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Mouth opening in patients irradiated for head and neck cancer: A prospective repeated measures study

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SUMMARY

Objectives: Aims of this prospective cohort study were (1) to analyze the course of mouth opening up to 48 months post-radiotherapy (RT), (2) to assess risk factors predicting decrease in mouth opening, and (3) to develop a multivariable prediction model for change in mouth opening in a large sample of patients irradiated for head and neck cancer.

Materials and methods: Mouth opening was measured prior to RT (baseline) and at 6, 12, 18, 24, 36, and 48 months post-RT. The primary outcome variable was mouth opening. Potential risk factors were entered into a linear mixed model analysis (manual backward-stepwise elimination) to create a multivariable prediction model. The interaction terms between time and risk factors that were significantly related to mouth opening were explored.

Results: The study population consisted of 641 patients: 70.4% male, mean age at baseline 62.3 years (sd 12.5). Primary tumors were predominantly located in the oro- and nasopharynx (25.3%) and oral cavity (20.6%). Mean mouth opening at baseline was 38.7 mm (sd 10.8). Six months post-RT, mean mouth opening was smallest, 36.7 mm (sd 10.0). In the linear mixed model analysis, mouth opening was statistically predicted by the location of the tumor, natural logarithm of time post-RT in months (Ln (months)), gender, baseline mouth opening, and baseline age. All main effects interacted with Ln (months).

Conclusion: The mean mouth opening decreased slightly over time. Mouth opening was predicted by tumor location, time, gender, baseline mouth opening, and age. The model can be used to predict mouth opening.

Introduction

Decreased mouth opening, a trismus, is a well-known side effect of treatment of head and neck cancer, including of radiotherapy (RT) [1–6]. The prevalence of trismus following RT ranges from 25% to 46% [4–6]. Trismus has a negative impact on function and quality of life [1,7–11]. It impairs eating, speech, oral hygiene, dental treatment, airway clearance, and oncological follow-up [1,5,12]. Trismus is often progressive, hard to treat, and once established, only a limited increase in mouth opening can be achieved [13,14]. Therefore, the focus should be on prevention.

Trismus is most likely to develop if RT includes the masticatory muscles and region of the temporomandibular joint, particularly, when RT is combined with chemotherapy, in case of larger tumors, or when trismus is induced by the tumor itself [4,6,10,15–17]. Fibrosis and atrophy of irradiated tissues contribute to trismus, which is likely to develop between 1 month and 1 year post-RT [10,18,19]. A progressive decrease in mouth opening can be observed even years after finishing RT [19]. Dosages higher than 50 Gy are associated with trismus [4,10,20–22]. Higher incidences of trismus have been observed after external beam RT than after interstitial RT [4,20].

The main limitations of previous studies that aimed at identifying risk factors for trismus were their retrospective design and relatively small sample sizes. The longitudinal course of mouth opening up to 1 year following surgery and/or RT (with or without chemotherapy) has been described in 4 prospective studies with 17 to 143 patients. The main limitations of these studies were the small sample sizes, limited primary tumor sites, or the lack of RT as part of the treatment modalities [17,19,23,24]. Consequently, when several risk factors are present, it has been

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impossible to statistically predict the longitudinal course of mouth opening of head and neck cancer patients after RT.

The aims of our prospective cohort study were (1) to analyze the longitudinal course of mouth opening up to 48 months post-RT, (2) to assess risk factors predicting decrease in mouth opening, and (3) to develop a multivariable prediction model for change in mouth opening based on a large sample size of patients undergoing RT for head and neck cancer.

Materials and methods

Study design and setting

This prospective longitudinal cohort study was conducted between March 2007 and June 2011 at the Department of Radiation Oncology of the University Medical Center Groningen, the Netherlands. The study was carried out according to the regulations of our institute.

Participants

All patients who underwent definitive or postoperative external beam RT for head and neck cancer, either alone or in combination with chemotherapy or cetuximab, were included. Patients were excluded if their primary tumor was located outside the head and neck region, intracranially, or if it originated from the nasal vestibule or the skin. Patients were also excluded if no data was collected regarding their mouth opening, or if the patient died during RT or within the first 6 months after the start of RT. Tumor classification was based on the Union for International Union Against Cancer (UICC) recommendation TN classification (2009).

Radiotherapy

Patients were treated with external beam RT using linear accelerators at the Department of Radiation Oncology according to the standard of care protocols. Details on RT have been described in detail previously [25].

Data

At the outpatient clinic of the Department of Radiation Oncology, mouth opening was prospectively measured prior to RT (baseline) and at regular follow-up appointments at 6, 12, 18, 24, 36, and 48 months post-RT. During these visits, patients were asked to open their mouth completely, and mouth opening was measured as maximal interincisal distance in millimeters, using a slide caliper. In case patients were edentulous and not wearing a dental prosthesis, mouth opening was measured from the alveolar ridge. Trismus was defined as a mouth opening of 35 mm or less [2].

Data on tumor and treatment were also prospectively collected. Missing and biologically implausible data were verified and retrieved from medical records.

Statistical analysis

The primary outcome variable was mouth opening at different time points (baseline, 6, 12, 18, 24, 36 and 48 months post-RT). Prior to data analysis, the association between time and mouth opening was explored. Time was modeled as a linear function, as a squared function, and as a logarithmic function. The model fit was best using a logarithmic function for time. Hence, Ln (months) was used in the analysis. The T stage of the tumor was dichotomized into stage T4 (yes, no) because plots showed that mouth opening over time was different in patients with T4 tumors compared to those with T1, T2, or T3 tumors. For the clinical interpretation, age was centered at 60 years.

The potential risk factors were selected based on the assumed risk to influence mouth opening: location of the tumor (oral cavity, oro- and nasopharynx, salivary glands and ear, hypo- and supraglottic larynx, glottic- and supraglottic larynx, nasal cavity and maxillary sinus, and lymph node metastases from an unknown primary (primary unknown)), squamous cell carcinoma (yes, no), time modeled as the natural logarithm of time in post-RT in months (Ln (months)), gender (male, female), baseline mouth opening (millimeters), stage T4 (yes, no), baseline age (years), total dose of irradiation (Gy), fraction dose of irradiation (Gy), target volume on primary tumor (yes, RT on primary tumor; no, RT on metastasis in head and neck region), RT neck (yes, RT on neck area; no, RT only on primary tumor), re-irradiation in locoregional area (yes, no), surgery on the primary tumor (yes, no), neck dissection (yes, no), and chemotherapy (yes, no).

All potential risk factors were entered in a linear mixed model analysis and successively eliminated (manual backward-stepwise elimination) to create a multivariable prediction model (SPSS 22.0 for Windows software (SPPS Inc., Chicago, IL, USA)). A risk factor was eliminated if the significance of the regression coefficient was larger than 0.05 and the model fit (−2log likelihood criterion) did not decrease significantly. In addition, interaction terms between time and risk factors significantly related to mouth opening, were explored. An interaction term remained in the model if the model fit increased significantly (−2log likelihood criterion). To verify post hoc if missing data may have influenced the results of the linear mixed model analysis, we performed the same analysis with patients with complete data. Because 59 patients had complete data up to 48 months follow-up, we did this analysis with the cohort with complete data up to 36 months, consisting of 104 patients.

Results

We initially included 788 head and neck cancer patients who were being treated with any form of RT We excluded 98 patients for the following reasons: primary tumor located outside the head and neck region, no data regarding mouth opening, and/or and deceased during or within the first 6 months post-RT. Patients with tumors originating from the nasal vestibule ($n = 11$), skin ($n = 33$), and intracranial ($n = 3$) were also excluded. For statistical reasons, patients ($n = 2$) with rare type of tumors (myxofibrosarcoma neck and epitheloid angio-sarcoma) were excluded as well. The study population therefore consisted of 641 consecutive patients (81.3% of the initial sample).

Descriptive data

The patient, tumor, and treatment characteristics of the study population ($n = 641$) and the cohort of patients with complete data at 36 months post-RT ($n = 104$) are shown in Tables 1 and 2. The majority of the patients were male (70.4%) and the mean age at baseline was 62.3 years (sd 12.5). Primary tumors were mostly located in the oro- or nasopharynx (25.3%) and oral cavity (20.6%).

Course of mouth opening

The mean mouth opening was 38.7 mm (sd 10.8) at baseline, 36.7 mm (sd 10.0) at 6 months post-RT, and 38.2 mm (sd 11.5) at 48 months post-RT. At baseline, 35% of the patients had trismus, which increased to 37% at 48 months post-RT. The highest percentage of patients with trismus was found at 6 months post-RT (42.9%) (Table 3). The course of mouth opening over time differed per tumor location (Fig. 1).

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