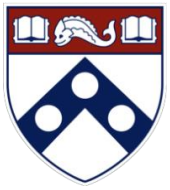

University of Pennsylvania School of Dental Medicine

^{18}F-FDG-PET/CT in Radiation Therapy-Induced Cerebellar Inflammation

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ABSTRACT

Background

^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) is used in the clinical diagnosis and management of oncologic and inflammatory pathologies. It may also have utility in detecting tissue damage induced by radiotherapy (RT) used to treat various types of cancer. The aim of the present study was to use ^{18}FDG-PET/CT to evaluate the effect of RT on the uptake of ^{18}FDG by the cerebellum.

Methods

Thirty patients with head and neck cancer (HNC) were included in this retrospective study. The patients were treated with photon, proton, or combined photon/proton RT, in addition to chemotherapy. All patients received ^{18}FDG- PET/CT imaging pre-treatment and 3 months post-treatment. The global mean standardized uptake value (SUVmean) of the cerebellum was determined for every patient by global assessment of ^{18}FDG activity using OsiriX MD software. A two-tailed paired t-test was used to compare global SUVmean pre- and post-RT.

Results

The pre-treatment and post-treatment global SUVmean for the photon group were 5.26 and 5.51 (p: 0.42), respectively. As for the proton only group, the pre- and post-treatment global SUVmeans were 7.06 and 6.05, respectively. In the combined RT group, the pre- and post-treatment global SUVmeans were 6.14 and 6.19 respectively (p: 0.92). The differences between the pre- and post-treatment values failed to reach statistical

significance for any of the treatment groups but it should be noted that there was a trend of increased ^{18}FDG uptake in the cerebellum following photon therapy. This trend was not clear in the combined group. As for the proton group, p-value was not calculated as only two patients were included.

Conclusion

Although not statistically significant, the results showed an incremental increase in global SUVmean following treatment with photon RT likely reflecting the presence of mild radiation-induced inflammation in the cerebellum.

Keywords: PET/CT, ^{18}F-FDG, Radiation therapy, Cerebellum, Head and neck cancer

INTRODUCTION

Head and neck cancers (HNC) represent approximately 4% of all cancers in the United States [1]. These malignancies affect various anatomic structures, including the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, paranasal sinuses, and salivary glands [2]. The treatment of these cancers can include surgery and/or chemotherapy along with radiation therapy (RT) as a definitive or adjuvant therapy [2].

The brain's response to radiation therapy is divided into three categories based on the time of onset. The symptoms or signs vary according to the part of the CNS irradiated. If they occur, acute symptoms are generally mild and of little consequence [3]. The acute effects occur within the first few weeks of RT and include increased cerebral edema which may result in drowsiness alongside headache and nausea. For acute reactions, the brain is directly irradiated. The early delayed (subacute) effects occur within 1-6 months after incidental irradiation of the spinal cord and include headache, somnolence, and fatigue. Both acute and subacute effects are reversible. The late (delayed) effects constitute the major hazard of CNS exposure to therapeutic irradiation. Onset may occur after more than 6 months of the onset of RT. The symptoms in this phase vary and may include seizures, significant memory loss and severe dementia [3].

The side effects of radiation therapy are not limited to the brain tissue. Other side effects of therapeutic radiation to an organ include radiation pneumonitis and radiation fibrosis of the lungs [4], damage to the pericardium, myocardium, or coronary vasculature [5] and xerostomia [6].

Traditional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have been used for staging cancer and monitoring structural changes. In contrast, positron emission tomography (PET) is used to visualize physiological and molecular changes [7]. ^{18}F-fluorodeoxyglucose (^{18}FDG), a radiolabeled glucose analog, is the most commonly used tracer for PET scanning. It is taken up by cells that rapidly consume and metabolize glucose, such as cancer and inflammatory cells [8-10]. Combined FDG-PET/CT modality allows for detection and quantification of glucose metabolism on the molecular level correlated with anatomical structures leading to a more accurate detection of malignancies and inflammatory changes [11,12].

The aim of this study is to compare cerebellar ^{18}FDG uptake before and after RT. Increased ^{18}FDG-uptake following RT may be indicative of radiation-induced inflammation.

MATERIALS AND METHODS

Patient Population

Between 02/09/2010 and 11/27/2018, 64 patients with primary tumors of the tongue, larynx, oropharynx, nasopharynx and hypopharynx who were treated with photon, proton, or combined photon/proton RT, in addition to chemotherapy with either cisplatin or cetuximab at the University of Pennsylvania. All patients were imaged pre- and 3 months post-treatment with FDG-PET/CT. Of the 64 patients, 34 were not included in the study due to an incomplete image of the cerebellum the pre- and/or the post-treatment scans,

technical issues associated with their FDG-PET/CT scans, inferior imaging quality in the head and neck region and/or mismatch between PET and CT images.

The collected clinical data included age, sex, and primary tumor location. The PET/CT scans used for the study were free from background noise, scatter, and metal artifacts. The study was approved by the Institutional Review Board. It was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

FDG-PET/CT Image Acquisition

The patients fasted for at least 6 hours prior to scanning and serum glucose levels were measured immediately before injecting the patients with ^{18}FDG. The patients were given intravenous injection of ^{18}FDG at a dose of 5.0 MBq/kg. After approximately 60 minutes PET/CT images were obtained. Imaging was performed on hybrid PET/CT scanners with comparable spatial resolution (Siemens Biograph 64 mCT [Siemens Healthineers AG, Chicago, IL, USA] and Philips Gemini TF 16 [Philips Medical Systems, Andover, MA, USA]). The images were acquired in accordance with international guidelines [13,14] and the institutional PET/CT protocol, including quality control, calibration and harmonization of PET/CT scanners and validation of standardized uptake value (SUV) measurements. Three acquisition protocols were used for patients with different body mass indices: one for body mass index (BMI) under 30, another for BMI between 30 and 35, and the third for BMI over 35 with the CT set at 50, 100 and 150 mAs for each BMI range, respectively, and all at 120 kVp. For the PET acquisitions, the time per bed was 1.5, 2, and 3 minutes for each BMI range, respectively. Low-dose CT imaging was performed for anatomic

localization and attenuation correction. PET images were corrected for scattering, attenuation, scanner dead time, and random coincidences.

FDG-PET/CT Image Analysis

^{18}FDG-PET/CT scans were analyzed using OsiriX MD software v.10.0.2 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland). Sequential sagittal PET/CT slices were used to draw regions of interest (ROIs) manually around the cerebellum using a closed polygon (**Figure 1**). The reader was blinded to the paired PET scans (pre- and post-treatment scans). The ROI borders were the tentorium cerebelli superiorly, brain stem anteriorly and base of the skull inferiorly.

The mean standardized uptake value (SUVmean) was calculated as the average value of all voxels in the ROI. To determine the global activity of the cerebellum, the SUVmean as well as area (mm^2) of each ROI at each sagittal slice, was measured and recorded. The SUVmean was multiplied by the area, and the products were summed, the result of which was divided by the sum of the total area of the ROIs (Sum [SUVmean*Area]/[Sum Area]). This resulted in the average SUVmean (Global SUVmean) representative of global neuronal function of the cerebellum. Statistical comparison was completed by using the Global SUVmean of all slices.

Statistical Analysis

Pre- and post-treatment global SUVmean was calculated for each patient. A two-tailed paired t-test in STATA software (Stata/IC Version 10.1, StataCorp, College Station, TX)

was used to compare the global SUVmean in the pre- and post-treatment scans. The level of significance was defined as a p-value of less than 0.05.

RESULTS

The data included in this study was collected from a total of 30 HNC patients (22 males and 8 females) with a mean age of 59.4 years (range: 37-76 years). Two patients were treated with proton RT, 22 with photon RT and 6 by a combination of both therapies. Primary tumor location, age, gender, and race are summarized in **Table 1**.

Measuring cerebellar global SUVmean, no statistically significant differences were found pre- and post-treatment in the proton only, photon only, or combined therapy groups (**Table 2**). The cerebellar global SUVmean in patients treated with proton RT only was 7.06 $\pm$ 0.42 pre-treatment and 6.05 $\pm$ 0.98 post-treatment (p: 0.24) **(Figure 2-3)**. As for patients treated solely with photon RT the global SUVmean changed from 5.26 $\pm$ 1.28 pre-treatment to 5.51 $\pm$ 1.25post-treatment (p: 0.42) **(Figure 4-5)** while patients treated with a combination of both treatments showed a change in the global SUVmean from 6.14 $\pm$ 0.72 pre-treatment to 6.19 $\pm$ 1.50 post-treatment (p: 0.91). (**Figures 6-7**).

DISCUSSION

This study aimed to compare cerebellar uptake of ^{18}FDG before and 3 months post-RT of patients with primary tumors of the tongue, larynx, oropharynx, nasopharynx and hypopharynx in order to draw conclusions regarding the indirect effects of HNC irradiation on the function of the cerebellum. While our results failed to show a statistically significant

indirect effect on ^{18}FDG uptake in the cerebellum following irradiation of their extra-cerebellar tumors via any of the three protocols, there was a trend toward enhanced uptake in subjects treated with photon RT.

Rege et al. using FDG, studied the effects of RT on normal tissues in the head and neck region. The authors concluded that the average metabolic ratio in the tonsils, nasal turbinates, soft palate, and gingiva did not change significantly after a 6-week course of radiation therapy. The subjects of this study had a biopsy-confirmed squamous cell carcinoma of the head and neck region [15]. In a recent study from our group by Mouminah et al, Parotid gland showed a significant increase in the uptake of FDG 3 months post-treatment in patients receiving photon radiation therapy. This suggested a radiation-induced inflammation of the parotid gland. The primary tumor location for the patients was tongue, oropharynx, nasoparhynx, hypopharynx or larynx [16].

Protocols utilizing photon beams are currently the most common form of RT for HNC while less than 1% of patients are treated with proton therapy [17]. When comparing proton to photon therapy, proton therapy has the advantage of lower dose and smaller number of beams [18]. In our study, while no statistically significant differences were found between pre- and post-treatment cerebellar ^{18}FDG uptake in patients treated with proton RT, photon RT or a combination of both, a trend towards increased post-treatment global SUVmean was observed in the group of patients that underwent photon therapy that might reflect radiation-induced inflammation **(Figure 3)**. Similar to our results, Abdulla *et al.* reported that relative to the non-irradiated contralateral lung, the directly irradiated lung parenchyma of patients undergoing treatment for lung cancer, exhibited an increase

in global SUVmean [19]. Jahangiri showed that the SUVmean increase is significant in locally advanced non-small cell lung cancer patients treated with photon therapy but not proton therapy [20] which is also similar to the trend we found even though our results did not reach statistical significance. Mouminah *et al.* showed a statistically significant increase in global SUVmean in the parotid gland of patients who underwent photon therapy for treatment of HNC [16]. Borja *et al.* found an increase in global SUVmean in the left common carotid and the arch of aorta in patients treated for HNC cancer indicating vasculitis [21]. The majority of the cited references show that there is a trend of an increase in global SUVmean following radiation therapy. Our study shows that there is a trend of an increased global SUVmean in the cerebellum despite cerebellum was not the primary target of RT.

In our study, we used global SUVmean to compare cerebellar glucose uptake before and after radiation therapy. The maximum standardized uptake value (SUVmax) which is the maximum voxel value of SUV in the target structure/ROI was not used in our analysis. While SUVmax is simple and observer-independent, we elected not to use it in our analysis as it is sensitive to image noise and therefore can be impacted by various patient characteristics and imaging parameters. Alternatively, global SUVmean accounts for all uptake within the ROIs and is more reflective of the total pathological changes in glucose metabolism, which suggests that global SUVmean is a more accurate value to use for the purpose of this study. Since we suspected that radiation therapy may affect glucose uptake by the cerebellar cells of the entire cerebellum, we used the global SUVmean as it is likely to be a more accurate indicator of the extent of the global glucose uptake.

It is important to acknowledge that our study has limitations including the relatively small sample size and the fact that it is a retrospective study. Prospective studies on a larger group of patients are recommended for the future to yield more meaningful results. More conclusions can be drawn from future studies involving the entire brain as the tissue of interest of the current study was limited to the cerebellum. Information regarding full tumor stage, type of radiation field and the exact dosage of RT administered to patients were not available for the current study, which limited the description of our patient cohort. In addition, because the patients who participated in the study received both chemotherapy and RT, it is not possible to differentiate between the effects of each treatment individually. Finally, there were only two time points assessed in this study, pre-treatment and 3 months post-treatment, which prevented the evaluation of ^{18}FDG uptake throughout the entire post-treatment period.

CONCLUSION

While statistical significance was not reached, the results showed an incremental increase in SUVmean in the cerebellum of patients whose primary extracerebellar tumors were treated with photon RT. This likely reflects the presence of mild inflammation following indirect irradiation of the cerebellum.

LIST OF ABBREVIATIONS

- FDG-PET/CT**:** ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography.
- RT: radiotherapy.
- HNC: head and neck cancer.
- CT: computed tomography.
- MRI: magnetic resonance imaging.
- PET: positron emission tomography.
- FDG: ^{18}F-fluorodeoxyglucose.
- HIPAA: Health Insurance Portability and Accountability Act.
- SUV: standardized uptake value.
- Global SUVmean: average mean standardized uptake value.
- Global SUVmax: average maximum standardized uptake value.
- ROI: region of interest.
- BMI: body mass index.
- IQ: Intelligence Quotient

DECLARATIONS

- Ethics approval and consent to participate: Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board. It was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).
- Consent for publication: Not applicable.
- Availability of data and material: All data generated or analyzed during this study are included in this article [and its supplementary information files].
- Competing interests: The authors declare that they have no competing interests.
- Funding: Not applicable.

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Table 1. Primary tumor location, age, gender, and race.

Primary Tumor Location	Number of Patients		Average Age (SD)	Race	
	Males	Females		White	Black
Tongue	12	2	60.59 (±6.39)	13	1
Larynx	3	2	56.59 (±11.97)	5	0
Oropharynx	5	2	61.08 (±10.59)	7	0
Nasopharynx	1	2	58.45 (± 2.40)	2	1
Hypopharynx	1	0	47.88	0	1

Table 2. Cerebellar average mean standardized uptake value (Global SUVmean) and in head-and-neck cancer patients pre- and post-treatment scans.

Global SUVmean (g/mL)	Pre-treatment (SD)	Post-treatment (SD)	P-value
Photon Therapy	5.26 (±1.28)	5.51 (±1.25)	0.42
Proton Therapy	7.06 (±0.42)	6.05 (±0.98)	0.24
Combined Therapy	6.14 (±0.72)	6.19 (±1.50)	0.92

Figure 1. A sample of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) of 3 different sagittal images. The region of interest (ROI) marked by the green closed polygon corresponds to the cerebellum.

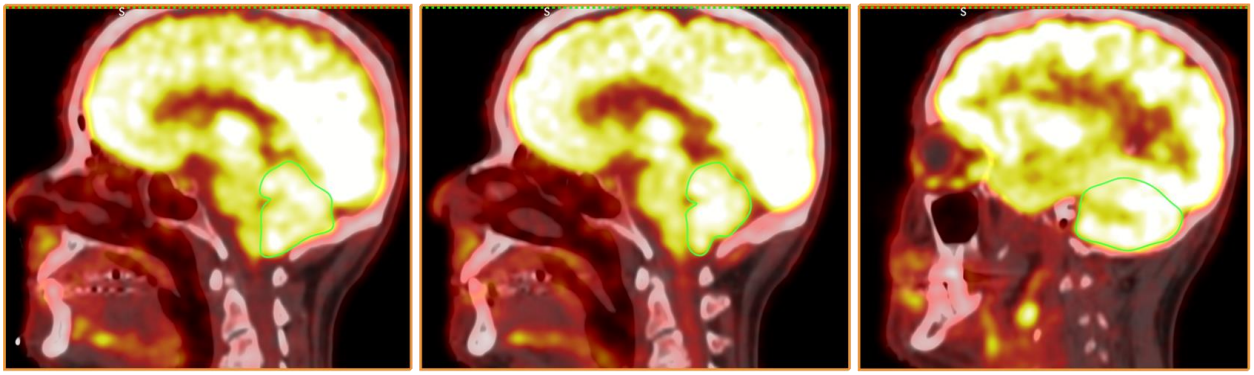

Figure 2. Changes in average standardized uptake value mean (Global SUVmean) of the cerebellum before and 3 months after treatment in patients treated with proton RT.

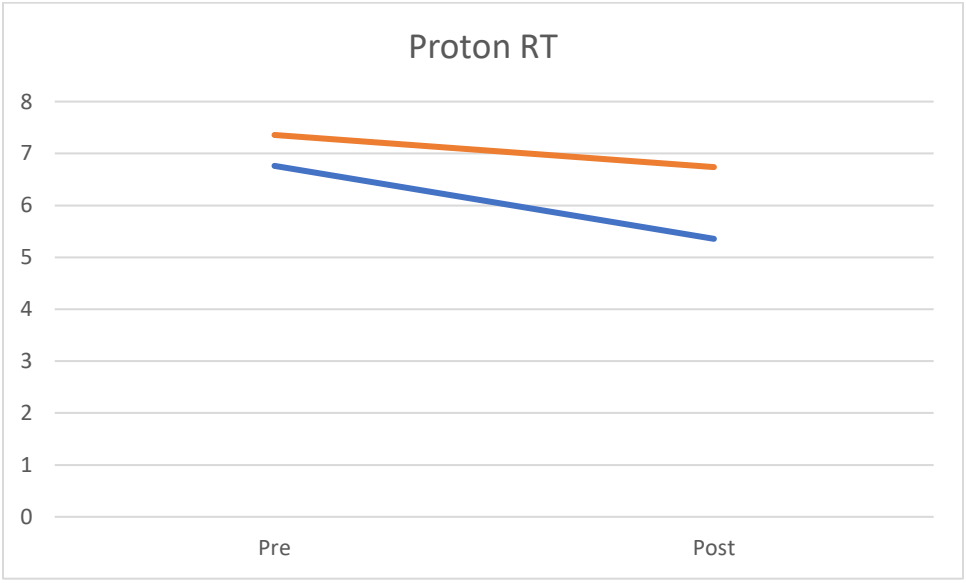

Figure 3. Mean and standard deviation of global SUVmean before and after treatment of patients treated with proton therapy only.

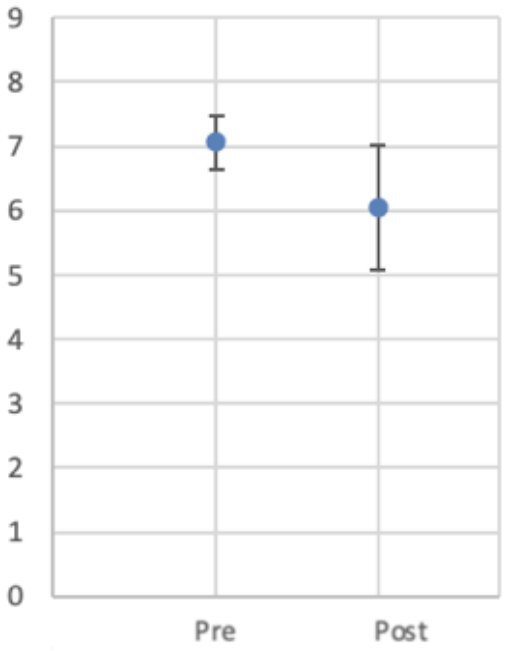

Figure 4. Changes in average standardized uptake value mean (Global SUVmean) of the cerebellum before and 3 months after treatment in patients treated with photon RT.

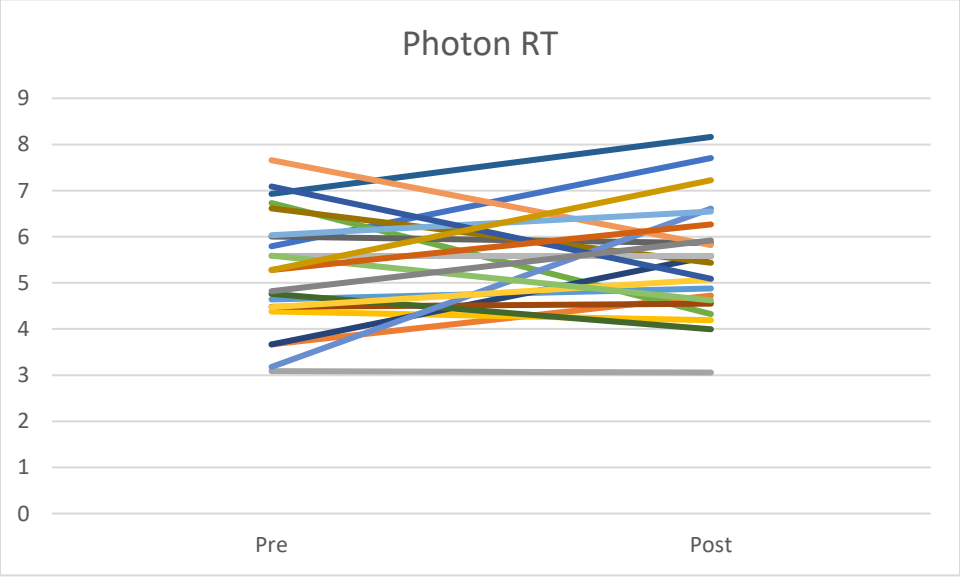

Figure 5. Mean and standard deviation of Global SUVmean before and after treatment of patients treated with photon therapy only.

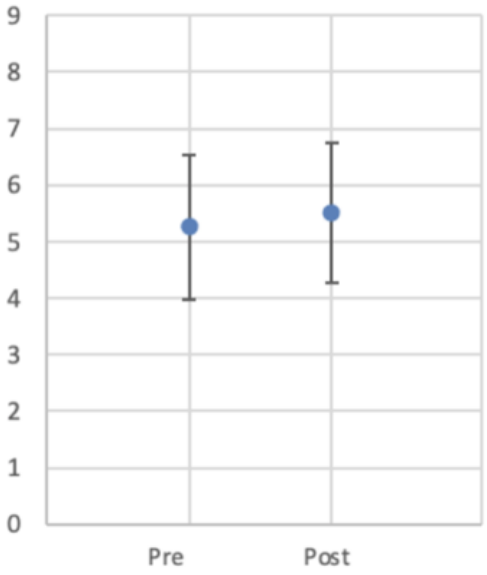

Figure 6. Changes in average standardized uptake value mean (Global SUVmean) of the cerebellum before and 3 months after treatment in patients treated with combined photon/proton RT.

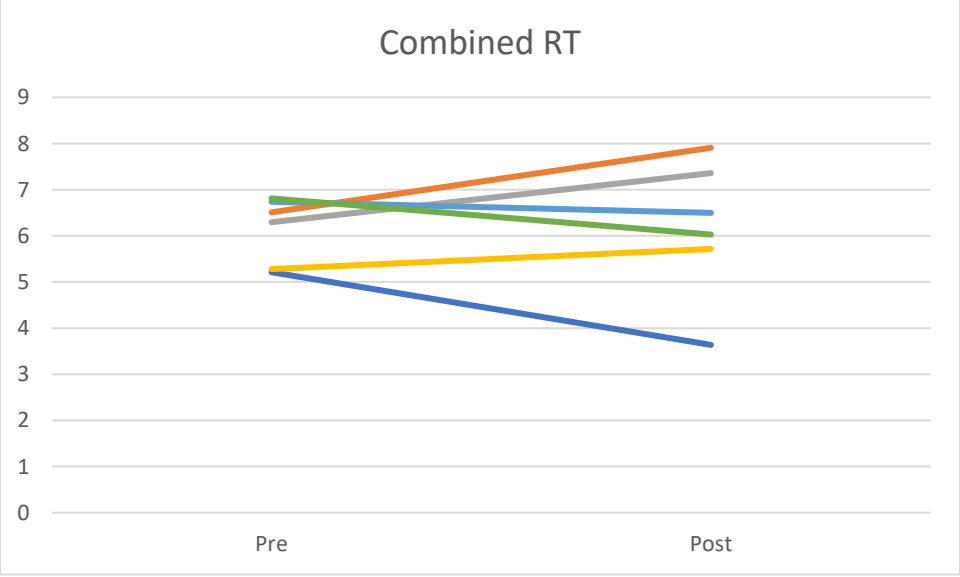

Figure 7. Mean and standard deviation of global SUVmean before and after treatment of patients treated with a combination of proton and photon radiation therapy.