 6 Gy/week for both the dose binned data and the vertebral maximum SUVs.

Conclusions—The change in SUV observed in head and neck cancer patients treated with chemoradiation shows the potential for using [¹⁸F]FLT PET images for identifying active bone marrow and monitoring changes due to radiation dose. Additionally, the change in [¹⁸F]FLT uptake observed in bone marrow for different weekly doses suggests potential dose thresholds for reducing bone marrow toxicity.

Keywords

FLT PET; bone marrow; toxicity; radiation response; dose

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1. Introduction

The design of effective chemoradiation therapies for cancer patients relies on finding the balance between normal tissue toxicities and a therapeutic dose. Organ tolerances to guide radiation therapy planning are fairly well established, but the dose response and limits to bone marrow has proved more elusive. This is partly due to the fact that bone marrow suppression is largely manageable for many treatment sites. However, treatments for disease in regions with a large reservoir of bone marrow such as the pelvis can impede the ability to deliver a full chemotherapy and radiation therapy regimen. A relevant example is shown in evidence documenting the toxicities, treatment delays, and missed treatments of cervical cancer patients undergoing chemoradiation therapy.¹⁻⁵

Another limitation in determining appropriate radiation dose tolerances to the bone marrow is the ability to identify and locate an individual patient's functional bone marrow. Strategies for identifying bone marrow have largely consisted of using fractional regional estimates from Ellis *et al* and using entire bone as a surrogate for bone marrow.⁶⁻⁹ Sulfur colloid SPECT imaging to identify active bone marrow has also been used, but this technique has a limited quantitative ability.¹⁰ [¹⁸F]FLT PET is a promising imaging modality that has been shown to identify proliferation in both tumors¹¹⁻¹⁸ and bone marrow¹⁹⁻²¹ as [¹⁸F]FLT uptake reflects the level of cells undergoing DNA synthesis. While [¹⁸F]FLT PET has not been used extensively to characterize bone marrow activity, Agool *et al* illustrated a correlation between FLT uptake and bone marrow activity.¹⁹ Hayman *et al* have also used [¹⁸F]FLT PET to quantify the relative distributions of active bone marrow throughout the body and noted significant individual variation.²⁰ For example, with [¹⁸F]FLT PET, the active bone marrow regions within the pelvis can be identified for individual patients so that doses to only the active bone marrow volumes can be accurately quantified and correlated with reduction in white blood cell counts in order to establish toxicity limits. Establishing these limits could provide clinically meaningful dose objectives to use during treatment planning in order to reduce marrow toxicity during chemoradiation therapy.

Previously, the data from a clinical trial at our institution for imaging head and neck cancer patients prior to, and following the first week of radiation therapy was shown to be useful for quantitatively monitoring changes in bone marrow metabolism due to chemoradiation.²¹ In the current study, the pre-therapy and post week 1 therapy images were correlated with the planned radiation dose distribution for 10 patients in an effort to establish preliminary measures of the relationship between radiation dose and change in bone marrow function.

2. Methods and Materials

[¹⁸F]FLT PET imaging to quantify cell proliferation in the pelvic bone marrow

FLT is a thymidine analog which is retained in the cell through phosphorylation by thymidine kinase 1 (TK₁).²² TK₁ is a key enzyme in the synthesis of DNA and shows markedly enhanced activity during the S-phase of the cell cycle. FLT uptake in tissue is considered a marker of active cellular proliferation and DNA replication, although FLT is not incorporated into the DNA.²³ The marked reduction in FLT uptake in the radiation field likely reflects the loss of precursor cells from the proliferative compartment in the bone marrow.

Patients with histologically proven squamous cell head and neck cancer (N = 10) scheduled to undergo chemoradiation therapy were enrolled in a prospective study (IRB #200502799 and IRB #200801758) at the University of Iowa Hospitals and Clinics to assess tumor changes post 1 week chemoradiation therapy. All patients were imaged within 30 days of initiation of chemoradiation therapy (pre-therapy scan) and after 5 daily fractions totaling 10

Gy of radiotherapy (post week 1 therapy scan). 9/10 patients also received one cycle of platinum based chemotherapy prior to post week 1 therapy scan. Acquisition of [^{18}F]FLT PET images was previously described by Menda *et al.*¹⁵ Briefly, FLT was produced based on the previously described method of Machulla *et al.*²⁴ Images were acquired on an ECAT EXACT HR+ PET scanner (Siemens Medical Solutions USA, Inc. Knoxville, TN) operated in the 3-dimensional mode after intravenous infusion (over 2 minutes) of [^{18}F]FLT (2.6 MBq/kg (0.07 mCi/kg), maximum dose =185 MBq (5mCi)). Whole-body images were obtained 74 $\pm$ 7 minutes post infusion. PET images from the whole-body scan were transferred to the Pinnacle v8.0 Treatment Planning system (Phillips Medical Systems, Fitchburg, WI) and registered with the radiation planning CT data set retrospectively to assess changes in bone marrow due to radiation dose under IRB #200902772.

Incorporation of [^{18}F]FLT PET images into radiation treatment plans

[^{18}F]FLT PET images were co-registered to the CT data set obtained for radiation treatment planning (Siemens Biograph 40 PET/CT Scanner). Because imaging was done on different days on different scanners and using different immobilization techniques, the neck was not in the exact same position for each scan. The area of interest for this study was the vertebral bone marrow located at the inferior radiation treatment field border; therefore, registration of the [^{18}F]FLT PET images to the CT data were optimized in this anatomic region. Registration of the post week 1 therapy image was particularly challenging because much of the bone marrow uptake in this region was depleted. For these data sets, vertebral bodies were identified in the thoracic region on the [^{18}F]FLT PET scans by counting in the superior direction from the sacrum to correspond to vertebral bodies identified on the CT scan by counting in the inferior direction from the skull base.

Quantitative analysis of [^{18}F]FLT PET images and radiation dose distribution

The pre- and post week 1 therapy [^{18}F]FLT PET scans were analyzed using standardized uptake values (SUVs) and dose profile measurements. A typical location for the line profile through the lower cervical and upper thoracic vertebral bone marrow located within the inferior border gradient of the planned radiation dose distribution for one subject is shown in Figure 1. Profile lines were placed using tools available in the treatment planning system so as to cross the center of as many vertebrae as possible along the dose gradient for all 10 patients. Data from all 10 profile measurements was combined for analysis to help eliminate bias. Profile analysis along the lower cervical and upper thoracic vertebrae provided pre-therapy and post week 1 therapy SUVs was limited by the pixel size in the PET images (4.3 mm $\times$ 4.3 mm $\times$ 4.3 mm, matrix size = 128 $\times$ 128 $\times$ number of slices e.g., 198).

The relationship between SUV change and radiation dose was also investigated for individual vertebrae to support the profile data without relying on profile location. Profile data has the advantage of more data points, but individual vertebral measurements are independent of a user chosen location. The active bone marrow in vertebrae C6 to T7 which incorporated the gradient dose region for each subject were contoured on the pre- and post week 1 therapy [^{18}F]FLT-PET scans for all ten patients. The maximum pre- and post week 1 therapy SUV and maximum dose value within each vertebra were measured. Maximum values were used instead of average values to eliminate any effects due to contouring and registration inconsistencies between subjects. The relative change in maximum SUV between the pre- and post week 1 therapy scans for each subject were then calculated for each vertebra and correlated to the maximum dose within that vertebra.

Statistical analysis of the profile data was done by separating [^{18}F]FLT PET voxel values into 1 Gy bins. The relative change in voxel values from pre-treatment values after 1 week of therapy in each bin were then compared to the other bins one at a time using a 2-sample t-

test. Relative change in each bin's voxel values was also compared to all other voxels in greater dose bins using a 2-sample t-test to establish a threshold dose for bone marrow uptake change. Statistical analysis of the vertebral SUV max data was performed using the relative change in SUV from pre-treatment values after 1 week of therapy combined for all 10 patients for each individual vertebra. The combined data was then compared between two vertebrae using a 2-sample t-test.

3. Results

Figure 2 shows a plot of the data measured along the length of the profile for the pre- and post week 1 therapy SUVs and radiation dose for the subject shown in Figure 1. Individual vertebrae are easily identifiable along the pre-therapy profile measurement due to the compartmentalization of active bone marrow within the vertebral body. The absence of this feature in the post week 1 therapy profile at higher radiation doses corresponds with the visual absence of [^{18}F]FLT uptake in Figure 1. Figure 2 also illustrates the variable reduction in [^{18}F]FLT uptake due to radiation dose at the gradient.

To determine the population-averaged relationship between [^{18}F]FLT uptake and radiation dose, pre- and post week 1 therapy SUVs measured along this profile for all 10 subjects were binned into groups ranging from 1 to 9 Gy in 1 Gy increments. The number of subjects that comprised each dose bin and the number of data points within each bin along the profile measurement were not equal due to the radiation dose distributions created during the IMRT planning process. However, all the bins had a minimum of 68 data points (range 68-621, avg. 253). The relative change in pre- and post week 1 therapy profile voxel SUV was calculated within each bin. The average relative change in SUV for each dose level bin is shown in Figure 3 and the average relative change in SUVs and standard deviations are also shown in Table 1. Of note, the relative differences in SUV between each bin between 1 and 7 Gy were statistically significant ($p < 0.01$ 2-sample t-test). The change in FLT uptake between pre- and post week 1 therapy scans between the 5 - 6 Gy bin were statistically different from the changes in the bins greater than 6 Gy ($p < 0.01$ 2-sampled t-test), but the 6 - 7 Gy bin was not statistically different from the change in the bins greater than 7 Gy ($p > 0.1$ 2-sample t-test). This is demarcated in Figure 3 with a dashed vertical line. Additionally, the 4 - 5 Gy bin is the first dose level at which 50% or greater of voxels have a relative SUV reduction of 70% or greater. The 2-3 Gy bin contains only 2% of voxels with a relative SUV reduction of 70% or greater. Therefore, a threshold dose of 4 Gy may enable bone marrow to maintain function within the first week of chemoradiation therapy. A scatter plot of the relative change in voxel SUV as a function of radiation dose shown in Figure 4 also illustrates a plateau in SUV change at an approximate 75% decrease starting at ~6 Gy. Each data point in Figure 4 represents the SUV change per dose value for a voxel along the profile line shown in Figure 1; these data are provided for all 10 patients and show similar relationships between dose, pre-therapy SUV, and post week 1 therapy SUV.

Analysis of the maximum SUVs and dose values found in individual vertebral regions of interest from C6 – T7 show the same trend as seen in the profile analysis. Figure 5 shows a plot of the relative change in maximum SUV as a function of maximum dose for each vertebra for all 10 patients. Again, the reduction is approximately proportional until a dose of 6 Gy is reached. After 6 Gy, the relative reduction plateaus at ~75%. The majority of the dose spectrum occurs from the T2 - T4 region in each subject since the sloping region from lower to higher change in SUV consists of data points representing those vertebrae. The average planned maximum dose to the T2, T3, and T4 vertebrae was 6.4 ± 1.5 , 4.5 ± 2.2 , and 1.8 ± 1.5 Gy respectively. This dose range is where a decrease in SUV is proportional to dose correlates with the binned data analysis, but the statistical difference in relative SUV change between these 3 vertebrae was not as strong ($p < 0.07$ 2-sample t-test). This is most

likely a result of where the inferior field borders were located in the IMRT plans. However, another factor in the relative SUV change and dose relationship may also be the absolute SUVs seen in the thoracic and cervical vertebrae. For the 10 patients studied, the SUV of the C6 vertebrae was 4.1 ± 1.2 while the SUV of the T4 vertebrae was 6.7 ± 1.1 . The relative change of the cervical vertebrae could be affected by absolute SUV due to doses greater than 7 Gy because it is limited by its pre-therapy value.

4. Discussion

Based on both the profile and individual vertebrae relative change in SUV, an approximately directly proportional relationship exists between radiation doses below 6 Gy and a marked decrease in [^{18}F]FLT uptake after 1 week of radiation therapy. However, there is large variation in SUV decrease at low doses (< 2 Gy per 5 days). This may be attributed to a number of factors including: 1. the ability of the treatment planning system to calculate low dose distributions accurately, 2. small patient treatment set up variations that will be more significant along a steep dose gradient, 3. variation in patient response to chemotherapy, 4. potential compensatory effects in bone marrow just outside the treatment field.

From a radiation treatment planning perspective, the reduction in SUV as a function of radiation doses between 2 and 6 Gy over 5 days offers guidance for determining bone marrow dose volume objectives. Preliminary work has been done at our institution to quantify proliferative changes in bone marrow due to radiation dose. Menda, *et al.*, have studied the relative influence of chemotherapy versus chemoradiation therapy exposure on bone marrow function with [^{18}F]FLT in subjects undergoing treatment for head and neck cancer²¹. Cervical spinal marrow, exposed to both chemotherapy and radiation, exhibited significant suppression of [^{18}F]FLT uptake, consistent with alterations in thymidine kinase activity, whereas lumbar spinal marrow, exposed only to chemotherapy, exhibited only small changes in [^{18}F]FLT uptake. This indicates that radiation dose will be the dominant mechanism for reductions in bone marrow proliferative activity and will be the most likely contributor to bone marrow toxicity early in the course of chemoradiation therapy. This is especially true for those patients treated with pelvic radiation where the majority of the bone marrow resides^{6, 20}.

Radiation treatment plans are designed with regard to the total doses to be delivered to the target volume and neighboring normal tissues. The head and neck bone marrow data in this study is limited in that only response after one week is measured. However, useful preliminary bone marrow dose objectives may be linearly extrapolated from this data. Weekly radiation doses in the range of 2 – 6 Gy appear to be the most useful for affecting bone marrow toxicity since the reduction in SUV is fairly constant after 6 Gy. This could be incorporated in a radiation treatment plan by reducing the volume of proliferating bone marrow that receives 10 – 30 Gy for a 5 week course of treatment. This range of values correlates well with the dose values (5 Gy – 20 Gy) Mell *et al.* and Albuquerque *et al.* have associated with hematologic toxicity even though bone was used as a surrogate for bone marrow.^{25, 26} Because the reduction in SUV increases with increasing dose, prioritizing the reduction of proliferating bone marrow that receives higher doses could also be useful. This strategy is an oversimplification of the critical total dose levels that may be significant in a bone marrow toxicity reduction but may serve as a useful starting point for bone marrow sparing radiation treatment planning design.

The change in bone marrow function throughout the course of chemoradiation therapy is largely unknown. Yang *et al.* studied patients undergoing radiation therapy for a range of treatment sites and found that leukocytes declined most dramatically during the first week of treatment.⁷ Everitt *et al.* also demonstrated that the largest change in FLT uptake in the bone

marrow of the ribs, sternum, and spine occurs in the first 15 days of radiation therapy for lung cancer patients.²⁷ Extrapolating bone marrow FLT uptake changes after one week of therapy may not represent the total response over the course of treatment. Weekly monitoring may offer more insight into how bone marrow response may change as radiation dose accumulates. This information may provide a more robust dose bone marrow objective scheme for radiation treatment planning which may provide the opportunity for reduced systemic toxicity and dose escalation.

This study offers a potential methodology for using FLT uptake to measure dose response in the bone marrow. Because the initial prospective study design from which this data was obtained was focused on tumor response monitoring with [¹⁸F]FLT PET imaging, the retrospective data analysis was presented with a number of challenges including: 1) patient position inconsistency between [¹⁸F]FLT PET and CT simulation imaging, 2) a limited amount of bone marrow located within a radiation dose gradient for study, 3) and the inability to study the effects of chemotherapy and radiation separately on the same subset of patients. Separating the effects of chemotherapy and radiation will be difficult in prospective clinical trials because the vast majority of patients for whom bone marrow toxicity is an issue receive chemoradiation therapy. This question may best be answered in animal studies, which are also needed to develop a correlation between FLT uptake change and histological change. Based on analysis done by our group, radiation therapy appears to be the dominate mechanism for FLT reduction in bone marrow and will most likely be the primary focus of future clinical trials.²¹ These trials should be developed to prospectively study the effect of radiation on bone marrow using [¹⁸F]FLT PET imaging to answer a number of questions including: 1) the effect of spatial location on bone marrow dose response, 2) effect of bone marrow activity on dose response, and 3) the effect of timing and repair mechanism in bone marrow dose response.

4. Conclusions

This study describes a preliminary response relationship between radiation dose and [¹⁸F]FLT PET SUV change as a surrogate for proliferation change. This information may be important to reduce bone marrow toxicity in radiation treatment planning. However, the effect of reducing radiation dose to proliferating bone marrow on patient outcome is still unknown. The correlation between [¹⁸F]FLT PET absolute SUV, change in SUV, and reduction in white blood cell counts over the duration of chemoradiation therapy would further our understanding of how [¹⁸F]FLT PET imaging can be used to reduce clinically significant bone marrow toxicity.

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Figure 1.

Pre- and 1 week post therapy [^{18}F]FLT PET images registered to the radiation treatment plan for a head and neck patient. Lines indicate the planned radiation dose and the colorwash indicates FLT uptake with the color scale of red to blue representing SUVs from 6.5 to < 1.

Figure 2.

The change in pre- and post week 1 therapy [^{18}F]FLT PET SUVs due to radiation dose along a spine profile. As radiation dose decreases, the change in pre- and post week 1 therapy SUV decreases.

Figure 3.

The average reduction in bone marrow [^{18}F]FLT PET voxel SUV for 1 Gy dose bins from 1 to 9 Gy. The dashed line shows where the change in relative decrease in SUV between bins is no longer statistically significant.

Figure 4.

A scatter plot of the reduction in bone marrow $[^{18}\text{F}]\text{FLT}$ PET voxel SUV as a function of radiation dose.

Figure 5.
The average reduction in bone marrow [^{18}F]FLT PET maximum SUV for the maximum dose in vertebrae C6 - T7 for 10 patients.

Table 1

The average reduction in bone marrow [^{18}F]FLT PET SUV for 1 Gy dose bins from 1 to 9 Gy.

Dose Bin (Gy)	Average SUV Reduction	Standard Deviation
1-2	30.14%	21.04%
2-3	47.25%	16.32%
3-4	60.38%	12.95%
4-5	70.51%	8.21%
5-6	76.23%	8.37%
6-7	78.24%	7.05%
7-8	77.23%	5.54%
8-9	81.62%	5.45%
>9	81.46%	4.11%