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Head and neck RT

Role of minor salivary glands in developing patient-rated xerostomia and sticky saliva during day and night

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ABSTRACT

Purpose: The purpose of this prospective study was to investigate the relationship between xerostomia during the day (XER_{day}) and night (XER_{night}) and sticky saliva during the day ($STIC_{day}$) and night ($STIC_{night}$) and dose distributions in different major and minor salivary glands among head and neck cancer (HNC) patients treated with primary radiotherapy (RT) or chemoradiation (CHRT).

Methods and materials: The study population was composed of 201 consecutive HNC patients treated with intensity modulated radiotherapy (IMRT) or 3-dimensional conformal radiotherapy (3D-CRT). All patients were included in a standard follow up programme in which acute and late side effects and quality of life (QoL) were prospectively assessed, prior to, during and after treatment.

The primary endpoints were XER_{day}, XER_{night}, $STIC_{day}$, $STIC_{night}$ as assessed by the Groningen Radiotherapy Induced Xerostomia questionnaire (GRIX) six months after completion of treatment. Organs at risk (OARs) potentially involved in salivary function were delineated on planning-CT, including the parotid, submandibular and sublingual glands and the minor glands in the soft palate, buccal mucosa and lips. Patients with moderate-to-severe xerostomia or moderate-to-severe sticky saliva, respectively, at baseline were excluded.

In order to determine which salivary glands were most important, a multivariate logistic regression analysis with an extended bootstrapping technique was used.

Results: In total, 29% and 19% of the cases suffered from XER_{day} and XER_{night}, respectively. The multivariate analysis showed that baseline xerostomia and the mean parotid gland dose were the most important predictors for XER_{day} and XER_{night}. At 6 months after (CH)RT, 10% and 12% of the cases reported $STIC_{day}$ and $STIC_{night}$ respectively. We were not able to identify prognostic factors related to dose distributions with regard to $STIC_{day}$. The mean submandibular gland dose was associated with $STIC_{night}$. Baseline xerostomia and sticky saliva scores on the GRIX were associated with XER_{day}, XER_{night}, $STIC_{day}$. Increasing age was correlated with both XER_{night} and $STIC_{night}$.

Conclusion: Organs at risk for XER_{day} and $STIC_{day}$ are similar to organs at risk for XER_{night} and $STIC_{night}$.

Radiotherapy is frequently applied to patients with head and neck cancer (HNC) either as single modality or as adjuvant treatment after primary surgery. Head and neck radiotherapy generally includes co-irradiation of the major and minor salivary glands located in the mucosal surfaces of the oral cavity [1]. Irradiation of the salivary glands results in salivary dysfunction which may lead to subsequent xerostomia and sticky saliva. Xerostomia is one of the most frequently reported side effects among patients after irradiation for HNC [2–7]. Salivary dysfunction may lead to subsequent side effects such as altered taste, swallowing problems, dental problems and speech problems which significantly hamper quality of life (QoL) [8–13].

The severity and aspects of xerostomia as reported by patients may differ among individual patients. Some patients mainly suffer from xerostomia at night while others have complaints predominantly during the day or during specific activities, such as during eating and/or exercise [14]. Content and production of saliva may differ between different salivary glands during different time points during the day, which may have various impacts on different aspects of symptoms related to salivary dysfunction [15,16]. The major salivary glands, including the parotid and submandibular glands are responsible for the main stimulated saliva production. Parotid flow markedly increases during eating, while the daily production of saliva at rest is mainly produced by the submandibular glands. During sleep, saliva is also produced by the sublingual and

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minor salivary glands lining the oral cavity. At night, the amount of saliva produced by the parotid glands is negligible [17].

The QUANTEC study group recently reported about the role of irradiation of the parotid glands and the development of xerostomia in general. These study results are widely used as dose constraints to parotid glands in the treatment of head and neck cancer patients with radiotherapy. These QUANTEC guidelines do not take into account the different aspects of xerostomia and sticky saliva as reported by patients at different time points [18,19]. In that perspective it would be interesting to investigate what the role of other salivary glands is in these different aspects of xerostomia and sticky saliva.

Recently, Langendijk et al. reported that xerostomia had a significant impact on the more general dimensions of health related quality of life (HRQoL), including on fatigue. In an additional analysis, they found that xerostomia significantly correlated with sleeping problems as well (personal communication), indicating that nocturnal salivary dysfunction is of particular importance for patients [8].

Recently, we developed and validated a new questionnaire, the Groningen Radiotherapy Induced Xerostomia (GRIX) questionnaire, allowing for differentiated assessments of patient-rated xerostomia and sticky saliva, during the day and during the night [20]. With this questionnaire it is possible to correlate different aspects of patient-rated xerostomia and sticky saliva to the dose distributions to different major and minor salivary glands. Therefore, the purpose of this study was to test if organs at risk for patient-rated xerostomia during the day differed from organs at risk for patient-rated xerostomia and sticky saliva during the night.

Material and methods

Patients

To be included in the analysis, patients had to fulfil the following eligibility criteria: (1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, paranasal sinuses or cervical lymph node metastases from unknown primary tumors; (2) treated with primary radiotherapy either alone (RT) or in combination with chemotherapy (CHRT) or cetuximab; (3) no previous surgery, radiotherapy and/or chemotherapy; (4) no previous malignancies; (5) no distant metastases, and (6) QoL assessments available prior to and at 6 months after completion of CHRT or RT.

The standardized follow up programme

All patients included in this analysis were subjected to a standard follow-up programme (SFP) as previously described [21,22]. The SFP includes a prospective evaluation of toxicity and QoL on a routine basis, prior to, during and at regular intervals, weekly during treatment, 6 weeks and every 6 months after curative CHRT or RT. For the purpose of this study, only the outcome of the GRIX questionnaire was used. All included patients completed the GRIX questionnaire at the outpatient clinic, just before the consultation with the radiation oncologist.

Endpoints

The endpoints for this study were defined as moderate-to-severe xerostomia during the day ($RespXER_{day}$), moderate-to-severe xerostomia during the night ($RespXER_{night}$), moderate-to-severe sticky saliva during the day ($RespSTIC_{day}$) and moderate-to-severe sticky saliva during the night ($RespSTIC_{night}$) as assessed at 6 months after completion of treatment using the GRIX [20].

The GRIX is organized into four functional multi-item scales (XER_{day}, XER_{night}, $STIC_{day}$, $STIC_{night}$). Each scale is composed of a number of questions using a 4-point Likert scale ranging from none, a bit, quite a bit, to a lot. For each scale the scores on the GRIX were linearly converted to 0–100 score according to the same guidelines as proposed by the EORTC. For the purpose of this study, patients were divided into two groups, i.e. a subgroup with a score from 0 to 50, corresponding with no-to-minor complaints for each scale, and a subgroup with a score from 51 to 100 corresponding with moderate-to-severe complaints ($RespXER_{day}$, $RespXER_{night}$, $RespSTIC_{day}$, $RespSTIC_{night}$). Patients with scores $\geqslant 50$ at baseline were excluded from the analysis. This was done, as we were primarily interested in xerostomia and sticky saliva induced by radiation treatment itself.

Treatment

In all patients, a planning CT-scan with contrast-enhancement was performed in treatment position. Radiotherapy was delivered using a 6 MV linear accelerator. The target volumes have been described previously [21]. In summary, the prophylactic clinical target volume was composed of the primary tumor and pathological lymph nodes plus a 1.0 cm margin, and the elective nodal areas on both sides of the neck, selected according to the guidelines reported by Gregoire et al. [23]. The therapeutic CTV consisted of the primary tumor and pathological lymph nodes with a 0.5 cm margin. In all cases, an additional 0.5 cm margin was applied for the planning target volumes.

Among patients treated with 3-dimensional conformal radiotherapy (3D-CRT), no attempts were made to spare the salivary glands. Patients with early glottic carcinoma were treated with a fraction dose of 2.5 Gy (5 times/week) up to a total dose of 60 Gy in 5 weeks or with a fraction dose of 2.0 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were only irradiated at the primary site.

Patients treated with concomitant CHRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced cases, which were considered not eligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were generally treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 h, up to a total dose of 70 Gy in 6 weeks. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumor and pathological lymph nodes to a total dose of 70 Gy. In some cases, radiotherapy only with conventional fractionation was used.

When treated with intensity modulated radiotherapy (IMRT) the mean dose to both parotid glands was reduced as much as possible without compromising the required dose to the target volumes. Patients were treated with step-and-shoot IMRT. In general, a seven-field equidistant, non-opposing beam configuration was used. All patients were treated with a simultaneous integrated boost (SIB) technique.

Contouring of organs at risk

Organs at risk (OARs) potentially involved in symptoms related to salivary function were delineated according to the guidelines as described by Van de Water et al. [1], including the parotid, submandibular and sublingual glands, as well as the minor salivary glands located in the soft palate, the inner surface of the lower and upper lip and the minor salivary glands in the inner surface of the cheeks. All OARs were delineated by an expert in head and neck radiation oncology (JL).