Oral Oncology 49 (2013) 42–48

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Scintigraphic assessment of salivary function after intensity-modulated radiotherapy for head and neck cancer: Correlations with parotid dose and quality of life

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ARTICLE INFO

Article history:
Received 27 April 2012
Received in revised form 5 July 2012
Accepted 6 July 2012
Available online 31 July 2012

Keywords:
Head and neck cancer
Xerostomia
Parotid gland function
Intensity-modulated radiotherapy
Quality of life

SUMMARY

Objective: We investigated salivary function using quantitative scintigraphy and sought to identify functional correlations between parotid dose and quality of life (QoL) for head and neck cancer (HNC) patients receiving intensity-modulated radiotherapy (IMRT).

Materials and methods: Between August, 2007 and June, 2008, 31 patients treated IMRT for HNC were enrolled in this prospective study. Salivary excretion function (SEF) was previously measured by salivary scintigraphy at annual intervals for 2 years after IMRT. A dose-volume histogram of each parotid gland was calculated, and the normal tissue complication probability (NTCP) was used to determine the tolerance dose. QoL was longitudinally assessed by the EORTC QLQ-C30 and H&N35 questionnaires prior to RT, and at one, three, 12 and 24 months after RT.

Results: A significant correlation was found between the reduction of SEF and the mean parotid dose measured at 1 year (correlation coefficient, $R^2 = 0.651$) and 2 years ($R^2 = 0.310$) after IMRT ($p < 0.001$). The TD_{50} of the parotid gland at 1 year after IMRT is 43.6 Gy, comparable to results from western countries. We further found that contralateral parotid and submandibular gland function preservation was correlated with reduced sticky saliva and a better QoL compared to the functional preservation of both parotid glands, as determined by the EORTC QLQ-H&N35 questionnaire.

Conclusion: A significant correlation was found between the reduction of SEF and the mean parotid dose. Preservation of contralateral parotid and submandibular gland function predicts a better QoL compared to preservation of the function of both parotid glands.

Introduction

Xerostomia is a common side-effect that occurs after radiotherapy (RT) in patients with head and neck cancer (HNC). Modern RT techniques, such as three-dimensional conformal RT, or intensity-modulated RT (IMRT), can spare salivary glands, thus preserving salivary flow rates and improving observer-accessed xerostomia compared to conventional RT.[1–3] The parotid gland dose-volume response following RT has been investigated in several large prospective studies.[4–8] A wide range (26–43 Gy) of threshold mean dose (TD_{50}), the dose resulting in a 50% probability of a complication for the whole organ irradiated uniformly, for parotid gland-stimulated salivary flow, has been reported. The mean dose reported to preserve parotid gland function in Asian studies varies from 31 to 43.9 Gy[9–11]; yet, none reported the TD_{50}.

Although the apparent improvement in objective salivary function and observed xerostomia was achieved by 3-D conformal or IMRT, the result does not necessarily improve the patient-reported xerostomia.[12] Since xerostomia is mainly a quality of life issue, a patient-reported quality of life questionnaire is more useful in assessing salivary function. Therefore, in the present prospective

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http://dx.doi.org/10.1016/j.oraloncology.2012.07.004

study, we longitudinally recorded the recovery of parotid gland function using salivary scintigraphy in patients receiving IMRT. The NTCP model was used to determine the TD_{50} of the parotid gland. The patient-reported quality of life (QoL) questionnaire, EORTC QLQ-C30, and the Head and Neck module (H&N35), were given to patients prior to, and periodically following, RT to assess perceived salivary function over time. Patient-, tumor-, and therapy-related factors were simultaneously assessed as predictors of parotid gland function and QoL.

Materials and methods

Patient and disease characteristics

The study population consisted of patients with HNC treated with IMRT at our hospital. All patients provided written informed consent approved by the institutional review board. Patients who suffer from Sjögren's syndrome or any other medical cause of xerostomia were excluded. Patient use of any medications known to affect salivary gland function was prohibited. During the period from August, 2007 to June, 2008, a total of 31 patients with primary ($n = 15$) or post-operative RT ($n = 16$) for HNC were entered into this prospective study. Patient and tumor characteristics are listed in Table 1. IMRT was delivered by the computer-controlled autosequencing segmented or dynamic multileaf collimator of a Varian linear accelerator (Linac 21 EX), according to methods described previously.[13] IMRT delivery directed at sparing the parotid glands (predominantly contralateral side), while treating the primary targets and lymph nodes at risk was conducted. The prescribed doses were 67.4–70.8 Gy (mean, 69.8 Gy) to the macroscopic tumor planning target volume, 54.8–70.8 Gy (mean, 62.0 Gy) to the surgical tumor bed planning target volume, and 46.8 Gy to the subclinical disease planning target volume, at 1.8–2 Gy per fraction. Nineteen patients received concurrent chemotherapy. Of these, five patients received additional adjuvant chemotherapy. Nineteen patients received concurrent chemotherapy with weekly CDDP (40 mg/m^2) for 5–7 courses ($n = 18$) or PF regimen (CDDP 80 mg/m^2 on day 1 + 5-FU 800 mg/m^2, days 1–5, every 21 days) for two courses ($n = 1$). Of these, five patients received additional adjuvant chemotherapy with PF regimen for 2–3 courses ($n = 4$) or TEF regimen (Taxol 60 mg/m^2 on day 1 + CDDP 20 mg/m^2 on day 1 + 5-FU 800 mg/m^2 on days 1–2) for one course ($n = 1$).

Table 1
Patients and tumor characteristics of 31 patients.

Characteristic	Value
Age (y)	
Mean	53
Range	28–78
Gender (n)	
Female	1 (3)
Male	30 (97)
Tumor site	
NPC	11 (35)
Oral cavity	14 (45)
Oropharynx	4 (13)
Larynx	1 (3)
Parotid	1 (3)
Stage (TNM staging system)	
T1	3 (10)
T2	12 (39)
T3	6 (19)
T4	7 (22)
Not applicable/recurrent	3 (10)
N0	16 (52)
N1	5 (16)
N2	7 (22)
N3	0 (0)
Not applicable/Recurrent	3 (10)
Surgery before RT	
Yes	16 (52)
No	15 (48)
Chemotherapy	
Yes	19 (61)
No	12 (39)

Data in parentheses are percentage.

Salivary scintigraphy

All patients received salivary scintigraphy prior to IMRT delivery. Patients fasted for 4 h prior to beginning the study. The study commenced with patients receiving 10 mCi $_{99m}$Tc pertechnetate intravenously. Sequential imaging of 1 frame/min was acquired for 30 min over the left- and right-anterior views of the head and neck. Salivary gland function was represented by saliva excretion following sialogogue stimulation with acidic material (lemon juice or 200 mg ascorbic acid tablet on the dorsal tongue). Salivary excretion factor (SEF) was quantified by determining the maximal excretion activity per gland as a function of maximal uptake, as described previously by Roesink et al.[6] The salivary scintigraphies are scheduled prior to IMRT and then 1 and 2 years after its completion. The excretion response was analyzed per patient and subsequently per individual gland. All patients received scintigraphies 1 year after RT, whereas only 25 patients (25/31, 81%) received examinations 2 years following RT. The six patients who did not receive scintigraphies were due to tumor recurrence ($n = 2$) or follow-up refusal ($n = 4$).

Normal tissue complication probability model

The data were applied to the NTCP model proposed by Lyman.[14] The NTCP model quantitatively assesses the effects of both the radiation dose and the volume of the gland irradiated on the probability of radiation-induced changes in parotid gland function. Three parameters are presented in the sigmoid dose–response curve: n, m, and TD_{50}, where n accounts for the volume effect of an organ, m describes the slope of the dose–response curve and the TD_{50} is the dose resulting in a 50% probability of a complication for uniform irradiation of the whole partial volume.

EORTC quality of life questionnaires (QLQ-C30 & H&N35)

Subjective salivary function was evaluated by the EORTC QLQ-C30 and H&N35 questionnaires. Patients were asked to answer the questions prior to receiving IMRT, and then 1, 3, 12, and 24 months later. The Traditional Chinese versions of the EORTC QLQ-C30 and H&N35 questionnaires were obtained from the Quality of Life Unit, EORTC Data Center in Brussels, Belgium.[15] All scales pertaining to the EORTC QLQ-C30 and H&N35 range from 0 to 100. A high score for a functional or global QoL scale represents a relatively high/healthy level of functioning or global quality of life, whereas a high score for a symptom scale represents the presence of a symptom or problem.

Statistical methods

A logistic regression statistical method was used to study the dose–response relationship and volume effects in parotid glands. Spearman's correlation was used to evaluate the factors associated with recovery of parotid gland function. Multivariate analysis was performed using a multiple regression model. The level of significance was set at $p < 0.05$. A paired sample t-test was used to compare the mean scores at each time point, with significance