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ARTICLE *in* NUCLEAR MEDICINE AND BIOLOGY · MAY 2010

Impact Factor: 2.41 · DOI: 10.1016/j.nucmedbio.2010.02.005 · Source: PubMed

Published in final edited form as:
Nucl Med Biol. 2010 May ; 37(4): 433–438. doi:10.1016/j.nucmedbio.2010.02.005.

Investigation of Pharmacokinetics of 3′-Deoxy-3′-[^{18}F] Fluorothymidine (FLT) Uptake in the Bone Marrow Prior to and Early After Initiation of Chemoradiation Therapy in Head and Neck Cancer

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Abstract

Introduction—The kinetics of bone marrow uptake of FLT prior to and early after initiation of chemoradiation therapy was investigated in patients with head and neck cancer.

Methods—Fourteen subjects with head and neck cancer underwent FLT PET at baseline and after 10 Gy of radiation. Thirteen subjects also received one cycle of platinum-based chemotherapy prior to the second FLT PET. Kinetic parameters including the flux constant based on compartmental analysis (K_{FLT}) and the Patlak constant (K_{Patlak}) for cervical marrow were calculated. Standardized uptake values (SUV) for the cervical (in radiation field) and lumbar spine marrow (outside radiation field) were also determined.

Results—There was a significant drop in FLT uptake in the bone marrow in the radiation field. Mean pre-treatment uptake values for the cervical spine were SUV = 3.08 ± 0.66, K_{FLT} = 0.045 ± 0.016 min^{-1} and K_{Patlak} = 0.039 ± 0.013 min^{-1} . After treatment these values were SUV= 0.74 ± 0.19, K_{FLT} = 0.011 ± 0.005 min^{-1} and K_{Patlak} = 0.005 ± 0.002 min^{-1}. Compartmental analysis revealed a significant drop in k_3 in irradiated cervical marrow. The FLT uptake in the bone marrow outside the radiation field exhibited a significantly smaller decrease.

Conclusions—There is a marked decrease in FLT uptake in irradiated bone marrow after 10 Gy of radiation therapy to the head and neck. The drop in FLT uptake in irradiated marrow is due to a significant decrease in net phosphorylation rate of FLT.

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Keywords

3′-Deoxy-3′-[^{18}F] Fluorothymidine; FLT; bone marrow; chemoradiation

INTRODUCTION

3′-Deoxy-3′-[^{18}F] Fluorothymidine (FLT) is a thymidine analog developed for imaging of cellular proliferation with positron emission tomography (PET). Externally delivered FLT is retained in the cell through phosphorylation by thymidine kinase 1 (TK_1). TK_1 is a key enzyme in the synthesis of DNA and shows markedly enhanced activity during the S-phase of the cell cycle[1]. Therefore, FLT uptake in tissue is considered a marker of DNA replication and active cellular proliferation. Other than actively proliferating tumor tissue, normal FLT uptake is observed in the liver reflecting hepatic glucuronidation of FLT, in the kidneys and bladder due to urinary excretion of FLT and in the bone marrow, likely reflecting active cell proliferation related to normal hematopoiesis[2].

In a previous report we have demonstrated that there is a significant change in FLT uptake in squamous cell head and neck cancers after 10 Gy of radiation and one cycle of platinum-based chemotherapy[3]. In the course of this study, we have also observed alterations in FLT uptake in the normal bone marrow tissue after chemoradiotherapy. Both radiation and chemotherapy are known to suppress bone marrow function. The objective of this report is to quantitatively evaluate the changes in FLT uptake in bone marrow in response to chemoradiation therapy.

METHODS

Subjects

Fifteen patients (13M, 2F; age = 55.3 ± 8.4 years), with histologically proven squamous cell head and neck cancer, Stage III or IV, were enrolled in this study. All patients were scheduled to undergo definitive concurrent chemoradiation therapy for treatment of head and neck cancer. One subject underwent the first study but declined the second FLT PET scan. The data for 14 subjects who underwent FLT PET imaging within 30 days prior to the start of treatment *(pretherapy scan)* and after 5 days of radiotherapy *(midtherapy scan)*, are included in this report. All midtherapy FLT PET scans were performed after the 5th and before the 6th radiotherapy fraction, which corresponded to 10 Gy of a prescribed dose of 70 Gy (with the exception of two subjects (designated as K and N) who received 11Gy administered in 5 fractions). All but one of the subjects also had one cycle of platinum-based chemotherapy regimen during this treatment interval. Due to technical difficulties, one subject did not have useable whole-body images resulting in elimination of this subject from that portion of the analyses. This study was approved by the local Institutional Review Board and each subject provided informed consent.

Preparation of 3′-Deoxy-3′-[^{18}F] Fluorothymidine (FLT)

Fluorine-18 fluoride was prepared by bombardment of 95% O-18 enriched water using the $^{18}O(p,n)^{18}F$ reaction. The fluorine-18 fluoride was isolated by trap and release on a anion exchange cartridge (Waters QMA). The fluorine-18 fluoride was reacted with 3′-anhydrothymidine-5′-benzoate following the procedure of Machulla et al[4]. The benzoate protecting group was removed with base hydrolysis and the product purified by semi-prep HPLC with 10% ethanol/90% isotonic saline as the mobile phase. The average specific activity of FLT was 5.41 ± 5.13 Ci/μmole with approximate yields of 5-8%.

FLT PET Imaging and Image Analysis

Image Acquisition: The FLT PET image acquisition parameters were described previously[3]. In summary, dynamic imaging of the neck was obtained for 60 minutes on a Siemens ECAT EXACT HR+ PET scanner (Siemens Medical Solutions USA, Inc., Knoxville, Tennessee) after the administration of 2.6 MBq/kg (0.07 mCi/kg) of FLT (maximum dose = 185 MBq (5 mCi)). Dynamic image acquisition was followed by whole body image acquisition from skull base to proximal thighs obtained at 74 ± 7 min (range: 65-100 min) post-initiation of the FLT infusion.

Determination of the Arterial Plasma Curve: Concurrent with dynamic imaging, venous and arterial blood sampling were performed. For the first 4 subjects, both arterial and venous samples were obtained. Because of the intrasubject consistency observed between arterial and venous samples and the intersubject consistency when a standard curve was scaled with venous samples[3], only venous sampling was performed in the remaining 10 subjects without hand warming. Venous samples were assayed for unchanged FLT and metabolites by HPLC or Sep-Pak methods as described by Shields et al[5]. These venous samples were used to calibrate the standardized curve for each patient. The fraction of unchanged FLT versus time in the venous samples was fit to a single exponential curve. The exponential coefficient from this fitted curve was used to correct the arterial plasma values for the presence of metabolites, whether the arterial plasma values were derived from the sampled or the scaled standard curve.

Image Analysis: Dynamic images were iteratively reconstructed (2 iterations/8 subsets, Gaussian 8.0 mm, zoom = 1.2). Time activity curves (TACs) were constructed for volumes-of-interest (VOIs) over the cervical marrow space within the field-of-view (FOV) using the PMOD Image Display and Analysis functions (PVIEW) and image fusion (PFUS) tools (version 3.0, PMOD Technologies, Ltd., Switzerland). VOIs were created by placing a bounding box around the marrow region of interest on the pre-therapy images and employing a 50% maximum activity threshold. The pretherapy and mid-therapy dynamic and the pretherapy and midtherapy whole-body images were co-registered and the same VOIs were applied to all datasets.

The dynamic image data for the cervical marrow were fit to a two tissue compartment model using the PMOD Kinetic Modeling Tool (PKIN, Version 3.1) with initial values equivalent to the typical value reported by Muzi et al.[6]. In this model, K_1 represents the rate constant for transport of FLT from blood into tissue, k_2 represents the rate constant of transfer of FLT from tissue back to blood, k_3 reflects the rate constant of phosphorylation of FLT and k_4 describes the rate of dephosphorylation. The metabolite-corrected plasma curve, as described above, was utilized as the arterial input function and the sampled or scaled whole blood curve was utilized for spillover correction in the implementation of the two compartment model. K_{FLT} was calculated based on the following equation [6]:

$$K_{FLT} = \frac{K_1 k_3}{k_2 + k_3}$$

The fraction phosphorylated was calculated based on the following equation [7]:

$$\text{Fraction} = \frac{k_3}{(k_2 + k_3)}$$

The Patlak influx rate constant, K_{Patlak}, was determined for the cervical marrow using the metabolite-corrected arterial plasma curve and the VOI data from 10 – 60 minutes [8]. To evaluate the time-course of FLT tissue uptake in the cervical bone marrow, standardized uptake values (SUV) were determined at each time point for the cervical marrow VOI during dynamic imaging. To evaluate the changes in non-irradiated marrow, FLT uptake in the lumbar spine was measured using the SUV determined from the whole-body images. In a manner similar to the creation of cervical marrow VOIs, lumbar marrow VOI's were created encompassing all lumbar vertebrae (except for one subject where the VOI was between T12-L2 because the lower lumbar spine was not imaged) on the pretherapy and midtherapy whole-body images. The pretherapy K_{FLT}, K_{Patlak} and SUV values for the cervical spine and SUV of the lumbar spine were compared with the parameters obtained on the midtherapy scan using paired 't' test uncorrected for the number of comparisons.

RESULTS

Pretherapy and midtherapy dynamic images of the neck were available for 14 subjects and pretherapy and midtherapy whole body images were available for 13 subjects. The midtherapy images showed absent/near absent FLT uptake in the cervical spine of all patients, which extended to variable levels of the upper thoracic spine (between T1 and T3) and to the proximal clavicles (Figure 1). Depending on the parameters assessed (i.e., K_{FLT}, K_{Patlak}, SUV, fraction phosphorylated), FLT uptake in the cervical bone marrow decreased between 68%-87% after 10 Gy of radiation therapy; which was highly significant ($p<0.001$) (Table 1). The FLT activity in the in the lumbar spine also changed significantly between the pretherapy and midtherapy scan (mean change = -0.8 ± 1.3 SUV units; $p=0.04$ or a mean 12% decrease), however, to a smaller degree than the change observed in the cervical marrow. Pretherapy, the cervical marrow had an average FLT uptake of 53% ± 12% of the uptake observed in the lumbar marrow; midtherapy, this average uptake dropped to 15% ± 6% of the lumbar FLT uptake (Figure 2).

Successful fit of the cervical marrow uptake data to the two tissue/four parameter compartment model was achieved on all dynamic studies except for one midtherapy scan due to very low uptake levels of FLT in the cervical marrow leading to particularly noisy data. Analysis of the 13 subjects who had successful fits of pretherapy and midtherapy data demonstrated a significant change in k_3, which resulted in a significant change in the fraction of FLT phosphorylated from 0.62 ± 0.18 to 0.19 ± 0.06 for the 13 subjects with complete compartmental fit parameter values ($p < 0.001$) (Table 1).

Because of noise in the data, especially at the critical later time frames, the impact of k_4 was explored in two ways. In the first approach, k_4 was initialized to the literature value and was fitted along with the other three model parameters and the tissue blood volume (V_b). If this fitting failed, k_4 was fixed to the literature value (i.e., $k_4 = 0.02$). Successful fits for k_4 were achieved for both the pre- and midtherapy scans for 10 subjects. In these subjects, there was a significant decrease in k_3 and an increase in k_4 after therapy with no significant change in K_1 and k_2 (Table 2). However, because of the small magnitude of k_4, a second approach in which k_4 was fixed to zero was also investigated. This approach yielded slightly different K_{FLT} estimates at 0.041 ± 0.015 and 0.007 ± 0.002 min^{-1}, respectively. Model fit criteria (e.g., AIC, chi-squared, or R^2) did not favor one approach over another, therefore, due to the potential information garnered by the full model fit, the results presented in Table 2 are based on a non-zero k_4. In addition to alterations in phosphorylation, the time-course of FLT uptake in the cervical bone marrow was altered between the pretherapy and midtherapy scans (Figure 3). In general, the pretherapy studies showed a steady increase of FLT uptake with time within the 60 minute dynamic time frame. After radiation therapy, there was a

rapid initial increase in concentration of FLT with a gradual washout to a plateau value (Figure 3).

DISCUSSION

Bone marrow is highly sensitive to radiation and to chemotherapeutic agents. Bone marrow of rats exposed to 2000 rads (20 Gy) shows sinusoidal dilation and decrease in cellularity already within 24 hours after exposure with complete absence of hematopoietic elements at 4 days [9]. One week following radiation, bone marrow cellularity starts to increase, likely due to an influx of cells from non-irradiated areas. This is however followed by a second phase of decrease in cellularity with regeneration delayed up to 6 months after treatment probably due to environmental changes less supportive of marrow proliferation after radiation [9]. Human studies of locally irradiated bone marrow show significant decrease in bone marrow cellularity with complete disappearance of myeloid and erythroid precursors after 10 Gy to the bone marrow [10]. The decrease in bone marrow cellularity is primarily from the precursor pool, which represents the proliferative compartment in the bone marrow [11,12]. The marked reduction in FLT uptake retention in the bone marrow subjected to fractionated radiation therapy in the current study likely reflects the loss of these actively proliferating precursor cells.

FLT PET imaging provides a mechanism by which the differential effects of radiation and chemotherapy on marrow function can be assessed. In the current study, marrow exposed to both radiation (i.e., 10 Gy) and chemotherapy (one cycle of a platinum-based regimen) exhibited an average 76% reduction (range −63% to −84%) in proliferation compared to baseline levels as measured by SUV whereas the non-irradiated marrow exposed only to the chemotherapy exhibited a more variable reduction averaging −12% (range −52% to + 16%). Despite the marked reduction of FLT uptake in the cervical spine, there was no significant change in the mean circulating platelet counts in these subjects after 10 Gy of radiation. This is due to the limited amount active marrow in the cervical spine, which contains only 3.4 % of total red marrow compared to 40% in the pelvis and 10.9% in the lumbar spine[13]. There was however good correlation between the change in FLT uptake in the lumbar marrow and change in the circulating platelet count after one cycle of chemotherapy (Spearman's coefficient: 0.727; p=0.016). It is expected that there will be more severe reduction in FLT uptake in the marrow with additional cycles of chemotherapy correlating with the chemotherapy-induced bone marrow toxicity as demonstrated by Buck et al in a patient after myeloablative treatment and failure of bone marrow transplant [14].

Preclinical studies with F-18 Fluorodeoxyglucose (FDG) in rats subjected to 10 Gy of radiation to the marrow showed an initial increase in FDG uptake 1 day after irradiation despite the moderate decrease in bone marrow cellularity[15]. After 9 days there was a severe decrease in bone marrow cellularity with an approximately 25% decrease in FDG uptake, which is significantly less than the drop in FLT uptake observed in this study. The increase in FDG uptake 1 day after radiation is believed to be due to infiltration with mature neutrophils with resultant increase in the rate of glycolysis. Although the radiation delivery in our study was different, we do not expect a similar increase in the uptake of FLT, as inflammatory responses appear to show significantly less FLT uptake compared to FDG[16] and the reduction in cellularity appears to be the primary determinant in FLT uptake. In fact, in a recent paper Everitt et al reported a significant decrease in FLT uptake in the bone marrow in two lung cancer patients after the first radiotherapy fraction of 2 Gy of a total of 60 Gy of radiation therapy[17]. They also noted complete absence of bone marrow activity within the radiation field in 2 patients after 10Gy of radiation therapy, which is consistent with our findings.

In clinical PET the most commonly used method for quantitation is the standardized uptake value (SUV). SUV provides a snapshot of FLT uptake at a specific time point after the injection of the radiopharmaceutical. Although SUV may be sufficient to evaluate the overall proliferation rate in the bone marrow, kinetic analysis of FLT uptake provides a mechanistic insight into the different processes of FLT uptake and retention in the tissue that cannot be obtained with simple SUV measurement. Based on the kinetic analysis, the posttherapy reduction in FLT uptake in the bone marrow after chemoradiation therapy can be attributed to the drop in the net phosphorylation rate of FLT (k_3) with no significant change in the rate of initial tissue delivery of the radiopharmaceutical. Thymidine kinase (TK_1) phosphorylates FLT and should therefore determine k_3. Radiation exposure in the range of 0.1 Gy to 4 Gy has been reported to decrease thymidine kinase activity in spleen and tumor cells[18]. TK mRNA levels are also decreased following irradiation [19]. The decrease in TK_1 activity after radiation is consistent with the pattern of FLT uptake and washout seen in these subjects.

The effects of radiation therapy on bone marrow structure and function have been also studied with MRI and radiocolloid scintigraphy. MRI of the irradiated spine showed no significant change in the appearance of marrow on spin-echo images in the first two weeks of fractionated radiation therapy although there was an increase in signal intensity on short-T1 inversion recovery (STIR) images, apparently reflecting marrow edema and necrosis[20]. Late changes between 6 and 14 weeks included either homogenous fatty replacement or a more heterogeneous pattern suggestive of a mixture of fibrosis and fat infiltration[20]. Radiocolloid scintigraphic imaging maps the distribution of the active reticuloendothelial system including the bone marrow. Rubin et al reported a uniform suppression of Tc-99m sulfur colloid activity in irradiated bone marrow at the completion of the radiation therapy course although changes early during radiation therapy were not studied [21]. FLT PET offers a number of advantages over both of these modalities. FLT uptake reflects the proliferative component of bone marrow, which is the portion of bone marrow most sensitive to radiation providing earlier information than MRI. Imaging with FLT PET can simultaneously provide information on the treatment response of the tumor and the bone marrow toxicity associated with the treatment. This may prove to be especially useful in the planning and monitoring of radiation therapy regimens for tumors located near large areas of metabolically active bone marrow such as pelvis. Through incorporation of FLT PET data in the radiation therapy planning, active marrow may be avoided to improve therapy tolerance.

In conclusion there is marked decrease in bone marrow uptake of FLT in irradiated marrow after 10 Gy of radiation therapy to the head and neck cancer. This is due to the drop in the net phosphorylation rate of FLT in the precursor bone marrow cells.

Acknowledgments

This research was funded in part by NIH grant 1R21 CA130281-01 and University of Iowa Carver College of Medicine and Holden Comprehensive Cancer Center grant. The authors would like to acknowledge the support and efforts of the technical staff of the University of Iowa, PET Imaging Center (John Richmond, Dean Clermont, Christine Mundt, Julie Riggert, Beth Johnson, Kelli Schlarbaum and Beth Schmitt), and our research nurses, Jo Clark and Jane Hershberger and our clinical research coordinator Kellie Bodeker-Goranson in the Department of Radiation Oncology. Part of this study was presented at the AMI/SMI Joint Molecular Imaging Conference 2007 in Providence, Rhode Island and at the SNM 2009 Annual Meeting in Toronto, Ontario, Canada.

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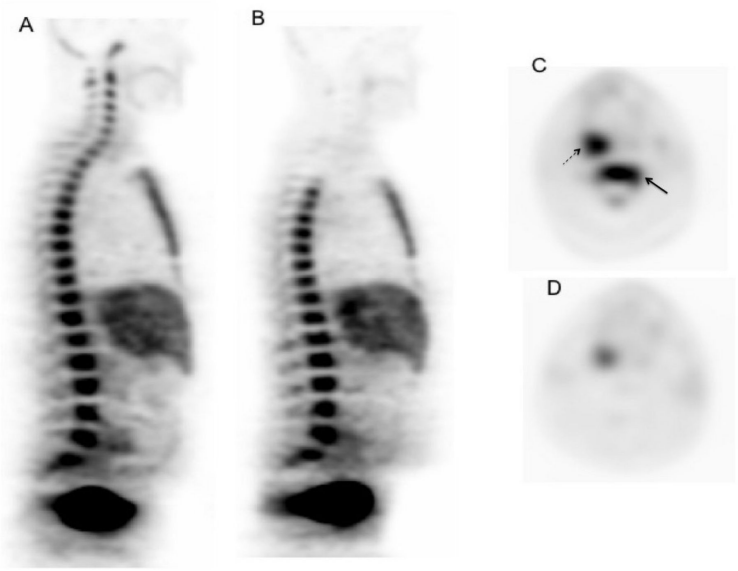

Figure 1.
FLT PET images pretherapy (A and C) and midtherapy (B and D), both obtained scan at approximately 75 minutes after the intravenous administration of 181 MBq of FLT. Note the disappearance of FLT uptake in the cervical spine and upper thoracic spine on sagittal images (A and B). The representative transaxial images (C and D) also show the drop in FLT uptake in the bone marrow (arrow) and right tonsillar squamous cell carcinoma (dashed arrow) after therapy.

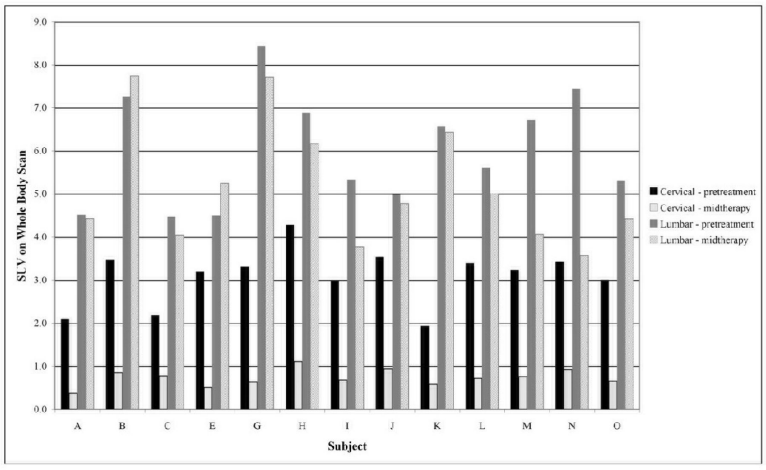

Figure 2.

FLT uptake in the cervical spine and lumbar spine bone marrow pretherapy and after 10 Gy of radiation therapy and one cycle of platinum-based chemotherapy. (i.e., midtherapy). Subject H did not receive chemotherapy prior to the midtherapy FLT PET scan.

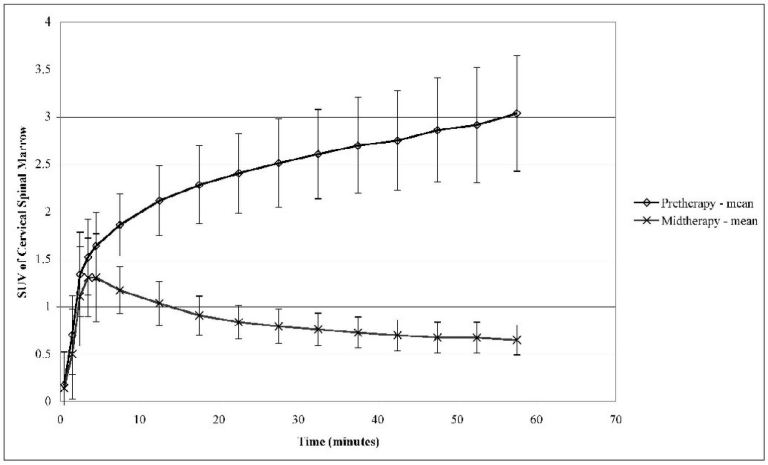

Figure 3.

Mean FLT uptake in cervical bone marrow over 60 minutes of dynamic imaging pretherapy (open diamonds) and midtherapy (X). Early stages of the dynamic uptake curves are similar indicating no significant change in initial FLT uptake with therapy. The significant difference in the curves after the initial 5 min reflects the drop in retention of FLT in the bone marrow after treatment due to decrease in phosphorylation (k_3).

Table 1

Average paired measures of FLT uptake in the bone marrow pretherapy and after 10 Gy of radiation therapy and one cycle of platinum based chemotherapy.

	K_{FLT}	K_{Patlak}	Fraction Phosphorylated	SUV
Cervical marrow				
Pretherapy	0.045 ± 0.016	0.039 ± 0.013	0.644 ± 0.196	3.08 ± 0.66
Midtherapy	0.011 ± 0.005	0.005 + 0.002	0. 229 ± 0.17	0.74 ± 0.20
Change (%)	−75 ± 11*	−87 ± 5*	−65 ± 21*	−76 ± 6*
Lumbar marrow				
Pretherapy				6.00 ± 1.31
Midtherapy				5.18 ± 1.41
Change (%)				−12 ± 19**

* p<0.001

** p=0.039

Table 2

Pretherapy and midtherapy kinetic parameters (mean ± SD) of FLT uptake in cervical marrow derived from a 2-tissue compartment model in subjects with full model fit (N = 10).

	K_1	k_2	k_3	k_4
Pretherapy	0.095 ± 0.071	0.200 ± 0.315	0.173 ± 0.083	0.009 ± 0.005
Midtherapy	0.076 ± 0.047	0.246 ± 0.081	0.061 ± 0.033*	0.019 ± 0.009†

* p = 0.003

† p = 0.02