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The role of parotid gland irradiation in the development of severe hyposalivation (xerostomia) after intensity-modulated radiation therapy for head and neck cancer: Temporal patterns, risk factors, and testing the QUANTEC guidelines

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ABSTRACT

Background: The aims of this study were to investigate temporal patterns and potential risk factors for severe hyposalivation (xerostomia) after intensity-modulated radiotherapy (IMRT) for head and neck cancer (HNC), and to test the two QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) guidelines.

Patients and methods: Sixty-three patients treated at the Memorial Sloan Kettering Cancer Center between 2006 and 2015, who had a minimum of three stimulated whole mouth saliva flow measurements (WMSFM) at a median follow-up time of 11 (range: 3–24) months were included. Xerostomia was defined as WMSFM $\leq$25% compared to relative pre-radiotherapy. Patients were stratified into three follow-up groups: 1: <6 months; 2: 6–11 months; and 3: 12–24 months. Potential risk factors were investigated (Mann–Whitney *U* test), and relative risks (RRs) assessed for the two QUANTEC guidelines.

Results: The incidence of xerostomia was 27%, 14% and 17% at follow-up time points 1, 2 and 3, respectively. At <6 months, the mean dose to the contralateral and the ipsilateral parotid glands ($Dmean_{contra}$, $Dmean_{ipsi}$) was higher among patients with xerostomia ($Dmean_{contra}$: 25 Gy vs. 15 Gy; $Dmean_{ipsi}$: 44 Gy vs. 25 Gy). Patients with xerostomia had higher pre-RT WMSFM (3.5 g vs. 2.4 g), and had been treated more frequently with additional chemotherapy (93% vs. 63%; all 4 variables: $p < 0.05$). At 6–11 months, $Dmean_{contra}$ among patients with xerostomia was higher compared to patients without (26 Gy vs. 20 Gy). The RR as specified by the one- and two-gland QUANTEC guideline was 2.3 and 1.4 for patients with <6 months follow-up time, and 2.0 and 1.2 for patients with longer follow-up (6–11 + 6 –24 months).

Conclusion: Xerostomia following IMRT peaks within six months post-radiotherapy and fades with time. Limiting the mean dose to both parotid glands (ipsilateral <25 Gy, contralateral <25 Gy) and reducing the use of chemotherapy will likely decrease the rate of xerostomia. Both QUANTEC guidelines are effective in preventing xerostomia.

1. Introduction

Intensity-modulated radiotherapy therapy (IMRT) is currently the standard of care for the treatment of head and neck cancer (HNC), and enables delivery of highly conformal dose distributions. Reduced salivary function or xerostomia is the most common long-

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term side effect observed in HNC patients following RT (Bjordal et al., 1994; Jensen et al., 1994; Wijers et al., 2002). Patients typically describe the condition as dry mouth, altered taste, and/or a reduction in salivary flow that often limits their quality of life concerning oral hygiene, halitosis, dental caries, and difficulty with speech, mastication, and/or swallowing. Based on animal models, the pathophysiology of RT-induced xerostomia has been described by an early phase starting at the end of RT and lasting up to two months post-RT, and by a late phase between around two months up to eight months post-RT (Coppes et al., 2001). Furthermore, the early phase may be attributed to apoptosis or membrane damage-induced dysfunction, and the late phase to an inability of replacing the apoptotic acinar cells due to radiation-induced reduction of the stem/progenitor cells (Coppes et al., 2001; Vissink et al., 2010; Jensen et al., 2010; Konings et al., 2005; Lombaert et al., 2008). Also, the study by Belli et al. showed that parotid gland volume and density changes occurred early during treatment and accurately correlated to acute xerostomia (Belli et al., 2014). The parotid glands produce up to 70% of the total stimulated saliva (Dawes and Wood, 1973; Humphrey and Williamson, 2001; Sreebny, 2000). Clinically significant hyposalivation is commonly defined as Grade 4 xerostomia according to the LENT-SOMA tables (LENT-SOMA, 1995) *i.e.* a preserved stimulated salivary function ≤25% post-relative to pre-RT. In two randomized controlled phase III trials, IMRT has been found to significantly reduce the risk of severe hyposalivation (xerostomia) compared with conventional RT (Nutting et al., 2011; Kam et al., 2007). However, limiting the dose to the surrounding critical structures completely, without compromising treatment efficacy can be challenging.

Previous studies aiming to establish a dose–response relationship for xerostomia have reported that parotid gland dysfunction is minimal at a mean dose (Dmean) < 10 Gy, that the gland function is further reduced as Dmean increases to ~40 Gy, and that a Dmean > 40 Gy typically involves complete parotid gland dysfunction (Chao et al., 2001; Blanco et al., 2005; Leslie and Dische, 1994). Within the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report devoted to salivary gland function post-RT, two guidelines to minimize the risk of salivary gland dysfunction in patients with HNC treated with RT were proposed: long-term severe xerostomia would be reduced if: i.) One of the parotid glands receives a Dmean < ~20 Gy, or ii.) Both parotid glands receive a Dmean < ~25 Gy (Deasy et al., 2010). It has previously been demonstrated that the one-gland guideline is effective in order to reduce the number of patients who would otherwise experience moderate to severe xerostomia (Moiseenko et al., 2012; Beetz et al., 2014). However, since the two-gland guideline has been studied to a much lesser extent, its applicability for preventing xerostomia and how it compares to the one-gland guideline remains unclear.

The goals of the current study were: 1.) To objectively evaluate the occurrence and rate of severe hyposalivation (xerostomia) following IMRT in HNC patients with a particular focus on temporal patterns; 2.) To investigate potential risk factors for its development, and; 3.) To explore the applicability of the two guidelines provided in the QUANTEC salivary gland function-specific summary.

2. Material and methods

2.1. Patient cohort

The Institutional Review Board approved this retrospective study including all HNC patients treated with IMRT at the Memorial Sloan Kettering Cancer Center between March 2006 and March 2015. Whole mouth saliva flow measurements (WMSFM) were prospectively collected from patients. To further qualify for inclusion, the following criteria applied: a minimum of three stimulated WMSFM [g/5 min], WMSFM >1 g/5 min assessed pre-RT to exclude potential predisposition of xerostomia pre-RT, reasonably high RT prescription dose (≥50.4 Gy) to the tumor site, and at least two WMSFM assessed within 24 months post-RT. In total, 63 patients fulfilled these inclusion criteria. A flow chart of the patients is presented in Fig. 1. During the study period, the standard of care was to systematically avoid Dmean > 26 Gy to the contralateral and the ipsilateral parotid glands ($Dmean_{contra}$, $Dmean_{ipsi}$).

2.2. Xerostomia definition and stimulated saliva measurements

Patients refrained from eating and drinking at a minimum of one hour prior to WMSFM. Saliva was collected in a pre-weighed plastic cup, and patients were asked to spit into the cup every minute for five minutes after the administration of a citrate solution to both sides of the tongue every 30 s during a two-minute period. Xerostomia was defined as Grade 4 according to the LENT SOMA tables (LENT-SOMA, 1995) *i.e.* WMSFM ≤ 25% post-relative to pre-RT.

2.3. Statistical analysis

Patients were stratified into three follow-up groups: 1: <6 months; 2: 6–11 months; and 3: 12–24 months. In each of these groups, patient- (gender (binary), N-stage T-stage, tumor site (categorical), age, and pre-RT WMSFM (continuous)), and treatment-related (concurrent chemotherapy, involved neck RT, surgery (binary), histology (categorical), $Dmean_{contra}$ and $Dmean_{ipsi}$ (continuous)) characteristics were compared between patients with and without xerostomia using a Mann–Whitney *U* test. The number of patients fulfilling/violating the QUANTEC guidelines was recorded, and the relative risk (RR) was assessed for each guideline (Eq. (1)):

$$RR = \frac{\left(\frac{N_{Xero=Yes,QUANTEC=No}}{N_{Xero=Yes,QUANTEC=No}+N_{Xero=Yes,QUANTEC=Yes}}\right)}{\left(\frac{N_{Xero=No,QUANTEC=No}}{N_{Xero=No,QUANTEC=No}+N_{Xero=No,QUANTEC=Yes}}\right)} \quad (1)$$

3. Results

The mean (±SD) age for the 63 included patients was 57 (±10) years, of which the majority were men (81%), diagnosed with squamous cell carcinoma (81%), treated to 70.0–70.2 Gy (65%) with involved neck RT (73%) for tumors of stage T1–T2 (65%), and nodal spread of disease of stage N1–N2 (75%).

3.1. Xerostomia <6 m post-RT is associated with chemotherapy use and tumor site

The incidence of xerostomia was 27% (n = 15), 14% (n = 5), and 17% (n = 5) at <6 months, 6–11 months, and 12–24 months, respectively. For the shortest follow-up time, the use of concurrent chemotherapy and WMSFM pre-RT were significantly higher among patients with xerostomia (chemotherapy: 93% vs. 63%, p = 0.02; WMSFM: 3.5 ± 1.5 g vs. 2.4 ± 0.8 g, p = 0.01; Table 1). At this follow-up time, the tumor site was significantly different between patients with xerostomia and those without xerostomia (p = 0.03) with tumors of unknown primary being present only among xerostomia patients, and tumors of the buccal mucosa, floor of mouth, larynx, nasal cavity, sinus, submandibular gland, retromolar trigone, and thyroid being present only in patients without