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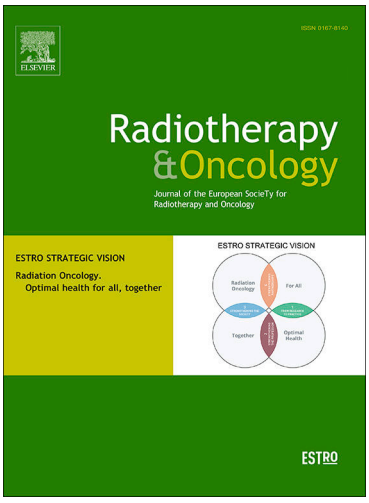

Mid-treatment 18F-FDG PET imaging changes in parotid gland correlates to radiation-induced xerostomia

Yuvnik Trada, Mark T Lee, Michael G Jameson, Phillip Chlap, Paul Keall, Daniel Moses, Peter Lin, Allan Fowler

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TITLE:

Mid-treatment 18F-FDG PET imaging changes in parotid gland correlates to radiation-induced xerostomia

AUTHORS:

Yuvnik Trada FRANZCR[1,2], , Mark T Lee FRANZCR[3,4], Michael G Jameson PhD[5,6], Phillip Chlap[3,4,7], Paul Keall PhD[2,8], Daniel Moses FRANZCR PhD[9,10], Peter Lin FRACP[4,11,12], Allan Fowler FRANZCR[3,4]

[1]Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, NSW, Australia

[2]Faculty of Medicine and Health, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

[3]Department of Radiation Oncology, Cancer Therapy Centre, Liverpool Hospital, Liverpool, NSW, Australia

[4]South Western Clinical School, School of Medicine, University of New South Wales, NSW, Australia

[5]GenesisCare, Sydney, NSW, Australia

[6]St Vincent's clinical school, Faculty of Medicine, University NSW, Australia

[7]Ingham Institute of Applied Medical Research, Liverpool, NSW, Australia

[8]Image X Institute, University of Sydney, Sydney, NSW, Australia

[9]Graduate school of Biomedical Engineering, Faculty of Engineering, University of New South Wales, Sydney, Australia

[10]Department of Medical Imaging, Prince of Wales Hospital, Randwick, NSW, Australia

[11]Department of Nuclear Medicine and PET, Liverpool Hospital, Liverpool, NSW, Australia

[12]School of Medicine, Western Sydney University, NSW, Australia

SHORT TITLE:

Mid-treatment FDG-PET and xerostomia

HIGHLIGHTS:

- We present results of prospective mid-treatment FDG-PET imaging biomarker study for xerostomia prediction
- 56 mucosal head and neck patients treated with definitive radiotherapy were evaluated with FDG-PET imaging at baseline and week 3 mid-radiotherapy
- We found early metabolic changes in the parotid gland improved prediction of subsequent risk of xerostomia

- There is a potential for FDG-PET changes in parotid gland to be utilised in future adaptive radiotherapy trials for toxicity minimisation

CORRESPONDING AUTHOR:

Dr Yuvnik Trada

Department of Radiation Oncology

Calvary Mater Newcastle

Edith St, Waratah 2298

NSW, Australia

Phone: +61 2 4014 3125

Fax: +61 2 4014 3169

Email: Yuvnik.Trada@calvarymater.org.au

ABSTRACT

BACKGROUND

The aim of this study was to measure functional changes in parotid glands using mid-treatment FDG-PET/CT and correlate early imaging changes to subsequent xerostomia in mucosal head and neck squamous cell carcinoma patients undergoing radiotherapy.

MATERIALS AND METHODS

56 patients from two prospective imaging biomarker studies underwent FDG-PET/CT at baseline and during radiotherapy (week 3). Both parotid glands were volumetrically delineated at each time point. PET parameter SUV_{median} were calculated for ipsilateral and contralateral parotid glands.

Absolute and relative change (Δ) in SUV_{median} were correlated to moderate-severe xerostomia (CTCAE grade ≥2) at 6 months. Four predictive models were subsequently created using multivariate logistic regression using clinical and radiotherapy planning parameters. Model performance was calculated using ROC analysis and compared using Akaike information criterion (AIC)

RESULTS

29 patients (51.8%) developed grade ≥2 xerostomia. Compared to baseline, there was an increase in SUV_{median} at week 3 in ipsilateral (8.4%) and contralateral (5.5%) parotid glands. Increase in ipsilateral parotid ΔSUV_{median} (p=0.04) and contralateral mean parotid dose (p=0.04) were correlated to xerostomia.

The reference 'clinical' model correlated to xerostomia (AUC 0.667, AIC 70.9). Addition of ipsilateral parotid ΔSUV_{median} to the clinical model resulted in the highest correlation to xerostomia (AUC 0.777, AIC 65.4).

CONCLUSION

Our study shows functional changes occurring in the parotid gland early during radiotherapy. We demonstrate that integration of baseline and mid-treatment FDG-PET/CT changes in the parotid gland with clinical factors has the potential to improve xerostomia risk prediction which could be utilised for personalised head and neck radiotherapy.

KEYWORDS

FDG-PET, mid-treatment, xerostomia, prediction, Head and Neck Neoplasm, radiotherapy

INTRODUCTION

Head and neck radiotherapy can be associated with damage to the parotid gland leading to long term xerostomia causing significant morbidity and impact on patient's quality of life.(1, 2) There are limited treatment options for radiotherapy induced xerostomia, hence prevention or minimisation of risk is crucial.(3) Currently, radiotherapy is designed without taking into account of an individual's radiosensitivity or changes occurring during course of radiotherapy.(4) Therefore, there is a scope for personalisation of treatment based on individual risk of xerostomia.

Conventional imaging shows anatomical changes in parotid volume can occur during radiotherapy.(5, 6) Functional imaging offers the advantage of non-invasively measuring early changes in normal tissue preceding and not evident on conventional imaging.(7)

Saliva production is an energy intensive process and parotid metabolism can be measured using 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET).(8, 9) FDG-PET can also measure radiation induced inflammation in the parotid gland which predisposes patients to xerostomia.(10) Hence, FDG-PET/CT performed during radiotherapy has potential to be used as an early predictive biomarker for subsequent risk of xerostomia. A mid-treatment predictive biomarker would allow adaptation of radiotherapy to the parotid gland reducing subsequent toxicities. Mid-treatment FDG-PET/CT has been utilised to predict tumour outcomes in several studies in head and neck cancer, however, it has not yet been utilised for normal tissue radiation toxicity prediction.(11-14) There are currently no studies that explore the utility of mid-treatment FDG-PET/CT imaging for xerostomia prediction.

Our hypothesis is that baseline and mid-treatment FDG-PET/CT changes in the parotid gland during radiotherapy can improve correlation of xerostomia compared to clinical features alone. We aim to:

1. Measure structural and functional imaging changes in parotid glands that occur early during radiotherapy
2. Correlate early imaging parotid changes to parotid dose and subsequent xerostomia
3. Build and compare predictive models using imaging features and clinical features

MATERIALS AND METHODS

Study design

Patients with newly diagnosed, biopsy-proven, non-metastatic mucosal head and neck squamous cell carcinoma treated with definitive radiotherapy from two prospective imaging biomarker studies were evaluated. Local research ethics committee approval was provided for both studies and all patients provided written informed consent.

All patients were evaluated and reviewed by a multidisciplinary head and neck team. Patients were treated using a simultaneous integrated boost intensity-modulated radiation therapy technique over 35 fractions. Radiotherapy treatment volumes were defined using consensus international guidelines and underwent a stringent peer review process.(15) Patients underwent contemporary radiotherapy planning aiming at minimising dose to parotid glands, oral cavity and swallowing structures without compromising target volumes as per departmental protocol.

Patient's radiotherapy planning parameters including ipsilateral parotid, contralateral parotid and oral cavity mean dose were collected. Patient's clinical parameters such as primary tumour site, tumour stage, age, gender, smoking, alcohol intake and chemotherapy use were also collected.

The primary endpoint was moderate-severe xerostomia defined as grade ≥2 by Common Terminology Criteria for Adverse Event (CTCAE) criteria at 6 months, collected prospectively by a physician as a part of clinical trial follow-up. Clinician reported patient toxicity was chosen because it is reproducible and clinically significant given its implication on patient specific quality of life measures.(9, 16-19) Grade ≥2 xerostomia has been used as an endpoint in seminal randomised phase III xerostomia studies.(20, 21) It has also previously been correlated to objective measures such as salivary flow and parotid scintigraphy.(17, 19)

Image acquisition

Each patient underwent 18F-FDG-PET/CT scans before and during week 3 of radiotherapy. FDG-PET studies were acquired in radiotherapy treatment position on a GE Discovery™-710 PET-CT time-of-flight positron emission tomography (PET)-CT (GE Healthcare, Waukesha, MI). All scans were performed on the same scanner with the same acquisition and reconstruction protocols. The uptake time of the mid-treatment study was kept within 10% of the uptake time of the baseline study to ensure standardisation. Details of the imaging technique have been described previously.(12)

Image analysis

Parotid gland was categorised as ipsilateral if a well lateralised primary site was present, or for a central tumour the parotid gland with the higher delivered radiotherapy dose. The parotid glands

were volumetrically segmented on the baseline and week 3 CT/PET by the same radiation oncologist with experience in management of head and neck malignancy. Rigid fusion between CT and corresponding FDG-PET was performed matching primarily to the parotid glands. Structure delineation and image fusion was undertaken using MIM Software (MIM Software Inc.; Beachwood, OH).

The parotid volume (CT volume) and median Standardised Uptake Value (SUV_{median}) at baseline and week 3 were measured. SUV_{median} value was chosen to minimise the impact of any PET avid lymph nodes adjacent to the parotid gland and has been utilised previously.(9, 24) Percentage change (Δ) in imaging parameters was calculated, defined as Δ = [(week 3 – week 0)/week 0] × 100%. An example of FDG-PET changes and parotid analysis undertaken is shown in Figure 1.

Statistical analysis

The change in imaging features (parotid gland SUV_{median} and CT volume) from baseline to week 3 was compared using the Wilcoxon signed-rank test. Clinical and radiotherapy dosimetry parameters were correlated to xerostomia (CTCAE grade ≥2) using Mann-Whitney U test.

Individual parotid gland level analysis was undertaken to correlate absolute value and change (Δ) in imaging features to mean parotid radiotherapy dose using Spearman's Rho.

Parotid imaging features were then correlated to xerostomia using univariate logistic regression. A multivariate logistic regression method was performed utilising imaging features and previously demonstrated predictive radiotherapy planning dosimetric parameters to select imaging features for predictive model building.(4, 22) A limited number of features were selected based on proportion of outcome events in our patient population.(25, 26)

Four predictive models were subsequently created to predict xerostomia using multivariate logistic regression to describe the potential additional utility of imaging features. A clinical model contained two *a-priori* selected baseline features (contralateral parotid dose and chemotherapy use Y/N) based on previously demonstrated predictive value was used as a reference model.(9, 27-29) Baseline xerostomia is also a recognised predictive factor for late xerostomia and utilised by Van Dijk *et al.*, however, no patients in our cohort exhibited xerostomia at baseline and hence was not included in the model.(24, 30) The imaging model consisted of the two most predictive imaging features on multivariate analysis above. The mixed baseline model consisted of two *a-priori* clinical features above and addition of one highest performing imaging feature from baseline (week 0) imaging. The mixed mid-treatment model consisted to two *a-priori* clinical features above and addition of one highest performing imaging feature from mid-treatment (Δ) imaging. Model performance was calculated by using receiver operator characteristic (ROC) analysis after logistically combining the variables. Area under the ROC curve (AUC) value and Accuracy values were calculated. Model

comparison was undertaken using Akaike Information Criterion (AIC), with a lower value signifying better predictive ability.

The data were analysed using SPSS statistical software (Version 24.0; IBM Corp, Armonk, NY, USA). Statistical significance was considered as $p < 0.05$.

RESULTS

A total of 58 patients were recruited in the two studies. 112 parotid glands contoured at baseline and again at week 3 for 56 patients were available for analysis. Patient, tumour and treatment details are summarised in *Table 1.* No patients had moderate-severe xerostomia at baseline. Assessments of xerostomia at 6 months was available for all patients; 27 patients (48.2%) developed nil-mild (CTCAE grade <2) xerostomia and 29 patients (51.8%) developed moderate-severe (CTCAE grade ≥2) xerostomia.

Statistically significant differences in ipsilateral and contralateral CT parotid volumes were noted at week 3 ($p <0.001$), supplementary table 1. Average changes in parotid volume at week 3 in ipsilateral and contralateral parotid were -16.7% and -13.5% respectively. Compared to baseline, there was an increase in SUV_{median} at week 3 in ipsilateral (8.4%) and contralateral (5.5%) parotid which did not reach statistical significance, supplementary table 1. However, when stratified by patients who developed xerostomia (CTCAE grade ≥2), a borderline significant difference in ipsilateral week 0 SUV_{median} ($p= 0.06$) and significant difference in ipsilateral ΔSUV_{median} ($p= 0.04$) was noted, see Figure 2A-B. On average, patients with xerostomia (CTCAE grade ≥2) had lower ipsilateral parotid week 0 SUV_{median} (1.35 vs 1.53). On average, patients with xerostomia (CTCAE grade ≥2) had a greater increase in ipsilateral parotid ΔSUV_{median} (16.8% vs -1.0%).

An individual parotid gland analysis was undertaken using all parotid glands (ipsilateral and contralateral) to correlate mean parotid radiotherapy dose and imaging features. A Spearman Rho correlation for individual parotid level analysis did not show correlation between week 0 SUV_{median} or change (Δ) in SUV_{median} to the mean parotid radiotherapy dose, supplementary Figure 1A-B. There was a weak correlation between change (Δ) in CT parotid volume and mean radiotherapy dose received ($r_s = -0.246$, $p<0.001$), supplementary Figure 1C. We also did not find any significant correlation between change in PET uptake (ΔSUV_{median}) and anatomical volume (ΔCT volume) of the parotid ($r_s = 0.156$, $p=0.11$).

Comparison of clinical and dosimetric parameters stratified by patients with moderate-severe xerostomia (CTCAE grade ≥2) are shown in Supplementary table 2. Only contralateral parotid mean dose was correlated to xerostomia, ($p = 0.04$), see Figure 2C. There was a trend towards a statistical significance for correlation of utilisation of concurrent chemotherapy to xerostomia ($p=0.06$).

Week 0 or change in CT parotid volume were not associated with xerostomia (CTCAE grade ≥2), see Table 2. From baseline imaging, there was a trend towards a statistical significance for correlation of ipsilateral parotid week 0 SUV_{median} to xerostomia on univariate analysis (p=0.06), see Table 2. On mid-treatment analysis, ipsilateral parotid ΔSUV_{median} was correlated to xerostomia on univariate (p=0.04) and also on multivariate analysis (p=0.05), see Table 2.

The reference, 'Clinical model' containing the variables contralateral parotid dose and chemotherapy use was fitted to xerostomia (CTCAE grade ≥2) using multivariate logistic regression. The clinical model performance measures (AUC 0.667, accuracy 60.4%, AIC 70.9) are shown in Table 3. The 'Imaging model' containing the variables ipsilateral parotid week 0 SUV_{median} and ipsilateral ΔSUV_{median} showed nil improvement in model performance (AUC 0.666, accuracy 62.7%, AIC 69.5).

'Mixed baseline model' containing addition of ipsilateral parotid week 0 SUV_{median} to contralateral parotid dose and chemotherapy use improved model performance (AUC 0.755, accuracy 77.4%, AIC 70.3). The highest model performance was noted with 'Mixed mid-treatment model' containing addition of ipsilateral parotid ΔSUV_{median} to contralateral parotid dose and chemotherapy (AUC 0.777, accuracy 78.5%, AIC 65.4). A visual representation of probability of developing xerostomia based on change in ipsilateral parotid SUV_{median} is shown in Supplementary figure 2.

Visual representation of the ROC analysis of the different models for prediction of xerostomia (CTCAE grade ≥2) are shown in Figure 3.

As an example, based on our results a patient receiving contralateral mean parotid dose of 26Gy and concurrent chemotherapy had a 52% predicted risk of xerostomia (CTCAE grade ≥2). If the same patient was found to have a 36% change in SUV_{median} in the ipsilateral parotid gland they would have a revised 79% predicted risk of xerostomia based on unfavourable mid-treatment PET changes.

DISCUSSION

This study is the first to identify mid-treatment FDG-PET metabolic changes in the parotid gland that could be utilised to predict xerostomia. It showed that low metabolic activity at baseline (week 0) and greater rise in activity in the ipsilateral parotid gland during radiotherapy (week 3) correlated to xerostomia. We also demonstrated that addition of FDG-PET features to clinical features further improved xerostomia correlation. Based on our novel results, FDG-PET/CT has the potential for patient-specific personalisation of radiotherapy in the future.

Our study confirms previous findings of shrinkage in parotid volume occurring during radiotherapy.(6, 30, 31) Ipsilateral parotid gland had a greater decrease (-17%) in volume compared to contralateral parotid gland (-14%) at week 3. A study by Marzi *et al*., found a similar decrease in parotid volume (-18%) based on T2-weighted MRI at end of week 2 of radiotherapy.(6) Similar to other studies, we also did not find anatomic changes in parotid volume provided additional utility for xerostomia prediction.(16, 30)

We did not find a correlation between FDG-PET parotid SUV_{median} to radiotherapy dose or anatomical volume. This suggests that baseline and mid-treatment FDG-PET imaging are potentially measuring independent processes that could be used for xerostomia prediction. We found that patients with xerostomia (CTCAE grade ≥2) had a lower ipsilateral week 0 SUV_{median} (1.35 vs 1.53) which is consistent with previous findings by Van Dijk *et al*.(24) Parotid glands are made up of many functional subunits and their combined metabolic activity based on FDG-PET glucose metabolism can be used to describe salivary gland function. Low baseline metabolic activity may be a measure of the reduced number of active acinar cells and hence lower functional reserve capacity of the parotid increasing the risk of xerostomia following radiotherapy. However, the influence of baseline parotid SUV_{median} on xerostomia prediction did not reach statistical significance based on multivariate analysis. Hence there is a need for additional measures to improve potential predictive ability.

Relative metabolic activity increased at week 3 in parotid glands compared to baseline. We found that patients with xerostomia had a greater increase in ΔSUV_{median} in ipsilateral parotid glands (16.8% vs -1.0%). There are currently no studies utilising mid-treatment FDG-PET for parotid gland assessment to allow comparison with our results. Studies by Elhalawani *et al.*, Roach *et al*., and Cannon *et al*., measured metabolic changes in parotid utilising the post completion of radiotherapy FDG-PET imaging.(8, 9, 17) Their results in summary suggest that metabolic activity of the parotid gland decreases following completion of radiotherapy. The differing result in our study is likely due to the critical importance of timing of FDG-PET assessment relative to radiotherapy. Studies by Feng *et al.* and Zhang *et al*., measured change in parotid gland from mid-treatment diffusion weighted MRI and revealed that mean ADC value (ADC_{mean}) increases at week 2-3 during radiotherapy.(16, 31) Restricted diffusion resulting in increased ADC_{mean} in the parotid during radiotherapy has been postulated to be due to inflammation leading to oedema or acinar cell lysis.(32) Along with our finding of relative increase in SUV_{median} in the parotid gland, this suggests that inflammation might be a significant process occurring early during radiotherapy.

Multiple cellular mechanisms are involved in radiation-induced salivary gland dysfunction, however, the exact mechanisms occurring shortly following radiation remains uncertain.(3, 33, 34) Contemporary research has identified the importance of progenitor stem cells that reside along the parotid ductal complex in the pathogenesis of radiation induced xerostomia.(35) Radiation is known to induce inflammation in the parotid gland which can lead to senescence and apoptosis of progenitor stem cells, microvascular injury and parasympathetic neuronal changes; known processes implicated in xerostomia in pre-clinical and animal studies.(3, 33, 36, 37) The variation in the inflammatory state within the parotid gland during radiotherapy might account for some of the individual patient's risk of xerostomia. Mid-treatment FDG-PET performed during radiotherapy could be utilised to measure this variation.

We utilised comparative predictive models to show the potential utility of imaging parameters. As expected we found the commonly utilised clinical features such as contralateral parotid gland could describe the risk of xerostomia (AUC 0.67). In our study, we demonstrated that addition of ipsilateral parotid FDG-PET parameters improved correlation to xerostomia at 6 months compared to clinical model alone. Addition of week 0 ipsilateral parotid SUV_{median} to contralateral parotid mean radiotherapy dose and concurrent chemotherapy use could correlate to xerostomia at 6 months with demonstrable accuracy (AUC 0.75). Use of mid-treatment FDG-PET based ipsilateral parotid ΔSUV_{median} to clinical factors resulted in the highest model performance as demonstrated by greater than 5 point decrease in Akaike Information Criterion and improvement in Area under the receiver operating characteristic curve value (AUC 0.78). A study by Elhalawani *et al*., utilised post-treatment FDG-PET performed at non-standardised time-points to build a xerostomia prediction model.(9) They found a model using contralateral parotid mean radiotherapy dose, patient age and contralateral parotid SUV_{median} measured at 3-6 month post completion of radiotherapy correlated to severe xerostomia at 3-6 months. However, they did not report the predictive performance of a model based on clinical factors alone in their cohort for a comparison.

Currently the management of xerostomia is based on symptomatic alleviation using adjuncts such as artificial saliva.(3) There are no proven treatments for reversal of xerostomia.(1) Hence, the primary goal of xerostomia management is prevention during radiotherapy planning and design.(1) The main advantage and novelty of our study findings is the use of mid-treatment imaging to describe risk of subsequent xerostomia allowing for early and actionable biomarker identification. A predictive xerostomia biomarker could potentially be utilised in a variety of ways. Studies show that significant changes in parotid gland occur during course of radiotherapy, which result in increased parotid gland mean dose that is cumulatively delivered compared to planned parotid dose at baseline.(38) Adaptive radiotherapy where treatment is modified mid-treatment based on changes during treatment can reduce the mean parotid gland dose delivered and is a promising avenue for normal tissue toxicity minimisation.(38) A predictive biomarker for xerostomia could allow personalised tailoring of adaptive radiotherapy, with replan and re-optimising dose to the parotid gland in patients at greatest risk of xerostomia, while limiting the resource implications for the remainder of the patients. Previous studies have also utilised mid-treatment FDG-PET/CT to predict tumour outcomes in head and neck cancer.(11-14) Along with results of our study, a biologically adaptive radiotherapy approach utilising mid-treatment FDG-PET/CT for combination of risk adapted toxicity minimisation and treatment de-intensification could be possible in patients at low risk of recurrence. There is also recent interest in designing radiotherapy based on parotid stem cell region avoidance.(39) A mid-treatment xerostomia predictive marker could identify patients who are likely to derive the greatest benefit from these additional resource intensive approaches.

Strengths of our study include prospective recruitment of patients, standardised imaging protocol and prospectively collected physician-reported toxicity assessment using a standardised tool (CTCAE). We also chose a global measure of parotid activity (SUV_{median}) due to its reproducibility and ease of clinical utility in future studies. There is potential that use of additional advanced radiomic features from FDG-PET imaging of the parotid gland may further improve on the results of our study. There are a few limitations of our study. Ours was a single institutional study with number of patients limited due to the novelty of mid-treatment imaging requirement. Our results are hypothesis generating and require validation in a larger cohort prior to clinical implementation. Given the limited number of outcome events, we were unable to test the impact of additional clinical factors on predictive performance of our models. The study could be strengthened by addition of objective measures such as salivary flow. Patient reported xerostomia is a complex and multifactorial process dependent not only on salivary flow, but also on saliva composition, oral mucosa atrophy and subjective patient response.(3) Several studies show parotid flow to have low reproducibility with limited correlation to patient reported xerostomia.(22, 40) Hence, patient reported xerostomia remains an important endpoint given its clinical importance and relationship to quality of life.(2, 22)

CONCLUSION

The results of our study show that anatomical and functional changes occur in the parotid gland early during radiotherapy. We demonstrate that integration of baseline and mid-treatment FDG-PET changes in the parotid gland with clinical factors has the potential to improve xerostomia risk prediction which could be utilised for personalised head and neck radiotherapy.

CAPTIONS

Table 1: Patient demographics

Table 2: Univariate and multivariate logistic regression correlating week 0 and mid-treatment change in CT volume and SUVmedian to moderate-severe (CTCAE grade ≥2) xerostomia at 6 months

Table 3: Comparison of imaging, clinical and mixed models in predicting moderate-severe xerostomia (CTCAE grade ≥2) at 6 months.

Figure 1: Study flow diagram with an example of FDG-PET parotid changes and analysis undertaken

Figure 2: Boxplot showing patients who developed moderate-severe xerostomia (CTCAE grade ≥2) at 6 months had lower ipsilateral parotid SUV_{median} (A); higher change in ipsilateral parotid SUV_{median} at week 3 (B); and higher contralateral mean parotid dose (C) compared to patients with nil or mild xerostomia. Parameters compared to xerostomia using Mann-Whitney U test

Figure 3: Receiver Operator Characteristic curve (ROC) displaying the model performance of clinical, imaging, mixed baseline and mixed mid-treatment model represented by area under the curve (AUC)

Supplementary table 1: Summary statistics of SUV_{median} and CT parotid volume and their change during treatment

Supplementary table 2: Comparison of clinical and radiotherapy parameters between patients with mild (grade 0-1) and moderate-severe (grade 2-3) xerostomia at 6 months.

Supplementary figure 1: Scatterplot showing nil correlation between parotid week 0 SUV_{median} (A) and change in SUV_{median} (B) to mean parotid radiotherapy dose and weak correlation of change in CT parotid volume (C) to mean parotid radiotherapy dose for individual parotid glands analysis (n=110).

Supplementary figure 2: Predicted probability of developing high grade xerostomia (CTCAE grade ≥2) at 6 months based on change in ipsilateral parotid SUV_{median} estimated using multivariate logistic regression containing variables; chemotherapy (Y/N) and mean contralateral parotid dose

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Table 1: Patient demographics

		Count (%)	Mean, SD
Age at diagnosis (years)			62 (9.4)
Gender	Male	52 (90%)	
	Female	6 (10%)	
Smoker	No	15 (26%)	
	Yes	43 (74%)	
Pack / year smoking history			28.3 (24.6)
Primary tumour site	Tonsil	21 (36%)	
	Base of tongue	15 (25%)	
	Soft palate	2 (3%)	
	PPW	2 (3%)	
	Nasopharynx	4 (7%)	
	Larynx	8 (14%)	
	Hypopharynx	7 (12%)	
T stage (TNM 7th ed)	T1	4 (7%)	
	T2	23 (39%)	

	T3	25 (42%)	
	T4	7 (12%)	
N stage (TNM 7th Ed)	N0	11 (19%)	
	N1	10 (17%)	
	N2a	4 (7%)	
	N2b	19 (32%)	
	N2c	12 (20%)	
	N3	3 (5%)	
TNM Stage (7th Ed)	Stage 2	6 (10%)	
	Stage 3	14 (24%)	
	Stage 4	39 (66%)	
Chemotherapy	No	12 (20%)	
	Yes	47 (80%)	
Ipsilateral parotid mean dose (Gy)			41.0 (14.4)
Contralateral parotid mean dose (Gy)			26.0 (11.2)
Oral cavity mean dose (Gy)			40.5 (12.1)

Table 2: Univariate and multivariate logistic regression correlating week 0 and mid-treatment change in CT volume and SUVmedian to moderate-severe (CTCAE grade ≥2) xerostomia at 6 months

	Univariate analysis			**Multivariate analysis**		
IMAGING FEATURES	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Ipsilateral parotid						
week 0 CT volume	1.018	0.975 - 1.063	0.421	1.025	0.977 - 1.075	0.312
week 0 SUV_{median}	0.167	0.027 - 1.052	0.057	0.156	0.022 - 1.092	0.061
ΔCT volume	1.005	0.966 - 1.046	0.790	1.015	0.968 - 1.065	0.534
ΔSUV_{median}	1.037	1.002 - 1.072	0.037 †	1.041	1.001 - 1.083	0.046 †
Contralateral parotid						
week 0 CT volume	1.027	0.980 – 1.076	0.267	1.031	0.979 - 1.085	0.250
week 0 SUV_{median}	0.237	0.037 - 1.522	0.129	0.219	0.032 - 1.510	0.123
ΔCT volume	0.989	0.945 - 1.034	0.618	1.010	0.955 - 1.068	0.731
ΔSUV_{median}	1.023	0.992 - 1.054	0.145	1.023	0.991 - 1.056	0.164

CLINICAL FEATURES						
Ipsilateral parotid dose	1.033	0.992 - 1.076	0.115			
Contralateral parotid dose	1.063	1.004 - 1.125	0.035			
Oral cavity dose	1.023	0.976 - 1.071	0.348			

Relative change in value (Δ) = (Week 3 – baseline)/baseline *100%

Odds ratio (HR); 95% confidence interval (CI)

Multivariate analysis: ipsilateral parotid dose, contralateral parotid dose, oral cavity dose

† Significant ($p<0.05$)

Table 3: Comparison of imaging, clinical and mixed models in predicting moderate to severe xerostomia (CTCAE grade ≥2) at 6 months.

MODEL	**FEATURES**	**p value**	**Accuracy**	**Nagelkerke**	**AUC**	**AIC**
CLINICAL	Contralateral parotid dose Chemotherapy Y/N	0.041†	60.4%	0.151	0.667 (0.037)	70.877 (0.041)
IMAGING	Ipsilateral Week 0 SUV_{median} Ipsilateral ΔSUV_{median}	0.027†	62.7%	0.176	0.666 (0.042)	69.461 (0.027)

MIXED BASELINE	Contralateral parotid dose Chemotherapy Y/N Ipsilateral Week 0 SUV_{median}	0.011†	77.4%	0.253	0.755 (0.001)	70.297 (0.011)
MIXED **MID-TREATMENT**	Contralateral parotid dose Chemotherapy Y/N Ipsilateral ΔSUV_{median}	0.004†	78.5%	0.306	0.777 (0.001)	65.371 (0.004)

Relative change in value (Δ) = (Week 3 – baseline)/baseline *100%

† Significant ($p<0.05$)

AUC: Area under the Receiver Operating Characteristic curve

AIC: Akaike information criterion

Figure 1

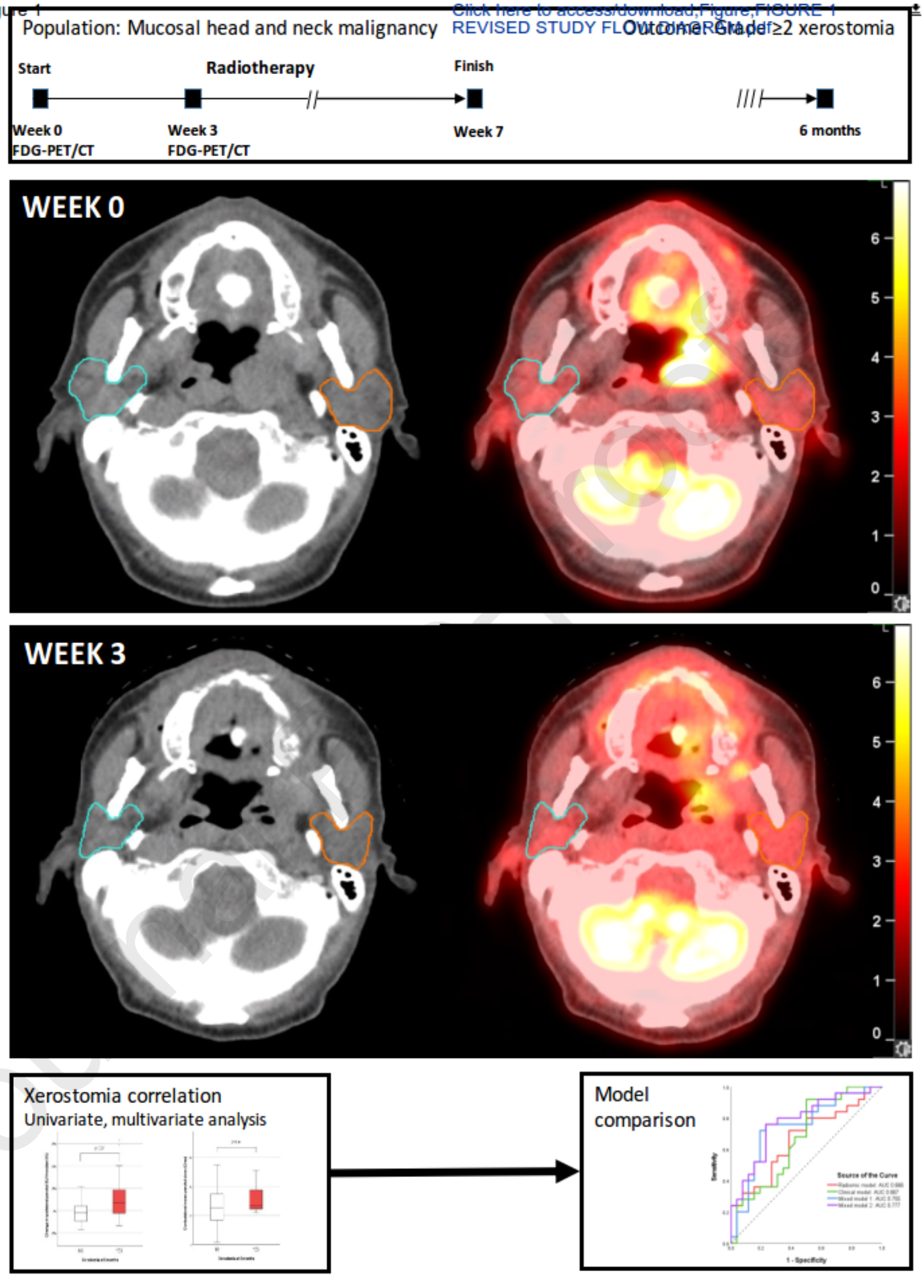

Figure 2A

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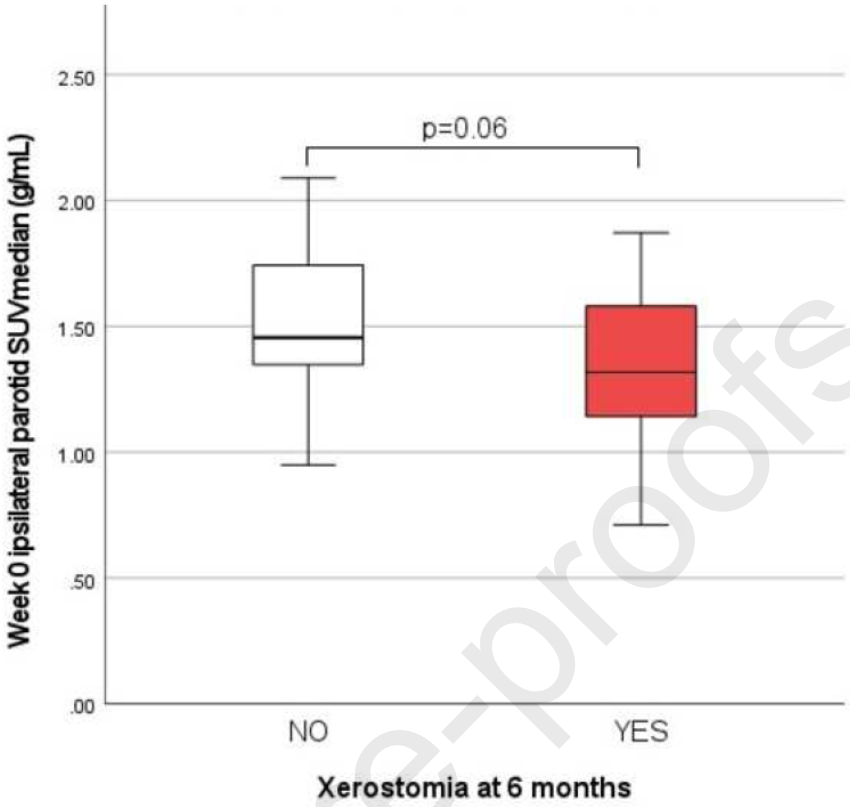

Figure 2B

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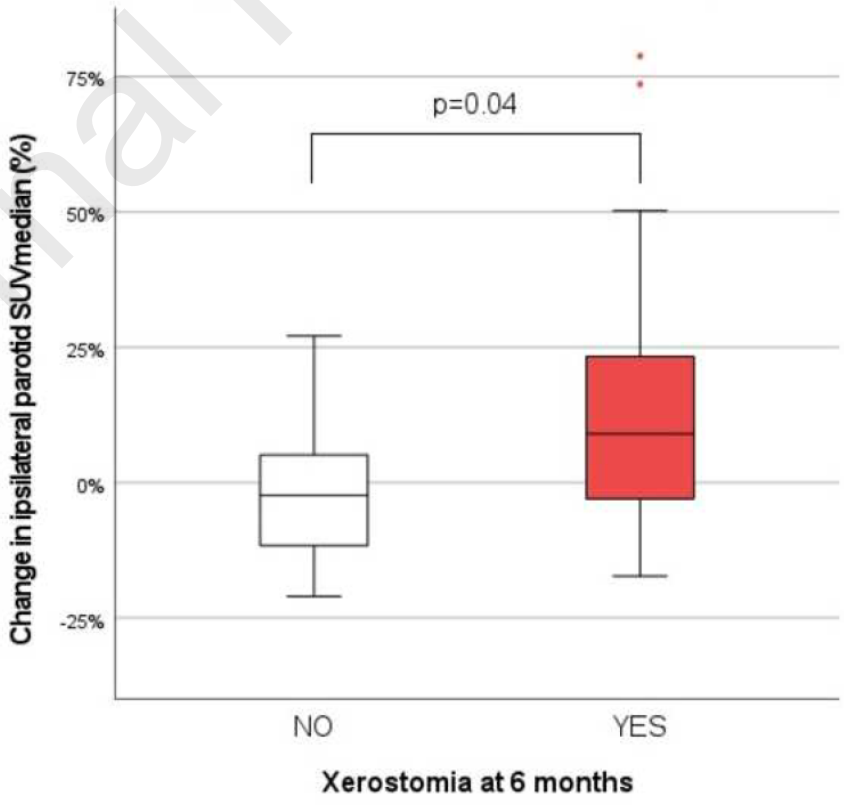

Figure 2C

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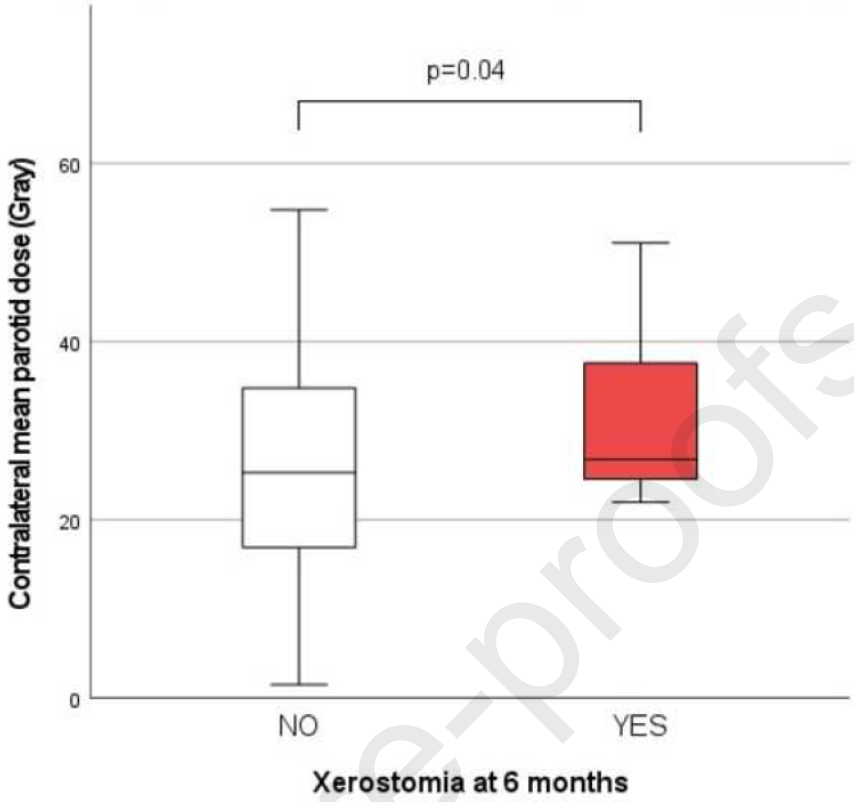

Figure 3

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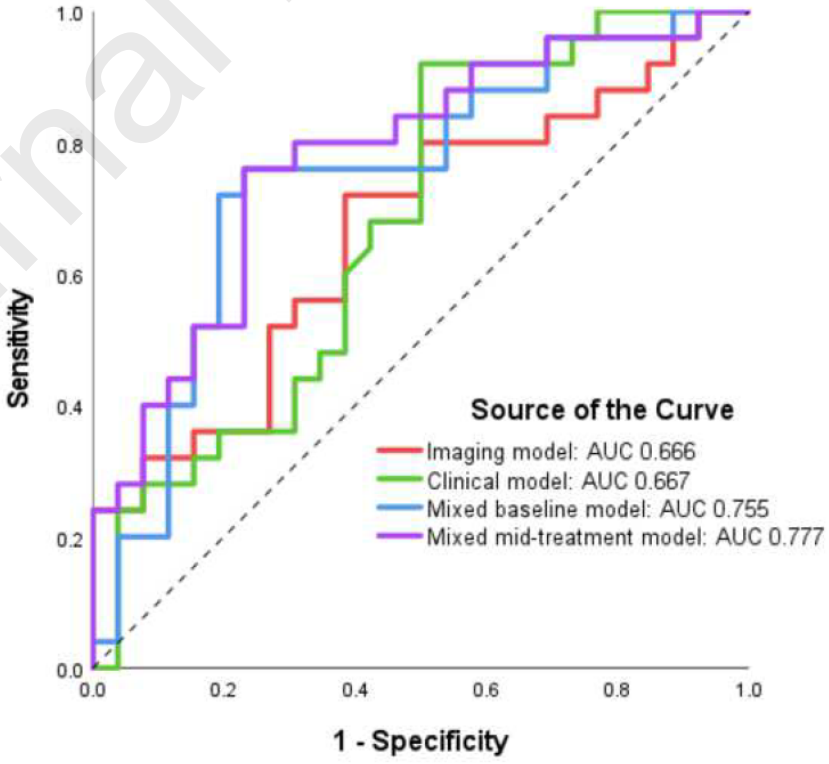

HIGHLIGHTS:

- We present results of prospective mid-treatment FDG-PET imaging biomarker study for xerostomia prediction
- 56 mucosal head and neck patients treated with definitive radiotherapy were evaluated with baseline and week 3 mid-radiotherapy
- We found early metabolic changes in the parotid gland improved prediction of subsequent risk of xerostomia
- There is a potential for FDG-PET changes in parotid gland to be utilised in future adaptive radiotherapy trials for toxicity minimisation