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Original article

# $^{18}$F-FDG PET image biomarkers improve prediction of late radiation-induced xerostomia

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ABSTRACT

*Background and purpose:* Current prediction of radiation-induced xerostomia 12 months after radiotherapy ($Xer_{12m}$) is based on mean parotid gland dose and baseline xerostomia ($Xer_{baseline}$) scores. The hypothesis of this study was that prediction of $Xer_{12m}$ is improved with patient-specific characteristics extracted from $^{18}$F-FDG PET images, quantified in PET image biomarkers (PET-IBMs).

*Patients and methods:* Intensity and textural PET-IBMs of the parotid gland were collected from pre-treatment $^{18}$F-FDG PET images of 161 head and neck cancer patients. Patient-rated toxicity was prospectively collected. Multivariable logistic regression models resulting from step-wise forward selection and Lasso regularisation were internally validated by bootstrapping. The reference model with parotid gland dose and $Xer_{baseline}$ was compared with the resulting PET-IBM models.

*Results:* High values of the intensity PET-IBM (90th percentile (P90)) and textural PET-IBM (Long Run High Grey-level Emphasis 3 (LRHG3E)) were significantly associated with lower risk of $Xer_{12m}$. Both PET-IBMs significantly added in the prediction of $Xer_{12m}$ to the reference model. The AUC increased from 0.73 (0.65–0.81) (reference model) to 0.77 (0.70–0.84) (P90) and 0.77 (0.69–0.84) (LRHG3E).

*Conclusion:* Prediction of $Xer_{12m}$ was significantly improved with pre-treatment PET-IBMs, indicating that high metabolic parotid gland activity is associated with lower risk of developing late xerostomia. This study highlights the potential of incorporating patient-specific PET-derived functional characteristics into NTCP model development.



$^{18}$F-FDG PET imaging provides functional information about the metabolic activity of tissue. This makes $^{18}$F-FDG PET a powerful and widely used diagnostic modality in oncology. In head and neck oncology, $^{18}$F-FDG PET can complement other image modalities in tumour staging and delineation for radiotherapy [1,2]. The common clinical use of $^{18}$F-FDG PET allows for the possibility to extract large amounts of patient-specific functional information that could contribute to prognosis for head and neck cancer (HNC) patients. Several studies have shown that PET image characteristics of the tumour can contribute to predicting overall, disease-free or event-free survival [3–6]. However, patient-specific image characteristics for predicting normal tissue radiation toxicities are less explored, while these are also crucial in supporting treatment decisions. Additionally, new radiation techniques (e.g. proton therapy [7] and magnetic resonance imaging (MRI) guided radiation [8]) may allow for better sparing of normal tissue. These new techniques demand improved prediction models, to select patients most at risk of developing toxicities [9].

Radiation-induced xerostomia is a major and frequent side effect for HNC patients, and has a considerable impact on these patients' quality of life [10]. Conventional Normal Tissue Complication Probability (NTCP) models that predict patient-rated xerostomia are based on dose–volume parameters and baseline complaints [11,12]. However, there is still a significant, unexplained variance in predicting xerostomia with these models. Therefore, the demand persists to improve the identification of patients at risk. Previous work showed that patient-specific CT characteristics of the parotid glands could significantly improve the prediction of patient-rated xerostomia, however, model performance improvement was marginal [13]. The hypothesis was that the predictive CT characteristic is related to the ratio of non-function to functional parotid tissue. It can be expected that this ratio would be better represented by image characteristics from functional imaging (i.e. PET or MR images).

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In this study, the relationship was tested between metabolic activity of the parotid gland and late xerostomia. Consequently, the patient-specific response to radiation in developing this toxicity was investigated. The purpose was to determine whether functional information from $^{18}$F-FDG PET images, which is quantified in PET-image biomarkers (PET-IBMs), was associated with patient-rated moderate-to-severe xerostomia 12 months after radiotherapy ($Xer_{12m}$). Since current NTCP prediction models are based on parotid gland dose and baseline complaints, the study subsequently addressed whether PET-IBMs could improve on the current prediction of $Xer_{12m}$

## Materials and methods

### *Patient demographics and treatment*

$^{18}$F-FDG PET/CT scans were acquired of 161 HNC patients in treatment position before the start of radiotherapy. The patients were treated with definitive radiotherapy either with or without concurrent chemotherapy or cetuximab, between November 2010 and August 2015. Patients without follow-up data 12 months after radiotherapy were excluded from this study. Patients were also excluded if they underwent surgery in the head and neck area before or within one year after treatment.

A detailed description of the radiotherapy protocols is given in previous studies [13,14]. In summary, all patients were treated with IMRT or VMAT using a simultaneous integrated boost (SIB) technique. The parotid glands and the swallowing structures were spared as much as possible without compromising the dose to the target volumes [14,15]. Patients received a total dose of 70 Gy (2 Gy per fraction, 5 or 6 times a week) to the primary tumour and, if present, pathological lymph nodes. A radiation dose of 54.25 Gy (1.55 Gy per fraction, 5 or 6 times a week) was delivered to the elective lymph node levels.

### *Endpoints*

The primary endpoint was patient-rated moderate-to-severe xerostomia 12 months after radiotherapy ($Xer_{12m}$), which corresponds to the 2 highest scores of the 4-point Likert scale of the EORTC QLQ-H&N35 questionnaire. This endpoint was prospectively assessed as part of a Standard Follow-up Program (SFP) for Head and Neck Cancer Patients (NCT02435576), as described in previous studies [11,12,16].

### *Dose and clinical parameters*

For treatment planning, parotid glands were delineated on the planning (PET/)CT scans. The mean dose to both the contra- and ipsilateral parotid and submandibular glands were extracted from the dose–volume information [11,17]. In addition, baseline patient-rated xerostomia ($Xer_{baseline}$) was also considered (none vs. any).

Patient characteristics such as age, sex, WHO-performance, tumour stage and body mass index did not significantly add to the parotid gland dose and $Xer_{baseline}$ in predicting $Xer_{12m}$ in previous studies [11,13,18]. This was again observed in the current cohort, therefore these variables were not further reported in this study.

### *$^{18}$F-FDG PET acquisition*

Approximately 2 weeks before the start of radiotherapy, $^{18}$F-FDG PET/CT images (Siemens Biograph 64-slice PET/CT scanner, Siemens Medical Systems, Knoxville, TN, USA) were acquired in with the patient positioned for radiotherapy. PET/CT system performance were initially harmonised conform the Netherlands protocol for FDG PET imaging [19] and later by EARL accreditation [20].

Patients were instructed not to eat or drink 6 h before scanning, but were encouraged to drink water to ensure adequate hydration. A body weight-based intravenous injection dose of 3 MBq/kg was administered 60 min prior to the $^{18}$F-FDG PET acquisition. $^{18}$F-FDG PET images were acquired in the caudal–cranial direction with an acquisition time of ~3 min per bed position.

### *Candidate PET-image biomarkers*

Intensity PET-IBMs were extracted, representing first order standardised uptake value (SUV) characteristics of the delineated contra-lateral parotid glands. Examples are mean, minimum, maximum, standard deviation and root mean square of the SUVs. For the complete list of the 24 intensity PET-IBMs, see Supplementary data 1. Fig. 1 shows a schematic representation of PET-IBMs' extraction process.

Furthermore, more complex, textural features were extracted describing the intensity heterogeneity. These textural PET-IBMs were extracted from the grey level co-occurrence matrix (GLCM) [21], grey level run-length matrix (GLRLM) [22,23], grey level size-zone matrix (GLSZM) [24] and neighbourhood grey tone difference matrix (NGTDM) [25]. GLCM describes the grey level transitions. GLRLM and GLSZM describe the directional and volumetric grey level repetitions, respectively. NGTDM describes the relationship of sum and averages of grey level differences of direct adjacent voxels.

For this study, the average of PET-IBMs from GLCM and GLRLM in 13 independent directions was used. The range of SUVs was binned with a fixed bin size of 0.25. Discretisation of SUV is necessary to reduce the number of possible intensity values, and so reduce noise when calculating textural features [26]. All 66 textural PET-IBMs (25 GLCM, 18 GLRLM, 18 GLSZM and 5 NGTDM) were normalised by subtracting the average from the PET-IBMs' values and then dividing by the standard deviation. For the complete list refer to Supplementary data 2. All PET-IBMs were extracted in MATLAB (version R2014a).

### *Univariable analysis*

Univariable logistic regression analysis was performed to evaluate the basic associations of PET-IBMs with late xerostomia. $p$-Values <0.05 were considered statistically significant. Coefficients ($\beta$) were evaluated to understand the effect that is described by the PET-IBMs in relation to $Xer_{12m}$. The univariable analysis was not used for the variable selection.

### *Multivariable analysis*

#### *Reference model*

A reference prediction model was evaluated for the current patient cohort. This model was based on the mean dose to the contralateral parotid gland and $Xer_{baseline}$. These were the predictors that were identified by Beetz et al. [11].

#### *Intensity and textural PET-IBMs*

First, a basic PET-IBM model was created by adding the 'mean SUV' of the parotid gland as an extra variable to the reference model. Since this variable is the simplest of PET-IBMs, it is the easiest to interpret.

Both step-wise forward selection and Lasso regularisation were performed for multivariable logistic analysis of the PET-IBMs, together with parotid dose and $Xer_{baseline}$. Step-wise forward selection was based on the largest significant log-likelihood differences

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