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Morbidity of head and neck radiotherapy

CT image biomarkers to improve patient-specific prediction of radiation-induced xerostomia and sticky saliva

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ABSTRACT

Background and purpose: Current models for the prediction of late patient-rated moderate-to-severe xerostomia (XER_{12m}) and sticky saliva ($STIC_{12m}$) after radiotherapy are based on dose-volume parameters and baseline xerostomia (XER_{base}) or sticky saliva ($STIC_{base}$) scores. The purpose is to improve prediction of XER_{12m} and $STIC_{12m}$ with patient-specific characteristics, based on CT image biomarkers (IBMs).

Methods: Planning CT-scans and patient-rated outcome measures were prospectively collected for 249 head and neck cancer patients treated with definitive radiotherapy with or without systemic treatment. The potential IBMs represent geometric, CT intensity and textural characteristics of the parotid and submandibular glands. Lasso regularisation was used to create multivariable logistic regression models, which were internally validated by bootstrapping.

Results: The prediction of XER_{12m} could be improved significantly by adding the IBM "Short Run Emphasis" (SRE), which quantifies heterogeneity of parotid tissue, to a model with mean contra-lateral parotid gland dose and XER_{base}. For $STIC_{12m}$, the IBM maximum CT intensity of the submandibular gland was selected in addition to $STIC_{base}$ and mean dose to submandibular glands.

Conclusion: Prediction of XER_{12m} and $STIC_{12m}$ was improved by including IBMs representing heterogeneity and density of the salivary glands, respectively. These IBMs could guide additional research to the patient-specific response of healthy tissue to radiation dose.

The survival of head and neck cancer (HNC) patients has improved remarkably in the last decade with the addition of systemic agents, including concurrent chemotherapy and cetuximab [1,2]. However, these treatment strategies have significantly increased acute and late toxicity [3]. Consequently, reducing treatment-induced side effects has become increasingly important. Despite the clinical introduction of more advanced radiation techniques, side effects related to hyposalivation, such as xerostomia and sticky saliva, are still frequently reported following radiotherapy (RT) for HNC. Accurate prediction of these side effects is important in order to individually tailor treatments to patients.

To predict moderate-to-severe xerostomia and sticky saliva, Normal Tissue Complication Probability (NTCP) models have been developed [4,5]. Current models are based on a combination of dose–volume parameters of salivary glands and baseline risk factors. However, these models cannot completely explain the variation in development of xerostomia between individuals. Therefore, identification of additional factors is needed to explain the patient-specific response to dose, and subsequently to optimise NTCP models.

In current clinical practice, three-dimensional anatomic information is acquired with planning CT scans for all patients receiving RT. These scans are used to delineate the target and organs at risk, and to calculate the dose distribution of the planned treatment. These scans yield reproducible information about patient-specific anatomy and tissue composition, and could therefore contribute to the understanding and prediction of the development of side effects in HNC patients.

Information about the structure, shape and composition of organs at risk from the CT can be quantified with image features. Features that correlate with treatment outcome or complications can be used as so called image biomarkers (IBMs). Extracted from CT data of the parotid (PG) and submandibular glands (SG), the different image features represent their CT intensity as well as geometric and textural characteristics.

Aerts et al. [6] investigated the relationship between CT IBMs of head and neck tumours and survival. Furthermore, the relationship between geometric changes of organs at risk after RT, and radiation

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induced complications, has been described in several studies [7–10]. Scalco et al. [11] investigated change after RT for a selected set of textural parameters. However, there are no studies so far that report on the relationship between IBMs of organs at risk before treatment and the risk of complications.

The aim of this study, therefore, was to investigate the prediction of xerostomia and sticky saliva, as assessed at 12 months after radiotherapy. The objective was to improve predictions by the addition of IBMs of the parotid and submandibular glands, determined from the planning CT-scans, to models that contain clinical and dosimetric information.

Method

Patient demographics and treatment

The study population of HNC patients was treated with definitive radiotherapy either in combination or not with concurrent chemotherapy or cetuximab, between July 2007 and August 2014. Patients with tumours in the salivary glands, those with excised parotid or submandibular glands and/or patients that underwent surgery in the head and neck area were excluded from this study. Furthermore, patients with metal streaking artifacts in the CT were excluded, due to the influence of CT intensity values that do not correspond to tissue densities. Moreover, patients without follow-up data 12 months after RT were also excluded. Patient characteristics are depicted in Table 1.

Table 1
Patient characteristics.

Characteristics	*N* = 249	%
Sex		
Female	61	24
Male	188	76
Age		
18–65 years	133	53
>65 years	116	47
Tumour site		
Oropharynx	74	30
Nasopharynx	14	6
Hypopharynx	31	12
Larynx	118	47
Oral cavity	11	4
Unknown primary	1	0
Tumour classification		
T0	3	1
T1	27	11
T2	81	33
T3	77	31
T4	61	24
Node classification		
N0	115	46
N1	23	9
N2abc	104	42
N3	7	3
Systemic treatment		
Yes	100	40
No	149	60
Treatment technique		
3D-CRT	23	9
ST-IMRT	92	37
SW-IMRT	124	50
SW-VMAT	10	4
Bi-lateral		
Yes	203	82
No	46	18

Abbreviations: CRT: Conformal Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy; ST-IMRT: standard parotid sparing IMRT; SW-IMRT: swallowing sparing IMRT; SW-VMAT: swallowing sparing Volumetric Arc Therapy.

For each patient, a planning CT (Somatom Sensation Open, Siemens, Forchheim, Germany, voxel size: $0.94 \times 0.94 \times 2.0\ mm^3$; 100–140 kV) with contrast enhancement was acquired. This CT was used for contouring and RT planning. The parotid and submandibular glands were delineated according to guidelines as described by Brouwer et al. [12].

Most patients were treated with standard parotid sparing IMRT (ST-IMRT) or swallowing sparing IMRT (SW-IMRT) [13,14]. All IMRT and VMAT treatments included a simultaneous integrated boost (SIB) and attempted to spare the parotid glands and/or the swallowing structures without compromising the dose to the target volumes [15]. The tumour and, if present, pathological lymph node target volumes, received a total dose of 70 Gy (2 Gy per fraction). Most patients received an elective radiation dose of 54.25 Gy (1.55 Gy per fraction) on the lymph node levels that were delineated as described by Gregoire et al. [16]. Radiation protocols were similar to those described by Christianen et al. [17].

Endpoints

The EORTC QLQ-H&N35 questionnaire was used to evaluate patient-rated xerostomia and sticky saliva before and after RT. This questionnaire is part of a standard follow-up programme (SFP), as described in previous reports [4,18,19], and uses a 4-point Likert scale that describes the condition as 'none', 'a bit', 'quite a bit' and 'a lot'. All patients included were subjected to the SFP programme, where toxicity and quality of life were evaluated prospectively on a routine basis; before, during and after treatment.

The endpoints of this study are moderate-to-severe xerostomia (XER_{12m}) and sticky saliva ($STIC_{12m}$) 12 month after RT. This corresponds to the 2 highest scores on the 4-point Likert scale.

Potential CT image biomarkers, dose and clinical parameters

Dose and clinical parameters

The planning CT, dose distribution and delineated structures were analysed in Matlab (version R2014a). The mean dose to both the contra- and bi-lateral parotid and submandibular glands was determined, since previous studies have shown that those were the most important parameters in the prediction of patient-rated xerostomia and sticky saliva at 6 and 12 months after RT [4,5,20].

Furthermore, different patient characteristics (age, sex, WHO-stage, weight, length and Body Mass Index), tumour characteristics (TNM stage, tumour location) and treatment characteristics (treatment technique and the use of systemic treatment) were also included. In addition, the patient-rated xerostomia and sticky saliva at baseline were taken into account.

CT intensity and geometric image biomarkers

Patient-specific characteristics of the parotid and submandibular glands were quantified by extracting potential CT IBMs, representing geometric, CT-intensity and pattern characteristics. In Fig. 1, extraction of different types of IBMs is explained schematically. The in–house developed software that was used to extract the IBMs was based on commonly used formulas (Supplementary data 1 and 2) and implemented in Matlab (version R2014a). The CT intensity IBMs (number = 24) were derived from the CT intensity information of the delineated volumes of interest. Examples of these features are mean, variance, minimum, maximum, quantiles, energy and skewness of CT intensity. The geometric IBMs (number = 20), such as volume, sphericity, compactness and major and minor axis length, were directly derived from the delineated structures.