

## Original Article

# Maxillary sinus inflammation assessment using FDG-PET/CT in head and neck cancer patients with photon, proton, and combined radiation therapy

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**Abstract:** Background: Head and neck cancer (HNC) patients frequently develop post-radiation maxillary sinusitis. This study investigated how different radiation therapy (RT) modalities, photon, proton, and mixed photon/proton RT, affect maxillary sinus inflammation, using 2-[<sup>18</sup>F]-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT). Methods: Seventy-seven HNC patients treated with RT (30 with photon, 20 with proton, and 27 with mixed photon/proton RT) underwent FDG-PET/CT imaging before and 3 months after treatment. Demographic information, tumor location, chemotherapy details, radiation dose (cGy), and post-radiation sinusitis ratings (scale 0-2) were collected. The mean standardized uptake value (SUVmean) of the maxillary sinus was measured by a radiologist with two years of experience using manually delineated regions of interest. Parametric paired t-tests were used to compare pre- and post-treatment SUVmeans for each RT modality. Pre-minus-post-treatment changes in SUVmean ( $\Delta$ SUVmean) between RT modalities were compared using independent t-tests. Correlation between radiation dose and  $\Delta$ SUVmean and correlation between  $\Delta$ SUVmean and clinical sinusitis scores were assessed using Pearson correlation analysis. Results: Photon RT was associated with a statistically significant increase in maxillary sinus SUVmean post-treatment (+14.32%,  $P = 0.0324$ ), while proton RT and mixed photon/proton RT did not result in significant changes (-3.39%,  $P = 0.6549$  and -5.33%,  $P = 0.4541$ , respectively). A significant difference was found between photon and mixed photon/proton RT ( $P = 0.0444$ ), whereas the difference between photon and proton RT approached significance ( $P = 0.0790$ ). Clinical inflammation ratings were highest for photon therapy (average 0.97), followed by mixed therapy (0.78), then proton therapy (0.65), though these differences were not statistically significant. Conclusion: Our findings demonstrate that photon RT leads to significant increases in maxillary sinus SUVmean as measured by FDG-PET/CT, while proton and mixed photon/proton RT do not show statistically significant changes. These preliminary results suggest that proton-based radiation modalities may be associated with reduced maxillary sinus inflammatory activity compared to photon RT alone, though larger studies with longer follow-up are needed to establish clinical significance and patient outcomes.

**Keywords:** Maxillary sinus, inflammation, 2-[<sup>18</sup>F]-fluoro-2-deoxy-D-glucose (FDG), positron emission tomography/computed tomography (PET/CT), Head and Neck Cancer (HNC), radiation therapy, photon therapy, proton therapy

## Introduction

Head and neck cancer (HNC) encompasses malignancies originating in the oral cavity, salivary glands, larynx, oropharynx, nasopharynx, hypopharynx, and paranasal sinuses. Squamous cell carcinomas constitute approximately 90% of all HNC diagnoses [1]. The anatomical complexity of these regions presents significant clinical challenges in diagnosis, treatment planning, and preservation of critical functions including speech, swallowing, and respiration. Management of HNC typically involves a multimodal approach combining surgical resection (endoscopic transoral surgery and transoral laser microsurgery),

chemotherapy, and radiation therapy (RT), with treatment selection based on cancer stage and anatomical location [2]. Advances in these treatment modalities have improved prognosis and survival rates for HNC patients.

RT remains a cornerstone in HNC management, available in three principal modalities: conventional photon RT, proton RT, and mixed proton/photon RT. While photon-based external beam radiation represents the standard approach, proton therapy has emerged as a promising alternative due to its unique Bragg peak phenomenon, enabling precise delivery of high radiation doses to tumor

**Table 1.** Demographic and clinical characteristics of HNC patients across photon, proton, and mixed photon/proton RT cohorts

Variable	Photon	Proton	Mixed
No. of Patients	30	20	27
Sex			
Male	24	14	21
Female	6	6	6
Tumor Location			
Tongue	13	16	17
Larynx	3	0	1
Oropharynx	9	4	6
Nasopharynx	4	0	1
Hypopharynx	1	0	2
Stage			
3	6	3	6
4	0	2	1
4a	19	13	20
4b	5	2	0
Chemotherapy			
Cisplatin	19	11	22
Cetuximab	1	3	1
Carboplatin/Paclitaxel	1	1	2
Combination	8	1	2
Other	1	4	0
Sinusitis Inflammation Rating			
0	9	8	9
1	13	11	15
2	8	1	3

volumes while substantially reducing exposure to surrounding tissues. This physical advantage potentially minimizes treatment-related toxicities and preserves organ function [3-7].

A significant concern in HNC RT is inflammation of the paranasal sinuses, with maxillary sinuses particularly vulnerable due to their proximity to common HNC sites. Radiation-induced sinusitis occurs in 30-40% of HNC patients following treatment [8]. This complication substantially diminishes quality of life through symptoms including chronic headaches, facial pain, nasal congestion, mucopurulent discharge, and olfactory dysfunction. The pathophysiology involves radiation-induced mucosal damage, ciliary dysfunction, vascular changes, and altered mucus composition, collectively impairing normal mucociliary clearance. Diagnosis of radiation-induced sinusitis begins with evaluation of cardinal symptoms and careful assessment of symptom duration to distinguish between acute (< 12 weeks) and chronic ( $\geq$  12 weeks) presentations. Clinical examination includes anterior rhinoscopy, nasal endoscopy for direct visualization of sinus drainage pathways, and CT scanning as the gold standard imaging technique. Additional approaches may include microbiological cultures in treatment-resistant cases and

MRI to evaluate suspected complications or rule out neoplasms in differential diagnosis [9, 10].

2-[ $^{18}$ F]-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) has become a valuable tool for staging, treatment planning, response assessment, and surveillance of head and neck cancers [11]. While conventional sinusitis diagnostics primarily examine anatomical changes and symptoms, FDG-PET/CT provides crucial functional data through its radiopharmaceutical glucose analog, which accumulates in metabolically active tissues including both malignancies and inflammatory sites [12]. This ability to visualize radiation-induced inflammation offers a potential biomarker for predicting clinical manifestations beyond standard diagnostic methods [13, 14].

The primary objective of this study is to systematically compare and quantify RT-induced inflammation of the maxillary sinuses in HNC patients treated with either photon RT, proton RT, or mixed proton/photon RT protocols. By using FDG-PET/CT as a quantitative imaging biomarker of inflammatory activity, we aim to determine whether proton RT confers significant advantages over conventional photon RT in minimizing radiation-induced sinusitis. We hypothesize that patients receiving proton therapy will demonstrate reduced inflammatory changes in the maxillary sinuses compared to those receiving conventional photon therapy. The findings from this investigation have potentially important implications for optimizing RT modality selection in HNC patients, refining treatment planning protocols to minimize sinonasal toxicity, and ultimately improving long-term quality of life outcomes in HNC survivors.

## Methods

### *Patient population*

A total of 86 HNC patients were treated with chemotherapy and one of three concurrent RT regimens. All patients underwent FDG-PET/CT imaging before treatment and three months after the completion of RT. Nine subjects were excluded from the study due to technical issues related to imaging. Demographic information, including age and sex, and clinical data, including tumor location, chemotherapy, radiation dose (cGy), and post-radiation sinusitis rating, were collected for the remaining 77 patients (Table 1). The clinical sinusitis inflammation score was assessed on a scale of 0-2, where 0 represented no inflammation, 1 indicated some inflammation, and 2 signified significant inflammation requiring substantial clinical intervention. This study included 30 patients who received photon RT, 20 patients who received proton RT, and 27 patients who received mixed photon/proton RT.

Treated tumor locations included the hypopharynx, larynx, oropharynx, nasopharynx, and tongue. The study was conducted in adherence to the Health Insurance

Portability and Accountability Act (HIPAA) and was approved by the Institutional Review Board #806168.

#### *FDG-PET/CT image acquisition*

Patients were injected intravenously with 5.0 MBq/kg of FDG. Approximately one hour after injection, FDG-PET/CT images were obtained using hybrid PET/CT scanners (Siemens Biograph 64 mCT (Siemens Healthineers AG, Chicago, IL, USA) and Philips Gemini TF 16 (Philips Medical Systems, Andover, MA, USA). Prior to image acquisition, patients were required to fast for at least six hours, and serum glucose levels were measured immediately before FDG administration. Acquisition protocols were tailored to patients' body mass index (BMI) and categorized into three groups: BMI < 30, BMI 30-35, and BMI > 35. The corresponding CT settings were 50 mAs, 100 mAs, and 150 mAs, respectively, all at 120 kVp. PET acquisition times were set to 1.5, 2, and 3 minutes per bed position, respectively. Low-dose CT imaging was performed for attenuation correction.

#### *FDG-PET/CT image analysis*

Using OsiriX MD software v.12.0.1 (DICOM viewer, image-analysis program, Pixmeo SARL; Bernex, Switzerland), regions of interest (ROIs) containing the entire left and right maxillary sinuses were manually delineated (**Figure 1**). Representative ROI snapshot slices are shown for the FDG-PET/CT scans for a photon, proton, and mixed therapy head and neck cancer patient for both the baseline and post radiation therapy (**Figure 1**).

Two types of ROIs were defined for each subject: 1) total maxillary sinus ROI and 2) cavitory ROI. The total maxillary sinus ROI encompassed the anatomic maxillary sinuses within the osseous borders, while the cavitory uptake was limited to the radiolucent portions of the maxillary sinuses, excluding any radiopacities or hyperplasia. ROIs encompassing the right and left maxillary sinuses were delineated using a closed polygon for each sinus on axial PET/CT slices. The mean standardized uptake value (SUVmean) was calculated as the average value of all voxels within the ROI. The pre- and post-treatment scans were blinded to the readers. Following the described process, a radiologist with two years of experience calculated the SUVmean for each patient before and after RT.

#### *Statistical analysis*

Normal distribution of data across treatment groups was confirmed using Q-Q plots. We conducted parametric paired t-tests to compare SUVmean before and after radiotherapy (RT) for each modality: photon, proton, and mixed photon/proton RT. To assess differences between treatment approaches, we calculated  $\Delta$ SUVmean (the change from pre- to post-treatment SUVmean) for each patient and compared these values across the three RT modalities using independent t-tests for the following

pairs: photon vs. proton, proton vs. mixed photon/proton, and photon vs. mixed photon/proton. For individual patient analysis, we plotted radiation dose (measured in cGy) against the corresponding  $\Delta$ SUVmean to evaluate dose-response relationships. Mean inflammation was calculated separately for photon, proton, and mixed radiation therapy groups, and assessed for correlation between  $\Delta$ SUVmean and clinical sinusitis inflammation score. All statistical analyses were performed using GraphPad Prism version 10.0.0 for Mac (GraphPad Software, Boston, Massachusetts, USA). Results are displayed as box plots with whiskers extending to the 10th and 90th percentiles, with outliers individually identified.

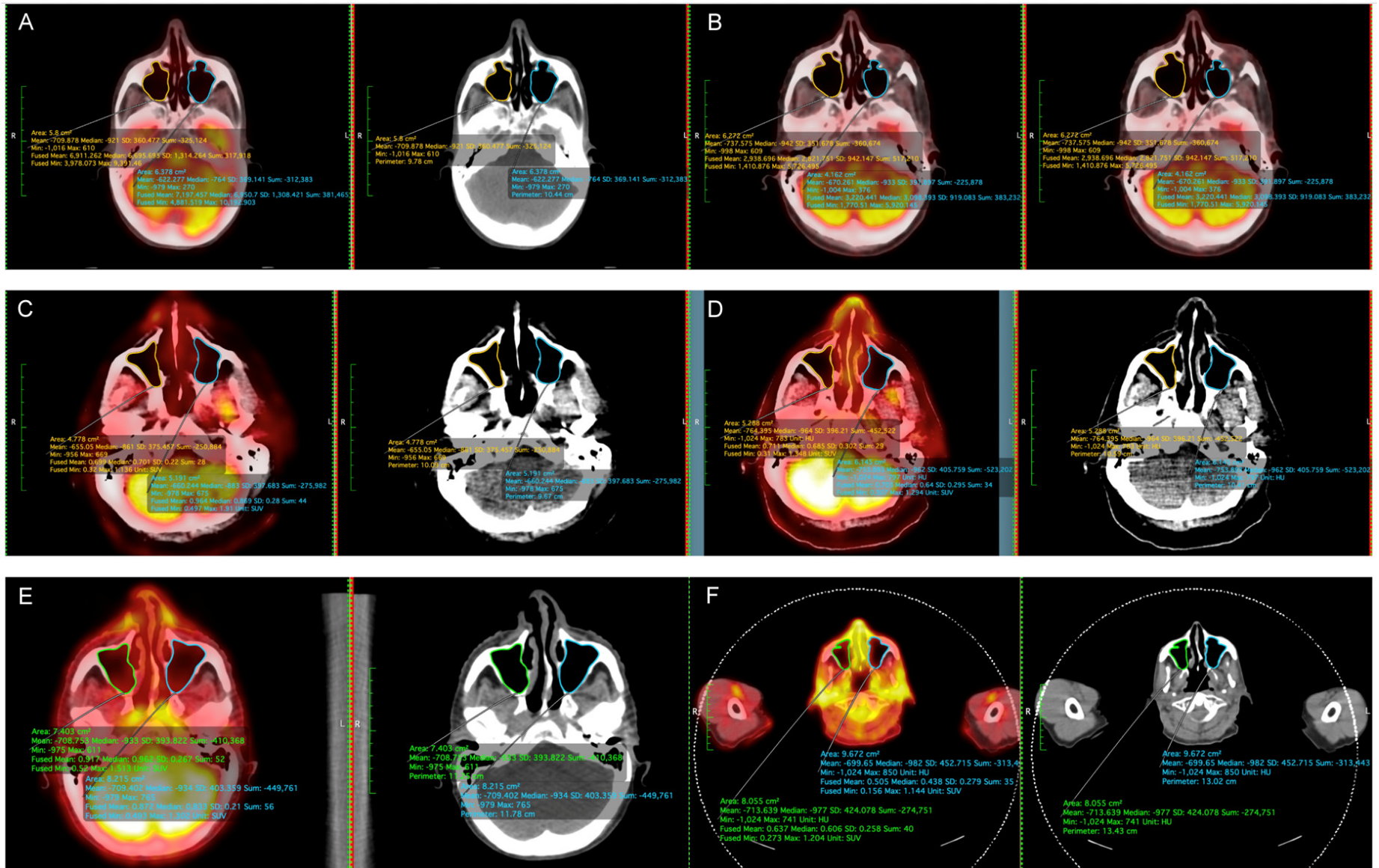
## Results

The cohort consisted of 59 males (mean age:  $61.8 \pm 5.3$  years; range: 47.2-84.5 years) and 18 females (mean age:  $58.3 \pm 10.1$  years; range: 42.5-89.2 years). Disease sites included the tongue (46 patients), oropharynx (19 patients), nasopharynx (5 patients), larynx (4 patients), and hypopharynx (3 patients). The staging of the patients was as follows: 15 patients with stage 3, characterized by a tumor larger than 4 cm without metastasis; 3 patients with stage 4 characterized by tumor invasion into adjacent structures or tissues without distant metastasis; 52 patients with stage 4A, where cancer has spread to nearby regions; and 7 patients with stage 4B, in which HNC has spread to deeper tissues (**Table 1**).

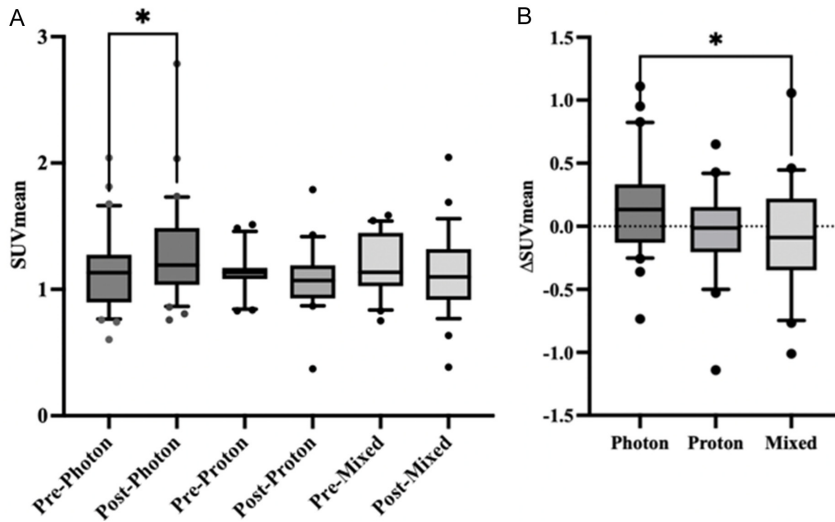
Patients receiving photon RT showed a significant increase in SUVmean from baseline 1.145 to post-treatment 1.309 (+14.32%,  $P = 0.0324$ ). In contrast, proton RT patients exhibited no statistically significant change, with SUVmean shifting from 1.122 to 1.084 (-3.39%,  $P = 0.6549$ ). Similarly, mixed photon/proton RT showed no significant difference, with SUVmean decreasing from 1.201 to 1.137 (-5.33%,  $P = 0.4541$ ) (**Figure 2A**). When comparing changes in  $\Delta$ SUVmean between modalities, a significant difference was observed between photon and mixed RT ( $P = 0.0444$ ); the difference between photon and proton RT approached significance ( $P = 0.0790$ ), and no significant differences appeared between proton and mixed RT ( $P = 0.8330$ ) (**Figure 2B**).

There was less variability in dosage received for proton therapy, with greater consistency in  $\Delta$ SUVmean compared to that in the photon and mixed therapy cohort (**Figure 3**). There was no statistically significant correlation between  $\Delta$ SUVmean between photon, proton, and mixed photon/proton RT and fraction received (cGy). Photon therapy average inflammation ratings were found to be the highest at an average of 0.97, followed by mixed therapy at 0.78, and proton therapy was lowest at 0.65 in this cohort. However, the difference in inflammation rating between proton and photon therapy approached significance ( $P = 0.1052$ ), while differences between proton and mixed therapy ( $P = 0.4874$ ) or between photon and mixed thera-

# Maxillary sinus inflammation assessment using FDG-PET/CT



**Figure 1.** ROI snapshot slices from three head and neck cancer patients (photon, proton, and mixed radiation therapy) showing the maxillary sinus at baseline and three months post-radiation therapy. A. Baseline FDG-PET/CT slice from photon patient. B. Post-RT FDG-PET/CT slice from photon patient. C. Baseline FDG-PET/CT slice from proton patient. D. Post-RT FDG-PET/CT slice from proton patient. E. Baseline FDG-PET/CT slice from mixed RT patient. F. Post-RT FDG-PET/CT slice from mixed RT patient. No statistically significant differences were observed between the delineated ROIs.



**Figure 2.** Maxillary sinus FDG uptake across radiation therapy modalities. A. SUVmean before and after treatment for patients receiving photon, proton, or mixed radiation therapy. B. Change in SUVmean ( $\Delta$ SUVmean) between pre- and post-treatment for each modality. Box plots display the 10-90% quartile range with outliers marked. \* indicates  $P < 0.05$ .

py ( $P = 0.3150$ ) were not statistically significant (**Figure 4**). Qualitatively, when comparing **Figures 2B** and **4**, there is concordance between SUVmean and sinusitis scores when comparing photon and proton therapy, with photon having a statistically significant increase in SUVmean and more patients clinically having sinusitis.

## Discussion

Our study investigated how different radiation therapy (RT) modalities affect maxillary sinus inflammation in head and neck cancer (HNC) patients using FDG-PET/CT imaging. Three months post-treatment, photon RT caused a statistically significant increase in maxillary sinus SUVmean, while proton RT and mixed photon/proton RT showed no significant changes. The difference in SUVmean change between photon and mixed photon/proton RT was statistically significant, though the difference between photon and proton RT approached but did not reach significance. Proton therapy demonstrated less dosage variability and greater consistency in  $\Delta$ SUVmean compared to photon and mixed therapy groups. While photon therapy showed the highest average inflammation ratings, this difference was not statistically significant; however, SUVmean measurements correlated with clinical sinusitis scores when comparing photon and proton therapy - photon therapy showed both significant SUVmean increases and more patients with clinical sinusitis. These findings align with previous research reporting high post-radiation sinusitis rates in HNC patients receiving photon RT, including one study finding 73% of nasopharyngeal carcinoma patients developed sinusitis following photon RT [15]. Our results suggest that proton RT and mixed photon/proton RT may cause less maxillary sinus inflammation than photon RT in the first three

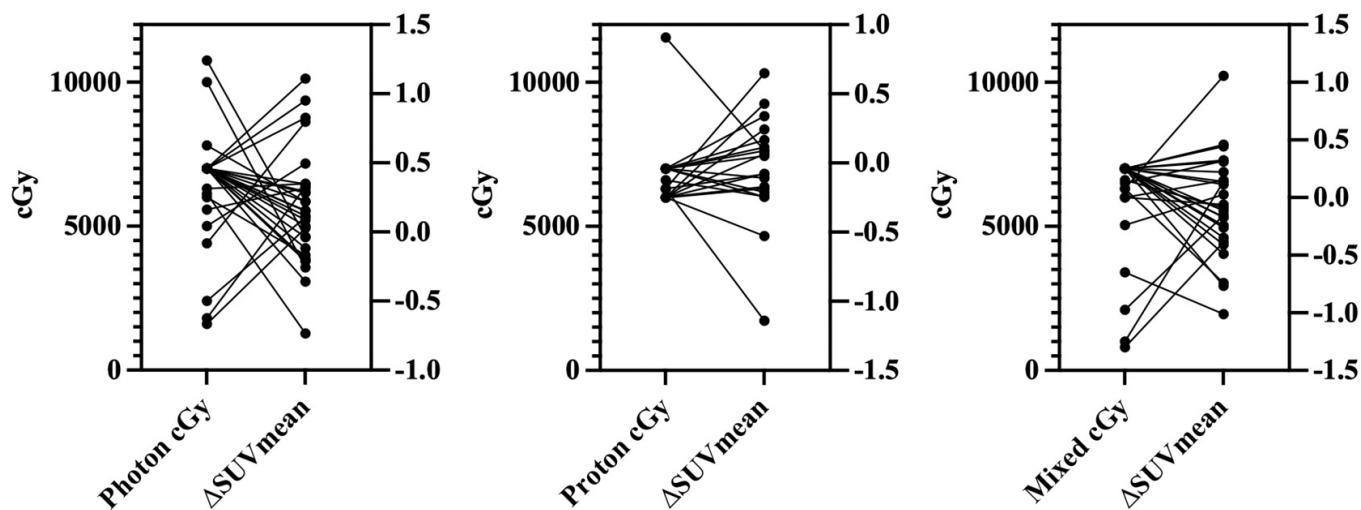
months after treatment, with our timing supported by research showing post-radiation sinusitis peaks at 3-6 months post-RT [16].

The potential benefits of proton RT in reducing radiation-induced toxicities, such as sinusitis, have been attributed to its unique dosimetric properties [16]. Previous studies have shown that proton therapy can deliver high doses to the target while minimizing exposure to adjacent normal tissues, such as the maxillary sinuses, oropharynx, salivary glands, and sinonasal region [17-22]. The lower degree of maxillary sinus inflammation observed in the proton RT and mixed photon/proton RT groups in our study is consistent with these dosimetric advantages. The difference in  $\Delta$ SUVmean between photon and proton RT that trends toward significance, and the significant difference between photon and

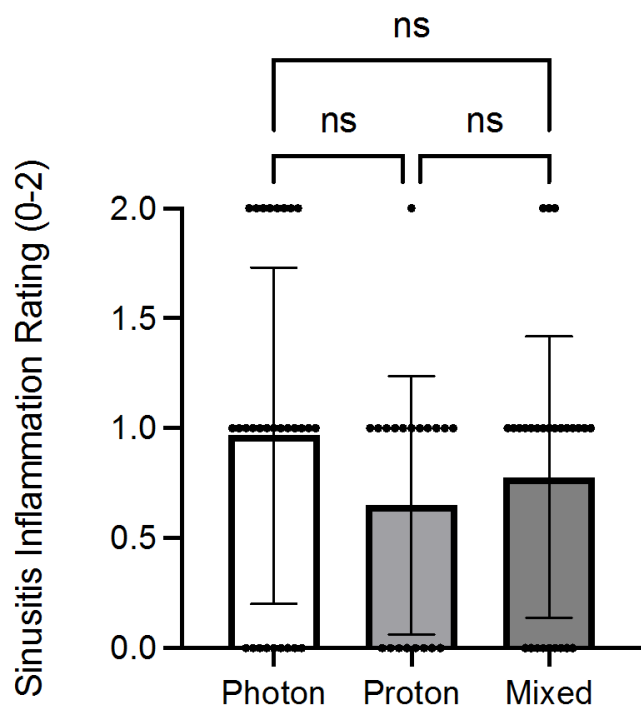
mixed photon/proton RT, further support the notion that proton therapy may limit damage to the maxillary sinus compared to photon therapy alone. This aligns with our findings and other clinical studies reporting lower rates of sinusitis in HNC patients treated with proton RT compared to photon RT [23].

RT-induced inflammation can confound the interpretation of FDG-PET/CT scans, leading to false-positives. In a study by Huang et al., presence of sinusitis was found to be a significant predictor of cancer recurrence in terms of freedom from local failure, freedom from distant failure, and disease-free survival six months following radiation completion [24]. By minimizing radiation-related inflammatory changes in the maxillary sinus, proton RT and mixed photon/proton RT may improve the specificity of FDG-PET/CT imaging in the early post-treatment period, potentially facilitating earlier detection of true recurrences and reducing the need for additional diagnostic procedures.

Importantly, the use of FDG-PET/CT imaging in our study not only allowed for the quantification of maxillary sinus inflammation but also highlights the potential role of this imaging modality in prognosticating the risk of developing post-radiation sinusitis. The reduced variability in dosage and subsequent inflammatory response observed in the proton RT cohort represents a clinically significant advantage of this modality. This consistency aligns with the physical properties of proton beam delivery, particularly the Bragg peak phenomenon, which enables more precise dose deposition with sharper dose fall-off compared to photons. Despite the absence of a statistically significant correlation between radiation dose and  $\Delta$ SUVmean across all modalities, the trend toward lower inflamma-



**Figure 3.** Relationship between radiation dose (cGy) and metabolic response ( $\Delta$ SUV mean) across different radiation treatment modalities: photon (left), proton (middle), and mixed photon/proton (right). Each line connects an individual patient or treatment site’s radiation dose with their corresponding change in metabolic activity.



**Figure 4.** Inflammation ratings between photon, proton, and mixed photon/proton RT for patients as measured by FDG PET/CT. ns indicates  $P > 0.05$ .

tion ratings in proton therapy compared to mixed and photon therapy further supports the clinical relevance of our findings. The concordance between increased SUVmean and higher clinical sinusitis rates in the photon cohort suggests that FDG-PET/CT may serve not only as a tool for detecting inflammatory changes but also as a predictor of clinical manifestations. FDG-PET/CT has been increasingly recognized as a valuable tool for evaluating inflammation and infection in various clinical settings [25]. By providing quantitative measures of inflammation,

FDG-PET/CT imaging may help to identify patients at higher risk of developing post-radiation sinusitis, allowing for early intervention. Post-radiation sinusitis can significantly impact patients’ quality of life, causing symptoms such as nasal congestion, facial pain, and headaches. Early identification of high-risk patients may allow for the implementation of preventive measures, such as nasal irrigation, decongestants, or antimicrobial therapy, which have been shown to reduce the incidence and severity of sinusitis in HNC patients [26]. Furthermore, using FDG-PET/CT imaging to monitor the development and progression of post-radiation sinusitis may help guide treatment decisions and optimize patient outcomes.

Several limitations should be acknowledged when interpreting our results. The limited sample size, particularly the unequal number of patients within each disease site group, may have affected our ability to detect clinically significant differences in maxillary sinus inflammation between RT modalities and disease sites. This is particularly relevant when considering the potential impact of tumor location on the risk of developing post-radiation sinusitis. While the maxillary sinus has been identified as the most frequently involved sinus in patients treated for NPC, the relevance of maxillary sinus inflammation in other HNC sites has been less well established [27]. Despite including a diverse range of HNC subsites in our study, we still observed statistically significant increases in maxillary sinus SUVmean in the photon RT group, suggesting that the impact of photon RT on maxillary sinus inflammation may extend beyond NPC. However, larger, disease-site-specific studies are needed to confirm these findings. The potential influence of confounding factors, such as allergic rhinitis, infections, and medication use, may have impacted our findings. While we expect these factors to be equally distributed among the different RT modality groups, the limited sample size may have ampli-

fied their effects. Future studies with more rigorous control of potential confounders through detailed medical history collection, stratified analyses, and multivariate modeling are necessary. The single time point assessment of maxillary sinus inflammation at three months post-RT provides only a snapshot of the short-term effects of different RT modalities. Long-term follow-up is necessary to fully understand the impact of RT on maxillary sinus inflammation and its potential clinical implications. Serial FDG-PET/CT imaging at multiple time points post-RT would help to characterize the temporal evolution of maxillary sinus inflammation and its relationship to clinical symptoms and cancer recurrence.

## Conclusion

In our study, FDG-PET/CT imaging demonstrated that photon RT resulted in a statistically significant increase in maxillary sinus SUVmean three months post-treatment, while neither proton RT nor mixed photon/proton RT produced statistically significant changes. A statistically significant difference in SUVmean change was observed between photon and mixed photon/proton RT, while the difference between photon and proton RT approached but did not reach statistical significance. These findings suggest that photon RT is associated with measurable increases in maxillary sinus metabolic activity indicative of inflammatory changes, while proton-based radiation modalities do not demonstrate similar increases in the early post-treatment period. However, the clinical significance of these SUVmean changes requires further investigation, as clinical inflammation scores did not reach statistical significance between treatment modalities. These preliminary findings indicate that FDG-PET/CT may serve as a sensitive imaging biomarker for detecting subclinical inflammatory changes in the maxillary sinuses following different radiation therapy modalities, though larger studies with extended follow-up periods are needed to determine whether the observed SUVmean differences translate to clinically meaningful patient outcomes.

## Disclosure of conflict of interest

None.

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