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Head and neck radiotherapy

# Selection of head and neck cancer patients for adaptive radiotherapy to decrease xerostomia

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## ABSTRACT

*Background and purpose:* The aim of this study was to develop and validate a method to select head and neck cancer patients for adaptive radiotherapy (ART) pre-treatment. Potential pre-treatment selection criteria presented in recent literature were included in the analysis.
*Materials and methods:* Deviations from the planned parotid gland mean dose (PG ΔDmean) were estimated for 113 head and neck cancer patients by re-calculating plans on repeat CT scans. Uni- and multivariable linear regression analyses were performed to select pre-treatment parameters, and ROC curve analysis was used to determine cut off values, for selecting patients with a PG dose deviation larger than 3 Gy. The patient selection method was validated in a second patient cohort of 43 patients.
*Results:* After multivariable analysis, the planned PG Dmean remained the only significant parameter for PG ΔDmean. A sensitivity of 91% and 80% could be obtained using a threshold of PG Dmean of 22.2 Gy, for the development and validation cohorts, respectively. This would spare 38% (development cohort) and 24% (validation cohort) of patients from the labour-intensive ART procedure.
*Conclusions:* The presented method to select patients for ART pre-treatment reduces the labour of ART, contributing to a more effective allocation of the department resources.
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During the course of head and neck radiotherapy, anatomical changes such as body weight and/or tumour volume may result in underdosage or dose inhomogeneity in targets, and overdosage in organs at risk (OARs) [1–4]. The largest dose differences between (estimated) delivered and planned OAR dose that have been reported are for the parotid glands (PGs). However there is a substantial difference in findings between studies, the median of the mean dose difference over 25 studies is 1.7 [interquartile range -1.9;10.4] Gy [5]. A larger PG dose than planned will increase the risk of xerostomia with subsequent deterioration of quality of life [6]. Adaptive radiotherapy (ART) is a strategy used to limit or even decrease the dose to the PGs. ART, however, comprises a labour intensive procedure, requires additional imaging and does not lead to a clinically relevant benefit for all patients [7]. It would therefore be helpful if the patients with expected clinically relevant PG dose deviations could be selected prior to radiotherapy. With such a

method in place, the selected patients would receive an ART procedure to monitor and/or minimize the delivered PG dose. The non-selected patients would be spared from this extensive procedure. Many attempts have been made to find parameters associated with anatomical and dosimetric changes of PGs [5], but there is no general consensus yet on how to select patients for ART to decrease xerostomia.

The aim of this study is therefore to develop a method using pre-treatment parameters to predict dose deviations from the planned PG mean dose, which can be used to select patients for ART pre-treatment. Two different patient cohorts were used to develop and validate the method, respectively.

## Materials and methods

### Patient cohort A

One-hundred and thirteen head and neck cancer patients were enrolled in a previous prospective cohort study [8–11]. All patients were treated between 2008 and 2012 with curative intent. They

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received primary conventional three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) up to a dose of 70 Gy in fractions of 2 Gy delivered over 6–7 weeks (5 or 6 fractions per week), following ICRU recommendations, either alone or in combination with concomitant chemotherapy (chemoradiation) or cetuximab (bio-radiation). All patients received a planning computed tomography scan (plan-CT) as well as a post-radiotherapy response CT scan (post-CT) in the treatment position, acquired 6 weeks after RT with a slice thickness of 2 mm. This cohort was used to develop the patient selection method.

### Patient cohort B

Data from 43 patient plans were used to validate the patient selection method. This patient group was treated in our department in 2014–2015 with definitive radiotherapy or concurrent chemoradiation or bio-radiation using IMRT or Volumetric Modulated Arc Therapy (VMAT). The dose prescription was up to 70 Gy in fractions of 2 Gy delivered over 6–7 weeks (5 or 6 fractions per week) according to ICRU recommendations. For each patient, the plan quality was monitored during treatment by recalculation on weekly repeated CT scans. In cases of relevant dose deviation (repeat-CT with respect to the plan-CT, as judged by the treating physician), the treatment plan was adapted. All CT scans were acquired in the treatment position, with a slice thickness of 2 mm.

### Parotid gland dose deviations

For both cohort A and B, the PGs were delineated on the plan-CT by a dedicated radiation therapist, and were warped to the post- and repeat-CTs respectively by deformable image registration using Mirada RTx (Mirada Medical Ltd., Oxford, UK). The warped PG contours were manually corrected if necessary. For cohort B, 2 ipsilateral PGs were excluded because of tumour invasion.

For cohort A, the clinical treatment plan was re-calculated on the post-CT. Subsequently, $\Delta$Dmean[A] of the PG for each patient was the mean dose of the PG on the post-CT minus that of the planned mean dose: $\Delta$Dmean[A] = Dmean_post[A] − Dmean_plan [A]. Since previous studies showed that the volume of the parotid gland does not significantly change after the last fraction of RT [12,13], we assume that $\Delta$Dmean[A] is an accurate estimate of the dose deviation between end and start of treatment.

For cohort B, the delivered dose was estimated by dose accumulation of the re-calculated dose distribution on weekly repeat-CT scans using deformable image registration (Raystation, Raysearch Laboratories AB, Stockholm, Sweden). Next, $\Delta$Dmean[B] for the PG per patient was calculated by subtracting the planned mean dose from the accumulated mean dose: $\Delta$Dmean[B] = Dmean_accumulated[B] − Dmean_plan[B].

### Candidate pre-treatment factors

Previously identified candidate pre-treatment factors [4,14] that were considered in the analysis were: initial weight, BMI, age, chemotherapy (yes/no), surgery (yes/no), T-stage (T3+ vs. T3−), N-stage (N2+ vs. N2−), planned dose to the PG (mean dose and V20, V30 and V40), initial PG volume, initial gross tumour volume (GTV), tumour location (pharynx vs. other) as well as overlap volume (OV) of the PG with the target (high dose) and elective (low dose) planning target volume (PTV); OVPG-PTV$_{high}$ and OVPG-PTV$_{low}$.

### Statistical analysis

The endpoint for the linear regression analysis was defined as the absolute value of $\Delta$Dmean, since anatomic changes can result

in positive as well as negative dose deviations (see Fig. S1), which are both of importance for a correct prediction of xerostomia.

To test whether pre-treatment parameters and endpoints significantly differed between cohort A and B, independent samples $t$-tests, Mann–Whitney $U$ tests and Fisher's exact tests were performed for normally distributed continuous variables, for continuous variables with skew distribution and for categorical variables, respectively. A $p$-value of $\leqslant 0.05$ was considered statistically significant.

Univariable and multivariable linear regression analyses were applied to the endpoint |$\Delta$Dmean[A]| for the contralateral and the ipsilateral parotid gland. For the continuous explanatory variables we checked for linear relationship with the endpoint using scatter plots of the variables vs. the endpoint, for the final model, we checked normality and constant variance of the residuals. Pre-treatment factors with a $p$-value < 0.2 in the univariable analyses were included in the multivariable analysis using forward selection (Likelihood ratio test, threshold $p < 0.05$). If the pre-treatment factors had a Pearson mutual correlation ($R$) > 0.80, only the factor with the highest correlation to the endpoint was included in multivariable analysis. Model performance was scored with the coefficient of determination ($R^2$).

The pre-treatment factor(s) from the final multivariable linear regression model were applied to the data to select patients for ART, i.e. patients with a |PG $\Delta$Dmean| > 3 Gy (both ipsi- and contralateral PGs included), which was assumed to be the minimum level of clinical relevance. Three Gy would result in NTCP differences of 3–10% for xerostomia (depending on the applied model and the steepness of the curve for the particular dose value) which is assumed as a clinical relevant threshold to select patients for advanced treatments [15]. Cut off values were determined by means of receiver operating characteristic (ROC) curve analysis, for sensitivities of 70%, 80%, 90% and 100%. The cut off values found were applied to dataset B. The sensitivity, specificity, and positive and negative predictive value were calculated and used to assess the performance and efficiency of the method.

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS Inc., Chicago, IL, USA) and the Statistics Toolbox in Matlab R2014a (MathWorks, Natick, MA, USA).

## Results

Patient characteristics of cohort A and B were significantly different regarding gender, weight, BMI, T-classification, N-classification, tumour location, use of chemotherapy, Dmean of the contra- and ipsilateral PG, GTV volume, and |$\Delta$Dmean| of the contralateral PG (Table 1).

The endpoint |$\Delta$Dmean| and the pre-treatment factor GTV volume were transformed by the natural logarithm to improve linearity and normality. In the univariable analysis, all pre-treatment factors were significantly associated ($\alpha = 0.05$) with the endpoint ln|$\Delta$Dmean| of the parotid glands (Table 2), with the exception of the initial patient weight (for the ipsilateral PG), age, surgery and initial PG volume.

The parameters included in the multivariable linear regression for both the contra- and ipsilateral PG were BMI (weight excluded due to the mutual correlation), chemotherapy, T-stage, N-stage, PG Dmean (PG V20, V30, V40 excluded due to the mutual correlation), tumour location, ln (GTV volume) and overlap PG-PTV56 (overlap PG-PTV70 excluded due to mutual correlation). From the multivariable linear regression analysis, the planned mean dose to the PG was the only significant factor (Table 3 and Fig. S2). The coefficient of determination for the final model was $R^2 = 0.59$ (contralateral PG) and $R^2 = 0.39$ (ipsilateral PG).

For 20% of the parotids in cohort A, |$\Delta$Dmean| of the parotid gland was higher than 3 Gy (Fig. 1 and Table 4). The results of

**Table 1**

Patient characteristics of cohort A and B (percentages for categorical variables, means (sd) for normally distributed continuous variables and medians [inter quartile range] for continuous variables with skew distributions). PG = parotid gland, GTV = gross tumour volume, ipsi = ipsilateral, contra = contralateral. *P*-Values resulting from independent samples *t*-test ([1], normally distributed continuous variables), Mann–Whitney *U* test ([2], continuous variables with skew distributions) and Fisher's exact test ([3], categorical variables). Statistically significant values presented in bold.

|  | Cohort A | Cohort B | p-Value |
|---|---|---|---|
| Gender |  |  | **0.001(3)** |
| Male | 87% | 63% |  |
| Female | 13% | 37% |  |
| Age (y) | 61.0 (10.4) | 59.8 (9.8) | 0.489(1) |
| Initial weight (kg) | 85.7 (16.1) | 77.0 (21.1) | **0.010(1)** |
| BMI (kg/m$^2$) | 27.2 (4.6) | 24.5 (6.4) | **0.029(1)** |
| Tumour classification |  |  | **<0.001(3)** |
| T1–T2 | 69% | 29% |  |
| T3–T4 | 31% | 71% |  |
| Node classification |  |  | **0.001(3)** |
| N0–N1 | 67% | 36% |  |
| N2a–N3 | 33% | 64% |  |
| Tumour location/primary site |  |  | **<0.001(3)** |
| Pharynx | 35% | 70% |  |
| Other | 65% | 30% |  |
| Chemotherapy |  |  | **<0.001(3)** |
| Yes | 20% | 58% |  |
| No | 80% | 42% |  |
| PG$_{contra}$ D$_{mean}$ (Gy) | 19.9 (14.1) | 25.6 (11.0) | **0.008(1)** |
| PG$_{ipsi}$ D$_{mean}$ (Gy) | 28.9 (20.4) | 36.0 (13.2) | **0.012(1)** |
| Initial volume PG$_{contra}$ (cm$^3$) | 31.3 (9.2) | 30.0 (11.5) | 0.398(1) |
| Initial volume PG$_{ipsi}$ (cm$^3$) | 30.7 (10.1) | 30.5 (12.6) | 0.738(1) |
| Initial GTV volume (cm$^3$) | 8.8 (18.3) | 24.5 (33.9) | **0.002(2)** |
| PG$_{contra}$ Δvolume (%) | −17.4 (13.1) | −15.4 (12.5)* | 0.398(1) |
| PG$_{ipsi}$ Δvolume (%) | −18.0 (13.5) | −17.1 (13.2)* | 0.738(1) |
| \|PG$_{contra}$ ΔDmean\| | 0.8 (1.9) | 1.4 (2.1) | **0.008(2)** |
| \|PG$_{ipsi}$ ΔDmean\| | 1.3 (2.7) | 1.6 (1.0) | 0.633(2) |

* difference in volume between start and final week of radiotherapy.

the ROC curve analysis for sensitivities of 100, 90, 80 and 70% are shown in Table 4. The Supplemental Material provides full details on the ROC curve analysis. For a sensitivity of 91%, the specificity was 45%, and 62% of the parotids would be selected for the ART procedure. The positive predictive value was 29%, meaning that 29% of the parotids that were selected for ART with our method were correctly classified. The negative predictive value was 95%.

The cut off values of PG Dmean (Gy) found for cohort A were applied to cohort B to validate the selection method, resulting in the performance measures for cohort B (Fig. 1 and Table 4).

**Table 2**

Univariable linear regression for the endpoint ln\|ΔDmean\| of the contralateral (contra) and ipsilateral (ipsi) parotid glands. Statistically significant values ($\alpha$ = 0.05) presented in bold.

| Pre-treatment factor | Regression coefficient | | Standard error | | p-Value | | Pearson R | |
|---|---|---|---|---|---|---|---|---|
|  | Contra | Ipsi | Contra | Ipsi | Contra | Ipsi | Contra | Ipsi |
| BMI | −0.136 | −0.172 | 0.041 | 0.043 | **0.0015** | **0.0001** | −0.317 | −0.380 |
| Weight | −0.030 | 0.558 | 0.011 | 0.465 | **0.0136** | 0.2336 | −0.240 | 0.121 |
| Age | −0.018 | −0.031 | 0.017 | 0.018 | 0.3053 | 0.0959 | −0.096 | −0.157 |
| Chemotherapy | 1.604 | 1.397 | 0.441 | 0.463 | **0.0004** | **0.0030** | 0.323 | 0.275 |
| Surgery | −0.234 | 0.670 | 0.615 | 0.679 | 0.7044 | 0.3257 | −0.036 | 0.094 |
| T-stage | 1.426 | 1.200 | 0.371 | 0.392 | **0.0002** | **0.0027** | 0.340 | 0.279 |
| N-stage | 1.685 | 1.678 | 0.356 | 0.371 | **<0.0001** | **<0.0001** | 0.407 | 0.395 |
| PG D$_{mean}$ | 0.107 | 0.063 | 0.009 | 0.007 | **<0.0001** | **<0.0001** | 0.759 | 0.621 |
| PG V$_{20}$ | 0.029 | 0.038 | 0.004 | 0.004 | **<0.0001** | **<0.0001** | 0.531 | 0.691 |
| PG V$_{30}$ | 0.037 | 0.039 | 0.004 | 0.004 | **<0.0001** | **<0.0001** | 0.638 | 0.644 |
| PG V$_{40}$ | 0.041 | 0.037 | 0.007 | 0.005 | **<0.0001** | **<0.0001** | 0.483 | 0.569 |
| PG volume | −0.017 | −0.002 | 0.020 | 0.019 | 0.3899 | 0.9331 | −0.080 | −0.008 |
| Ln(GTV volume) | 0.781 | 0.698 | 0.121 | 0.134 | **<0.0001** | **<0.0001** | 0.529 | 0.453 |
| Tumour location | 1.720 | 1.325 | 0.362 | 0.391 | **<0.0001** | **0.0010** | 0.408 | 0.306 |
| Overlap PG-PTV$_{70}$ | 0.502 | 0.120 | 0.205 | 2.154 | **0.0159** | **0.0335** | 0.226 | 0.203 |
| Overlap PG-PTV$_{56}$ | 0.270 | 0.160 | 0.062 | 0.033 | **<0.0001** | **<0.0001** | 0.384 | 0.419 |

**Table 3**

Results of the multivariable linear regression analysis for the endpoint ln\|ΔDmean\| of the contralateral (contra) and ipsilateral (ipsi) parotid gland.

|  | Regression coefficient | | Standard error | | p-Value | |
|---|---|---|---|---|---|---|
|  | Contra | Ipsi | Contra | Ipsi | Contra | Ipsi |
| Intercept | −2.78 | −2.22 | 0.231 | 0.264 | <0.001 | <0.001 |
| PG D$_{mean}$ | 0.107 | 0.063 | 0.009 | 0.007 | <0.001 | <0.001 |

For 18% of the parotids in cohort B, \|ΔDmean\| of the parotid gland was higher than 3 Gy (Fig. 1 and Table 4). Applying the cut off value for PG Dmean of 22.2 Gy, the sensitivity was 80% and 76% of the parotids would be selected for the ART procedure (Table 4). The positive predictive value was 19% and the negative predicted value 81%.

## Discussion

In univariable analysis, many of the pre-treatment parameters were significantly associated with the change in mean dose to the parotid gland (Table 2). Still, Pearson correlation with the endpoint was low for most of the parameters. Also, many parameters were tested with an alpha level of 0.05, which increased the overall alpha, requiring validation of these results in another, large, cohort. The only parameter that remained significant in a multivariable analysis was the planned mean dose to the parotid gland. By selecting only patients with a planned PG mean dose ⩾ 22.2 Gy for an ART procedure, 80% of patients in the validation cohort who needed replanning (i.e. having PG \|ΔDmean\| > 3 Gy) were selected (Table 4). This would spare 24% of patients in the validation cohort from the ART procedure, which would contribute to a more effective allocation of the department resources.

In our previous review study [14] we found a number of candidate pre-treatment parameters to identify patients that might benefit from ART. In seven studies, the PG mean dose was significantly associated with PG volume loss [12,16–21], suggesting its potential as a predictor for dose changes. In the multivariable analysis of the current study, the direct relationship between the planned PG mean dose and deviations from the planned PG mean dose was confirmed ($R^2$ = 0.59 and 0.39 for contra- and ipsilateral PG, respectively). The BMI [19] and initial parotid volume [16] were previously significantly associated with PG volume loss in multivariable analysis. In the current study these factors were only significantly correlated to PG volume loss in univariable analysis (Table 2), but not in multivariable analysis.
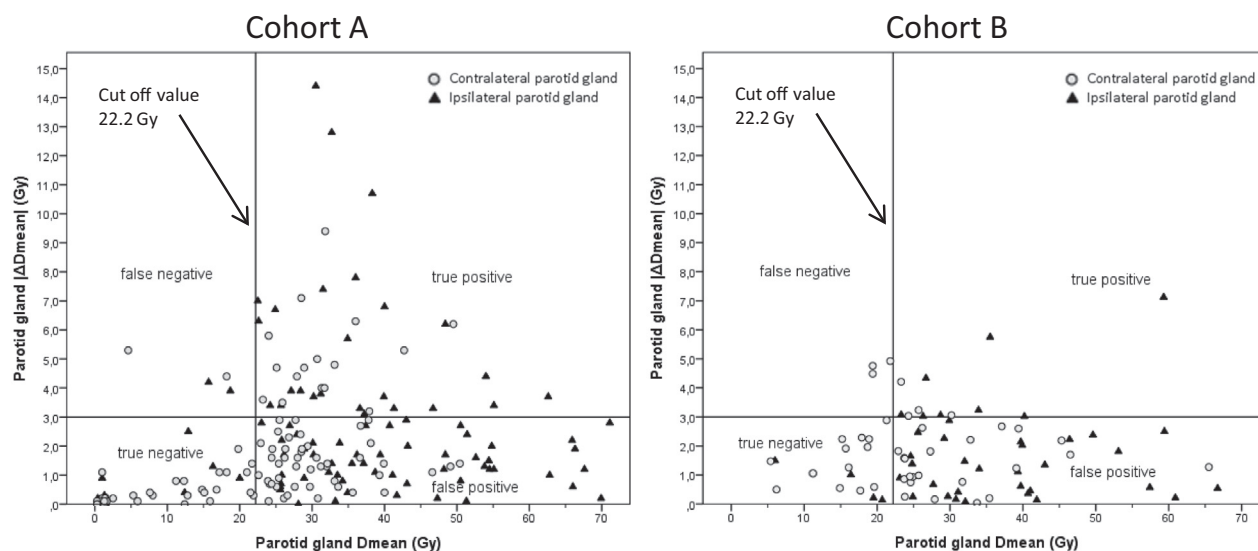
**Fig. 1.** Deviation from the planned parotid gland mean dose (|ΔDmean|) vs. the planned parotid gland mean dose. Selection of patients for |ΔDmean| > 3 Gy with 91 and 80% sensitivity could be performed by using a threshold of Dmean = 22.2 Gy, for cohort A and B, respectively (for more information refer to Table 4).

**Table 4**

Performance of the classification of patients for |ΔDmean| of the parotid glands > 3 Gy by using the planned mean dose of the parotid glands (PG D$_{mean}$). n.a. = not applicable.

| Cut off value PG D$_{mean}$ (Gy) | 0 | 3.6 | 22.2 | 24.7 | 27.0 |
|---|---|---|---|---|---|
| *Cohort A (n = 226)* | | | | | |
| Sensitivity (%) | 100 | 100 | 91 | 80 | 71 |
| Specificity (%) | 0 | 33 | 45 | 50 | 60 |
| % selected for ART | 100 | 74 | 62 | 56 | 46 |
| Positive predictive value (%) | 20 | 27 | 29 | 29 | 30 |
| Negative predictive value (%) | n.a. | 100 | 95 | 91 | 89 |
| *Cohort B (n = 84)* | | | | | |
| Sensitivity (%) | 100 | 100 | 80 | 60 | 40 |
| Specificity (%) | 0 | 0 | 25 | 38 | 46 |
| % selected for ART | 100 | 100 | 76 | 62 | 51 |
| Positive predictive value (%) | 18 | 18 | 19 | 17 | 14 |
| Negative predictive value (%) | n.a. | n.a. | 81 | 81 | 78 |

The inferior performance of the linear model for the ipsilateral PG compared to the contralateral PG could be explained by the fact that the ipsilateral PGs are often encompassed by an (elective) target volume. Consequently, the ipsilateral PGs are more often receiving a high, homogenous dose, and are located further away from high dose gradients. Anatomical changes will therefore have little or no dosimetric impact for the ipsilateral PGs receiving high doses (>∼50 Gy). Furthermore, we found that PG volume loss was linearly associated with the PG mean dose up to a level of ∼60 Gy, but for PG doses >60 Gy, little or no PG volume loss (i.e. anatomical changes) occurred (Fig. S3).

Brown et al. [4] also attempted to predict the need for ART in head and neck cancer patients. The authors concluded from their multivariable analysis that oropharyngeal and nasopharyngeal patients with N2–3 disease, an initial weight >100 kg and larger initial nodal sizes have a probability ⩾80% of requiring replanning. In our multivariable analysis, only the mean dose to the PG persisted. While Brown et al. did not include this factor in their analysis, in our data the PG mean dose was significantly associated with N2–3 disease ($R = 0.51$) and larger initial nodal sizes ($R = 0.43$). Furthermore, the difference in findings between our study and those reported by Brown et al. can be explained by a number of reasons. First, Brown et al. used a different endpoint, i.e. 'the need for replan', which was defined by the treating radiation oncologist. As the authors stated in their discussion, the need

for replan was mostly defined by the dose to the optic structures and brachial plexus. In our study, the need for replan was determined by the dose to the parotid gland. Secondly, our study cohort contained fewer patients with oro- and nasopharyngeal cancer. Thirdly, our patients with pharyngeal cancer had lower initial weights, not exceeding the 100 kg threshold described by Brown et al. [4]. It will be necessary to repeat the multivariable analyses in sufficiently large, properly selected patient cohorts, in order to untangle the confounding factors.

In the study by Brown et al. [4], only 5 of 110 patients (4.5%) were selected for replanning. In our study, 18–20% of the patients were selected for replanning if their difference in mean dose to the PG was larger than 3 Gy. The question arises whether the arbitrary threshold of 3 Gy is the most clinically relevant threshold. In the linear range of the mean dose NTCP model (from a mean dose of ∼25 up to 55 Gy) [22], a difference of 1 Gy in mean dose to the PG corresponds to a difference of about 3% in NTCP. For dose values <25 or >55 Gy however, a difference of 1 Gy in mean dose to the PG corresponds to a difference of about 1% in NTCP. Still, it is hard to prove that a dose increase of 3 Gy will result in more complications. Some authors [23,24] compared the intensity of side effects and global quality of life of a group of patients selected for replanning with those without replanning. They found significantly fewer side effects and improved quality of life for the replanned group. However, it should be noted that in these studies patients were not randomly allocated to the different strategies. Therefore the differences found in these studies can also be explained by other factors, such as differences in socioeconomic status between the two populations [25].

The strengths of our study are the relatively large number of patients included and the use of two independent patient groups for development and validation of the selection method. We were therefore able to perform multivariable analysis to select the most important pre-treatment parameter(s) related to the endpoint, and eventually to validate this approach in an independent subsequent patient cohort.

A limitation of our study is the absence of imaging during the course of RT for cohort A. Therefore, the approximated delivered dose to the PG for cohort A may be overestimated. However, we expect the post-CT scan acquired six weeks after RT to be a valid approximation for the anatomy of the parotid gland, since previous research showed no significant change in volume of the parotid

glands 6–8 weeks after treatment in relation to the end of treatment [12,13]. We choose to calculate ΔDmean[B] using all available imaging during the course of radiotherapy, to obtain the best approximation of the actual given dose. This approach is expected to result in lower values of ΔDmean than the approach taken in cohort A. The fact that resulting ΔDmean values for cohort B are even higher than the values in cohort A can be explained by the differences between the cohorts, i.e. tumour location and initial GTV volume (cohort B having a larger amount of pharynx patients, and a larger initial GTV volume).

The focus of this study was the dose deviations of the PG, for two reasons. The first is that previous studies have shown that this organ receives the largest dose deviations [1–3]. The second is because the dose to the PG is related to one of the most important long term side effects of head and neck radiotherapy i.e. xerostomia. At present, we are conducting studies investigating the consequences of dose inhomogeneities of target volumes, and potential overdosage of other organs at risk due to anatomical changes. The same method as described in this study could be used to study pre-treatment parameters associated with dose changes and to classify patients suitable for ART.

Absolute changes from the planned PG mean dose were considered in this study, i.e. positive as well as negative dose changes. If the dose change to the PG is positive, a plan adaptation is needed to prevent a higher risk of xerostomia than predicted at the planning stage. Although negative dose changes result in a lower risk of xerostomia, it is also important to monitor since the original treatment plan might become compromised, requiring further optimization of the target volume or other organs at risk.

The patient characteristics of patient cohort A and B showed several significant differences, with regard to tumour location, tumour and node classification, chemotherapy, GTV volume and planned PG mean dose and |ΔDmean| of the contralateral PG (Table 1). The performance of the classification of patients for PG |ΔDmean| > 3 Gy was moderate for cohort B (Table 4). With the low threshold of 3.6 Gy, all patients were selected for ART (the minimum PG mean dose was 5.4 Gy). With high thresholds however (24.7 and 27.0 Gy), the sensitivity was only 60% and 40% respectively, which would generally not be accepted in clinic. Nevertheless, the threshold of 22.2 Gy is applicable to both cohort A and B with sensitivities of 91% and 80%, respectively. Therefore a threshold for the mean dose to the parotid gland of 22.2 Gy seems optimal for the selection of head and neck cancer patients for ART, with reasonable overall performance (Table 4). The sensitivity level accepted is obviously discussable, and depends on the desired level of accuracy and the availability of resources for ART. The somewhat disappointing performance of the selection tool in general pleads for future studies using more specific patient populations, i.e. with focus on a specific tumour location.

In summary, we have presented a method to select patients for ART pre-treatment by using the planned mean dose to the parotid gland. Additional studies focusing on dosimetric changes to target volumes and organs at risk in large specific patient cohorts could help to further specify appropriate parameters to select patients for ART.

## Conflict of interest

None.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.05.025.

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