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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.

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, ΔDmean[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: ΔDmean[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 ΔDmean[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, ΔDmean[B] for the PG per patient was calculated by subtracting the planned mean dose from the accumulated mean dose: ΔDmean[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 ΔDmean, 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 |ΔDmean[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 ΔDmean| > 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 |ΔDmean| of the contralateral PG (Table 1).

The endpoint |ΔDmean| 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|ΔDmean| 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, |ΔDmean| of the parotid gland was higher than 3 Gy (Fig. 1 and Table 4). The results of