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Original Article

Clinical and dosimetric predictors of physician and patient reported xerostomia following intensity modulated radiotherapy for nasopharyngeal cancer – A prospective cohort analysis

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ABSTRACT

Background and purpose: To compare physician and patient reported xerostomia and correlate xerostomia with dosimetric and clinical parameters for nasopharyngeal cancer (NPC) patients treated with intensity modulated radiotherapy (IMRT) and chemotherapy.
Patients and methods: We analyzed the data of 172 patients with locally advanced NPC. Xerostomia was evaluated via physician-rated xerostomia based on RTOG morbidity score (E1), patient-rated dry mouth (E2) and patient-rated sticky saliva (E3) based on EORTC QLQ-HN35 questionnaire. Primary endpoint was the presence of moderate to severe xerostomia at 2-year after completion of IMRT.
Results: The levels of physician reported xerostomia (E1) were consistently lower than patient reported dry mouth (E2) over time. The incidence of patients with xerostomia at 3-month post RT was 58% based on E1, 70% based on E2, and 51% based on E3. The corresponding incidence rates at 2-year post RT was 26% (E1), 36% (E2) and 21% (E3). The incidence of patients with xerostomia at 1-year post RT was close to that at 2-year post RT for all the 3 endpoints. The average Dmean of parotid glands was 41.5 Gy (range: 31.0 Gy-65.9 Gy, median: 40.7 Gy). No dosimetric parameters were significantly associated with xerostomia.
Conclusion: Significant proportion of patients still experienced long term xerostomia with IMRT. Dose-effect relationships between xerostomia and the parotid glands were not observed in this study.
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In the last two decades, advances in combining systemic therapy and radiation technology such as intensity modulated radiotherapy (IMRT) have allowed for improved survival with decreased rates of toxicities in nasopharyngeal cancer (NPC) [1–7]. Several randomized controlled trials have demonstrated the superiority of IMRT in parotid salivary gland sparing and in reducing xerostomia compared to conventional techniques such as two dimensional radiotherapy and 3DCRT (three dimensional conformal radiotherapy) [8–12]. However, even with modern IMRT planning, xerostomia is still one of the most common and disabling radiation-induced toxicities. In fact, the incidence of late and clinically significant xerostomia is reported in up to 30% of patients after treatment of IMRT [13,15–18].

Long term xerostomia can adversely affect dentition, speech, swallowing and mastication. Most patients with xerostomia experience difficulty eating their usual diet. Chewing and swallowing of food can become uncomfortable or even painful with most patients needing frequent sips of water while they eat, and food particles get stuck in their mouth or throat. Long term xerostomia is frequently associated with dental problems, oral discomfort, dysphagia for solid food and poor quality of life (QOL) [19–21]. Research on xerostomia and how it affects QOL has been the subject of many studies. Deterioration in physical, emotional and social functioning and global QOL was common among patients with radiation-induced xerostomia [20,22–24].

Because of the significant impact xerostomia can have on the QOL of NPC survivors, improvements in treatment delivery or technique are desirable when possible. As such, it is crucial to identify predictors of xerostomia in order to refine planning techniques and intensify rehabilitation efforts for patients at greatest risks of xerostomia. In this study, we prospectively investigated the relation of physician and patient rated xerostomia with the 3-dimensional dose distribution in the parotid and submandibular glands and with clinical and treatment related factors.

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Methods

Patients

Patients for the study were selected from a randomized phase II/III trial that was conducted between September 2004 and August 2012 at the National Cancer Centre Singapore [14]. The trial randomized 172 locally advanced NPC patients to either concurrent chemoradiation alone (CCRT arm, $n = 86$) or induction chemotherapy of gemcitabine, carboplatin and paclitaxel (GCP) in combination with CCRT (GCP arm, $n = 86$), and compared the survival, tumor control, toxicities and quality of life of patients between the 2 study arms. Details of the trial have been published elsewhere [14]. Briefly, all newly-diagnosed biopsy-proven NPC patients with Union for International Cancer Control (1997) stage T3-4NxM0 or TxN2-3M0; World Health Organization type II or III histology; Eastern Cooperative Oncology Group performance status 0 to 1; and adequate bone marrow, renal, and hepatic functions were eligible for the trials. The trial was approved by the SingHealth centralized institutional review board, and patient written informed consent was obtained before study entry.

Among the 172 patients recruited in the trial, the first 14 patients (6 from GCP arm and 8 from CCRT arm) who were recruited before 2007 were excluded from the study as their dosimetric data were not available.

Treatment and follow-up

Patients randomized to the CCRT arm received radiation therapy (RT) 69.96 Gy with weekly cisplatin 40 mg/m^2 for 8 weeks, and those randomized to the GCP arm received induction GCP (3 cycles of gemcitabine 1000 mg/m^2, carboplatin area under the concentration–time-curve 2.5, and paclitaxel 70 mg/m^2 given days 1 and 8 every 21 days) followed by CCRT. After treatment, patients were followed up every 2 months in the first year, every 4 months in the second year, every 6 months from the third to fifth year, then yearly afterward.

Radiation therapy

Patients included in this study were all treated with IMRT. Registration of diagnostic magnetic resonance imaging with planning computed tomography (CT) images was performed for all patients to aid delineation of target volumes and critical structures. The gross target volume (GTV) included all known gross disease (primary and lymph nodes) determined by clinical examination and imaging findings. A clinical target volume at 70 Gy (CTV_70) includes the entire nasopharynx and GTV with 3–5 mm margin. A further margin of 3–5 mm was added to generate planning target volume at 70 Gy (PTV_70). This margin was allowed to be compromised when the PTV_70 would overlap with critical structures (ie. Brainstem, spinal cord, optic nerves, optic chiasm). CTV at 60 Gy (CTV_60) covers the CTV_70, local structures at risk of microscopic spread (ie. Inferior half of sphenoid sinus, cavernous sinus, base of skull, anterior half of clivus, retropharyngeal nodes, parapharyngeal space, pterygoid fossae, posterior third of maxillary sinus and nasal cavity) and regional lymphatics (bilateral retropharyngeal lymph nodes, level II-V). Neck level Ib was electively irradiated if there were nodal involvement on the ipsilateral level II. PTV at 60 Gy (PTV_60) would cover PTV_70 and CTV_60 with 3 mm margin. The entire volume encompassing nasopharynx and both sides of the neck was treated in 1 volume with a simultaneous integrated boost to the primary tumor and pathologic lymph nodes. The dose to gross disease with margin was 69.96 Gy in 33 2.12-Gy fractions, whereas the rest of the volume received 60 Gy in 1.82-Gy fractions over the same period.

Dosimetry parameters

Dosimetric parameters were retrospectively retrieved from the respective dose volume histogram (DVH) in the RT planning system. These parameters included mean dose (Dmean) to the bilateral/ipsilateral/contralateral parotid glands and submandibular glands, absolute volume of the bilateral/ipsilateral/contralateral parotid glands, and the percentage of the bilateral/ipsilateral/contralateral parotid glands receiving >10 (V10), 20 (V20), 30 (V30), 40 (40), 50 (V50), 60 (V60) and 70 Gy (V70).

Xerostomia assessment

Xerostomia was evaluated based on 3 different assessments: physician-rated xerostomia (E1), patient-rated dry mouth (E2) and patient-rated sticky saliva (E3). For E1, salivary gland toxicity was assessed by physician using the Radiation Therapy Oncology Group (RTOG) acute toxicity morbidity scoring criteria from the start of CCRT until follow-up month 5, and the RTOG late radiation morbidity scoring criteria from follow-up month 6 onwards. E2 and E3 were respectively based on patient's ratings of dry mouth and sticky saliva in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-H&N35 questionnaire at baseline, induction cycle 2 (for patients on GCP arm only), CCRT week 4 & week 8, end of treatment, follow-up month 3, month 13, month 25, month 37, month 49 and month 60.

Endpoints and analysis cohorts

The primary endpoint was the presence of moderate to severe xerostomia at 2-year after completion of RT. Moderate to severe xerostomia was defined as patients assessed with grade 2 and over salivary gland toxicity (E1), and patients rated "Quite a bit" or "Very much" for dry mouth (E2) and sticky saliva (E3).

All patients completed their RT, except for 1 patient who had passed away due to neutropenia sepsis while on treatment. The latter was excluded from the analysis of this study, along with the other patients who were dead within 2 years after completion of RT (Fig. 1). Patients without RTOG late toxicity assessment at follow-up month 25 were excluded from the analysis of E1, and those without EORTC quality of life assessment at follow-up month 25 were excluded from the analysis of E2 and E3. In addition, patients who had moderate to severe xerostomia assessed based on EORTC QLQ-H&N35 questionnaire prior to start of CCRT were also excluded from the analysis of E2 and E3 as the interest of this study was to examine xerostomia because of IMRT.

Statistical analysis

Agreement between physician-rated and patient-rated xerostomia (E1 vs E2 and E1 vs E3) was assessed based on percentage agreement and Cohen's Kappa (κ). Strength of agreement based on Cohen's Kappa was interpreted as poor ($\kappa < 0$), slight ($\kappa = 0.00$–0.20), fair ($\kappa = 0.21$–0.40), moderate ($\kappa = 0.41$–0.60), substantial ($\kappa = 0.61$–0.80) and almost perfect ($\kappa = 0.81$–1.00) [25].

To detect significant differences in clinical variables and dosimetric parameters between patients with and without xerostomia at 2-year post RT, continuous characteristics were compared using the Mann-Whitney U test, and categorical characteristics were compared using the Chi-square test or Fisher's exact test, as appropriate.

The association of various clinical and dosimetric parameters with the presence of xerostomia at 2-year post RT was tested by fitting logistic regression models to estimate the odds ratio (OR). Multivariate analyses were performed on variables with $p < 0.10$ from the univariate analyses. Goodness of fit between the observed

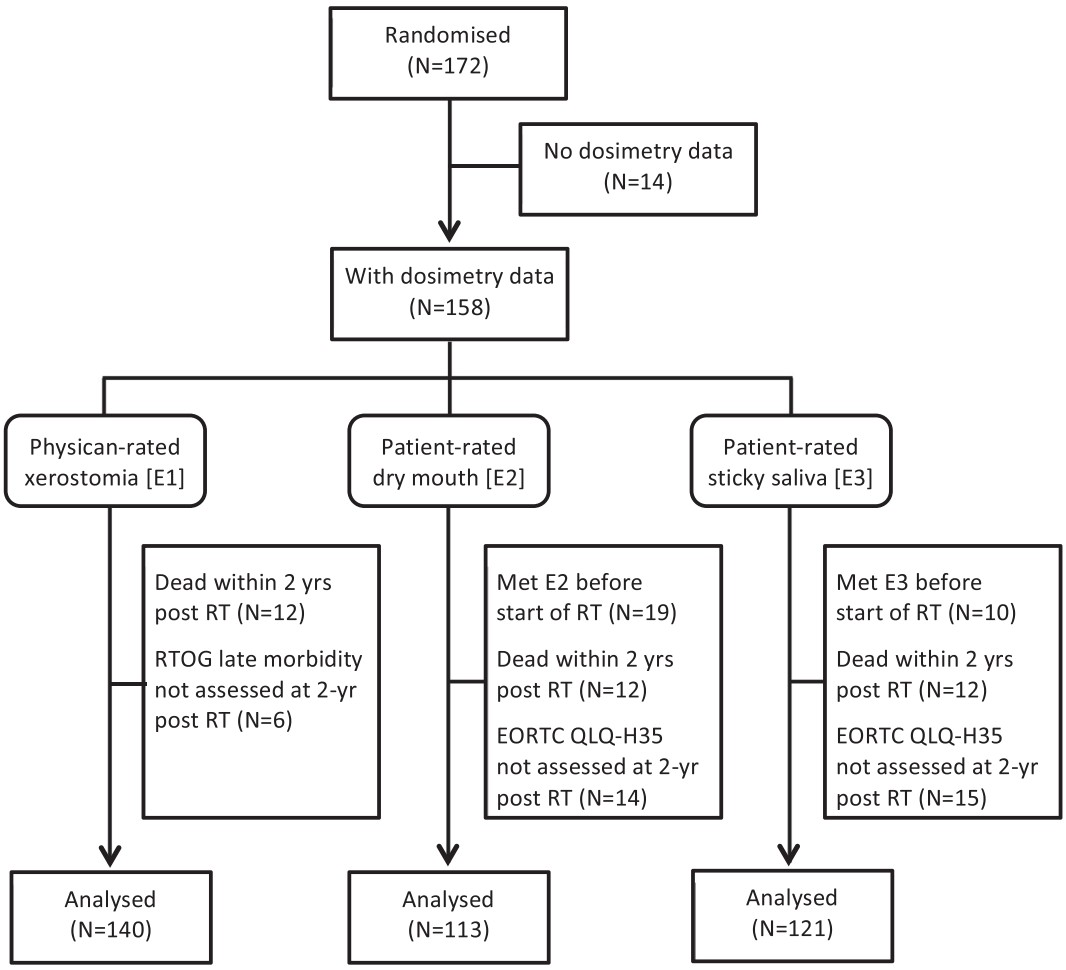


Fig. 1. Selection of patients for analysis of each endpoint.

and predicted number of outcomes of the multivariate model were assessed based on the Hosmer–Lemeshow (H–L) test. Discrimination ability of the multivariate model was assessed based on the area under the receiver operating characteristics curve (AUC).

All p-values were 2 sided and a p-value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results:

A total of 140, 113 and 121 patients were analyzed for E1, E2 and E3, respectively (Fig. 1). The percentage of patients with xerostomia at 2-year post RT was 26% based on E1, 36% based on E2, and 21% based on E3. In all patients, the average Dmean of bilateral parotids, ipsilateral and contralateral parotids were 41.5 Gy (range: 31.0 Gy-65.89 Gy), 41.5 Gy (range 30.1 Gy-69.9 Gy) and 41.4 Gy (range: 30.7 Gy-62.0 Gy) respectively.

Concordance between physician-rated and patient-rated xerostomia

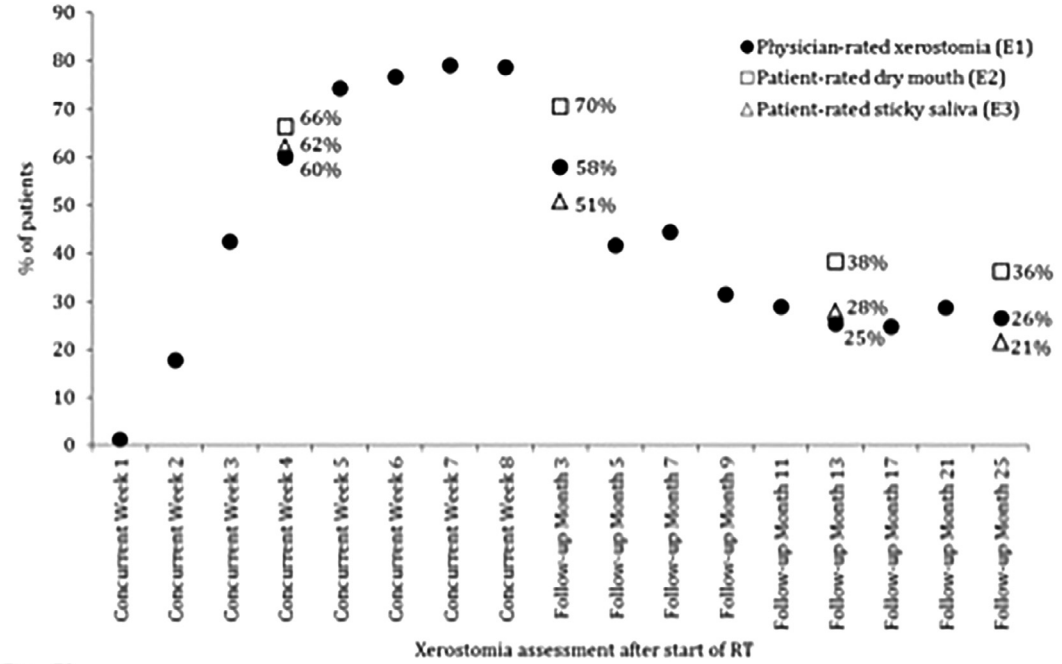
Based on physicians' assessments, most patients (74%) developed xerostomia within 5 weeks after starting RT (Fig. 2). Peak xerostomia toxicity was observed during CCRT week 7 and 8 with 79% of patients having grade 2 and over salivary gland. The percentage of patients with xerostomia dropped to 58% at follow-up month 3, 44% at month 7, 25% at month 13 and 26% at month 25. The trend of xerostomia as reported by patients based on either E2 or E3 was similar to that of E1. The percentage of patients with xerostomia at 1-year post RT was close to that at 2-year post RT for all the 3 endpoints.

The levels of xerostomia as assessed by physicians (E1) were consistently lower than those based on patient-reported dry mouth (E2) over time. Concordance between E1 and E2 were generally fair with Cohen's κ between 0.23 and 0.39. In comparison, the concordance between physician-rated xerostomia (E1) and patient-rated sticky saliva (E3) was poorer with Cohen's κ between 0.12 and 0.34.

Physician-rated xerostomia (E1)

Patient, tumor and treatment characteristics between patients with and without xerostomia are summarized in Table 1. Compared with patients with xerostomia, there were proportionately more patients without xerostomia who had received induction GCP (54% vs 38%, $p = 0.085$). Patients without xerostomia also had shorter RT duration (median: 44 vs 45 days, $p = 0.066$).

Among all patients, the median total volume of bilateral parotid glands was 67.7 ml and the median Dmean to the bilateral parotid glands was 40.8 Gy (range: 31.0–65.9 Gy). The median Dmean to the bilateral, ipsilateral and contralateral submandibular glands was 64.9 Gy (range: 53.4–72.2 Gy), 65.3 Gy (range: 51.3–72.2 Gy) and 65.3 Gy (range: 53.7–70.8 Gy) respectively. Dosimetry parameters for patients with and without xerostomia were comparable (Table 2).



E1 vs E2				
% agreement	62.2	65.2	73.1	70.8
Kappa	0.225	0.252	0.389	0.322
E1 vs E3				
% agreement	57.5	57.1	72.6	76.0
Kappa	0.124	0.141	0.299	0.336
E2 vs E3				
% agreement	63.5	53.1	32.5	28.2
Kappa	0.104	0.063	0.045	0.030

Fig. 2. Presence of moderate to severe xerostomia assessed at various timepoints.

Table 1
Clinical and treatment characteristics between patients with and without moderate to severe xerostomia at 2-year post RT.

	Physician-rated xerostomia (E1)			Patient-rated dry mouth (E2)			Patient-rated sticky saliva (E3)		
	Xerostomia (*N* = 37) (%)	No xerostomia (*N* = 103) (%)	*p*-value*	Xerostomia (*N* = 41) (%)	No xerostomia (*N* = 72) (%)	*p*-value*	Xerostomia (*N* = 26) (%)	No xerostomia (*N* = 95) (%)	*p*-value*
Age at randomisation (years)									
Median (range)	52 (21–69)	49 (21–74)	0.135	52 (21–69)	48 (23–74)	0.382	51 (21–66)	50 (23–74)	0.607
Gender									
Female	9 (24.3)	22 (21.4)	0.710	9 (22.0)	13 (18.1)	0.615	4 (15.4)	22 (23.2)	0.393
Male	28 (75.7)	81 (78.6)		32 (78.0)	59 (81.9)		22 (84.6)	73 (76.8)	
UICC 1997 T-stage									
0–2	17 (45.9)	44 (42.7)	0.734	18 (43.9)	33 (45.8)	0.843	12 (46.2)	42 (44.2)	0.860
3–4	20 (54.1)	59 (57.3)		23 (56.1)	39 (54.2)		14 (53.8)	53 (55.8)	
UICC 1997 N-stage									
0–1	9 (24.3)	18 (17.5)	0.365	11 (26.8)	13 (18.1)	0.273	6 (23.1)	20 (21.1)	0.824
2–3	28 (75.7)	85 (82.5)		30 (73.2)	59 (81.9)		20 (76.9)	75 (78.9)	
UICC 1997 overall stage									
III	26 (70.3)	64 (62.1)	0.376	30 (73.2)	46 (63.9)	0.312	20 (76.9)	64 (67.4)	0.349
IVA/IVB	11 (29.7)	39 (37.9)		11 (26.8)	26 (36.1)		6 (23.1)	31 (32.6)	
WHO histologic type									
II	1 (2.7)	9 (8.7)	0.291	1 (2.4)	5 (6.9)	0.415	2 (7.7)	7 (7.4)	1.000
III	36 (97.3)	94 (91.3)		40 (97.6)	67 (93.1)		24 (92.3)	88 (92.6)	
ECOG performance status									
0	18 (48.6)	42 (40.8)	0.407	17 (41.5)	30 (41.7)	0.983	12 (46.2)	40 (42.1)	0.712
1	19 (51.4)	61 (59.2)		24 (58.5)	42 (58.3)		14 (53.8)	55 (57.9)	
Induction GCP chemotherapy									
Yes	14 (37.8)	56 (54.4)	0.085	18 (43.9)	39 (54.2)	0.294	10 (38.5)	53 (55.8)	0.117
No	23 (62.2)	47 (45.6)		23 (56.1)	33 (45.8)		16 (61.5)	42 (44.2)	
RT treatment duration (days)									
Median (range)	45 (43–49)	44 (43–52)	0.066	44 (43–48)	44 (43–52)	0.667	44 (43–48)	44 (43–52)	0.372

* Based on Mann–Whitney *U* test for continuous characteristics such as age and RT treatment duration, and Chi-square or Fisher's exact test for categorical characteristics.

Table 2
Parotid and submandibular gland dosimetry parameters between patients with and without moderate to severe xerostomia at 2-year post RT.

	Physician-rated xerostomia (E1)			Patient-rated dry mouth (E2)			Patient-rated sticky saliva (E3)		
	Xerostomia (N = 37)	No xerostomia (N = 103)	p-value*	Xerostomia (N = 41)	No xerostomia (N = 72)	p-value*	Xerostomia (N = 26)	No xerostomia (N = 95)	p-value*
Bilateral parotid:									
Total volume (ml)	67.9 (42.3-146.8)	67.6 (35.8–140.2)	0.810	67.6 (35.8–123.6)	68.6 (42.1–140.2)	0.731	68.2 (36.0–111.1)	67.6 (42.1–140.2)	0.789
Mean dose (Gy)	40.6 (31.0–65.9)	40.8 (33.2–56.2)	0.759	40.4 (31.0–53.0)	40.8 (33.4–51.7)	0.470	40.6 (35.5–49.1)	40.2 (31.0–51.7)	0.374
% volume receiving >10 Gy	100 (99.9–100)	100 (100–100)	0.099	100 (99.9–100)	100 (100–100)	0.191	100 (100–100)	100 (99.9–100)	0.615
% volume receiving >20 Gy	97.6 (52.5–100)	96.7 (72.5–100)	0.623	95.8 (52.5–100)	96.7 (75.2–100)	0.667	96.8 (79.7–100)	96.2 (52.5–100)	0.339
% volume receiving >30 Gy	57.8 (36.1–100)	59.9 (36.2–99.4)	0.762	58.7 (36.1–96.4)	58.7 (37.0–97.8)	0.756	59.5 (44.3–96.4)	56.9 (36.1–97.8)	0.362
% volume receiving >40 Gy	44.7 (28.4–99.3)	44.4 (26.8–85.1)	0.607	43.0 (28.4–78.0)	44.4 (27.2–73.0)	0.591	45.0 (28.7–68.0)	43.2 (26.8–73.0)	0.389
% volume receiving >50 Gy	33.9 (20.3–95.9)	34.0 (14.3–63.0)	0.707	33.0 (19.9–63.0)	34.0 (19.3–62.4)	0.412	32.0 (20.0–54.1)	33.0 (18.0–62.4)	0.860
% volume receiving >60 Gy	24.3 (9.8–80.8)	22.9 (8.3–52.0)	0.618	22.0 (9.8–46.1)	23.2 (10.1–52.8)	0.407	22.0 (9.8–46.1)	22.4 (10.1–52.8)	0.900
% volume receiving >70 Gy	2.5 (0–39.5)	2.7 (0–24.1)	0.977	2.1 (0–11.2)	2.5 (0–19.3)	0.752	2.1 (0.02–10.8)	2.1 (0–19.3)	0.820
Ipsilateral parotid:									
Total volume (ml)	34.7 (19.8–74.5)	33.9 (19.0–66.0)	0.989	33.2 (19.0–61.2)	35.0 (20.1–66.0)	0.635	34.5 (19.0–56.1)	33.9 (20.1–66.0)	0.543
Mean dose (Gy)	40.6 (30.1–69.9)	40.6 (31.5–59.3)	0.714	40.6 (30.1–56.9)	40.5 (31.5–59.3)	0.635	42.5 (33.6–48.4)	40.0 (30.1–59.3)	0.352
% volume receiving >10 Gy	100 (99.9–100)	100 (100–100)	0.099	100 (99.9–100)	100 (100–100)	0.191	100 (100–100)	100 (99.9–100)	0.615
% volume receiving >20 Gy	97.4 (51.7–100)	96.4 (64.3–100)	0.853	96.5 (51.7–100)	96.7 (64.3–100)	0.760	97.2 (83.7–100)	96.3 (51.7–100)	0.110
% volume receiving >30 Gy	57.4 (36.6–100)	58.0 (36.1–100)	0.945	58.6 (36.6–99.0)	56.0 (36.1–99.0)	0.665	59.5 (41.8–96.2)	54.5 (36.1–99.0)	0.352
% volume receiving >40 Gy	43.4 (22.5–100)	43.8 (16.6–89.7)	0.714	42.9 (22.5–88.9)	43.1 (24.3–84.3)	0.633	43.6 (22.5–61.3)	42.0 (24.3–84.3)	0.534
% volume receiving >50 Gy	33.6 (12.5–100)	34.7 (8.0–72.7)	0.837	33.0 (12.5–72.6)	33.9 (13.4–72.7)	0.506	33.5 (12.5–52.0)	32.5 (13.4–72.7)	0.828
% volume receiving >60 Gy	22.8 (6.1–97.1)	24.8 (3.2–62.0)	0.843	23.0 (6.1–48.6)	24.8 (3.7–62.0)	0.439	22.9 (6.1–43.9)	22.5 (3.7–62.0)	0.972
% volume receiving >70 Gy	2.5 (0–62.8)	2.3 (0–32.2)	0.906	2.2 (0–18.5)	1.9 (0–32.2)	0.607	2.2 (0–15.6)	1.9 (0–32.2)	0.689
Contralateral parotid:									
Total volume (ml)	35.4 (20.6–72.2)	33.5 (16.8–74.2)	0.610	34.4 (16.8–62.3)	33.9 (20.1–74.2)	0.814	33.8 (16.8–55.1)	33.5 (20.1–74.2)	0.862
Mean dose (Gy)	41.4 (31.7–62.0)	41.0 (31.3–56.2)	0.473	40.1 (31.3–52.5)	41.1 (33.5–54.3)	0.515	40.6 (35.2–52.5)	39.4 (31.3–54.3)	0.603
% volume receiving >10 Gy	100 (100–100)	100 (100–100)	1.000	100 (100–100)	100 (100–100)	1.000	100 (100–100)	100 (100–100)	1.000
% volume receiving >20 Gy	97.0 (53.1–100)	97.1 (65.9–100)	0.757	96.4 (53.1–100)	97.0 (73.4–100)	0.370	96.9 (71.0–100)	97.0 (53.1–100)	0.942
% volume receiving >30 Gy	56.5 (35.6–100)	57.3 (33.1–99.0)	0.623	55.8 (33.1–96.7)	55.0 (34.9–96.6)	0.828	56.9 (42.8–96.7)	53.4 (33.1–96.6)	0.455
% volume receiving >40 Gy	44.4 (28.5–98.5)	42.5 (24.9–81.3)	0.299	41.0 (25.9–75.3)	42.8 (24.9–72.3)	0.718	42.2 (28.1–75.3)	42.0 (24.9–72.3)	0.482
% volume receiving >50 Gy	34.7 (21.0–91.9)	32.9 (17.4–65.3)	0.247	32.3 (18.4–56.2)	33.7 (17.4–63.6)	0.667	32.1 (18.4–56.2)	32.3 (17.4–63.6)	0.686
% volume receiving >60 Gy	24.5 (10.1–66.2)	23.6 (9.9–51.6)	0.231	23.1 (9.9–48.4)	23.7 (10.1–55.2)	0.560	22.8 (9.9–48.4)	22.1 (10.1–55.2)	0.803
% volume receiving >70 Gy	2.2 (0–25.1)	2.1 (0–29.7)	0.962	1.7 (0–16.7)	2.2 (0–29.7)	0.425	1.6 (0–16.7)	2.1 (0–29.7)	0.877
Bilateral submandibular: Mean dose (Gy)	64.7 (58.4–72.2)	65.0 (53.4–70.9)	0.684	65.7 (54.0–72.2)	64.1 (53.4–70.9)	0.079	66.0 (61.0–70.9)	64.2 (53.4–72.2)	0.067
Ipsilateral submandibular: Mean dose (Gy)	66.2 (56.2–71.4)	64.8 (51.3–72.2)	0.321	65.1 (53.3–71.4)	64.8 (51.3–72.2)	0.434	66.2 (59.3–71.4)	64.9 (51.3–72.2)	0.120
Contralateral submandibular: Mean dose (Gy)	65.6 (57.7–70.6)	65.3 (53.7–70.8)	0.422	65.4 (53.7–70.8)	65.1 (54.4–70.2)	0.237	66.0 (61.9–70.8)	65.1 (53.7–70.2)	0.099

Values were median (range).
* Based on Mann–Whitney U test.

On univariate analyses, receipt of induction GCP (OR = 0.51 [95% CI = 0.24–1.10], $p = 0.087$) and V40 (OR = 1.03 [0.99–1.06], $p = 0.074$), V50 (OR = 1.03 [0.99–1.06], $p = 0.071$), and V60 (OR = 1.03 [0.99–1.07], $p = 0.084$) of the contralateral parotid glands were potential predictors for presence of xerostomia at 2-year post RT (Table 3). Other dosimetry parameters, such as Dmean to the parotid glands, did not reach statistical significance. On multivariate analyses, receipt of induction GCP (OR = 0.50 [0.23–1.09], $p = 0.083$) and V60 of the contralateral parotid glands (OR = 1.03 [0.99–1.07], $p = 0.080$) were associated with near statistical significance with presence of xerostomia at 2-year post RT. The model achieved good calibration (H–L test's $p = 0.753$) but not discrimination (AUC = 0.64).

Patient-rated dry mouth (E2)

Based on E2, patients with and without xerostomia were similar in terms of their clinical and treatment characteristics and dosimetry parameters (Tables 1 and 2).

V20 of the contralateral parotid glands (OR = 0.96 [0.92–1.00], $p = 0.066$) was the only potential predictor for presence of xerostomia at 2-year post RT (Table 3). While the actual and predicted probability of xerostomia at 2-year post RT based on V20 had good agreement (H–L test's $p = 0.451$), V20 did not separate patients into those with and without xerostomia well (AUC = 0.55).

Patient-rated sticky saliva (E3)

There were no significant differences in the clinical and treatment characteristics and dosimetry parameters between patients with and without xerostomia based on E3 (Tables 1 and 2). On univariate analyses, V20 of the ipsilateral parotid glands (OR = 1.09 [0.99–1.19], $p = 0.053$), Dmean to the bilateral submandibular glands (OR = 1.13 [0.99–1.29], $p = 0.082$), Dmean to the ipsilateral submandibular glands (OR = 1.12 [0.99–1.27], $p = 0.077$), and Dmean to the contralateral submandibular glands (OR = 1.16 [0.99–1.35], $p = 0.051$) were potential predictors for the presence of xerostomia at 2-year post RT (Table 3). On multivariate analyses, V20 of the ipsilateral parotid glands was the only parameter that was associated with near statistical significance with the presence of xerostomia at 2-year post RT. Similar to the multivariate model of E1 and E2, V20 of the ipsilateral parotid glands achieved good calibration (H–L test's $p = 0.312$) but not discrimination (AUC = 0.60).

Discussion

Our study showed that there was no strong concordance between xerostomia assessments as scored by physician and reported by patients. This finding may not be surprising as studies have consistently demonstrated that physicians underestimate the incidence and severity of treatment toxicities when compared to patients' self -reporting, particularly for more subjective symptoms such as dry mouth and fatigue [26–28]. Traditional outcome measures of normal tissue toxicities to radiotherapy depend heavily and often exclusively, on physician reporting using grading scales or scoring systems whereas patient-reported outcomes (PROs) are measures of health-related quality of life obtained by patient self-reporting, without interference of their response by physicians. The discrepancy between physician-reported and PROs is widely reported and may reflect a real difference in perception between physicians and patients regarding toxicity or could be due to a defect in communication between physicians and patients.

PROs are increasingly important because they provide the patients' perspective on the impact of their disease or treatment on their health, function and quality of life that might not be captured by physician [29,30]. The recently published RTOG 1016 phase III trial is an example of a study that evaluated both survival and PROs in patients receiving cetuximab versus cisplatin in conjunction with radiotherapy. In addition to physician assessments of toxicity, RTOG 1016 also incorporated relevant PROs such as EORTC QLQ-C30 and EORTC QLQ-H&N35 [31]. The effectiveness of any therapeutic intervention has few dimensions, including not only the clinical effectiveness of the intervention, but also the benefit felt by patients as a result of receiving the intervention [32,33]. The results from our study demonstrated that even when prospectively collected within a phase III trial, subjective toxicities are subjected to under-reporting by physicians. Our findings strongly support the integration of PROs into clinical trials as primary outcome measures or to complement primary outcome measures.

Secondly, the results of this study showed that the 2-year physician- rated grade 2 or worse xerostomia incidence was 26% indicating that xerostomia is a significant long term effect after IMRT. Our results are consistent with most other reports. The authors of a retrospective study of 775 NPC patients reported a 20.1% incidence of grade 2 or greater physician-rated xerostomia at 1 year [16]. Another study by Zhao et al found that the incidence of $\geq$grade 2 xerostomia was 33% in patients with more than 1 year of follow up after IMRT [3]. Similarly, Wang et al reported an incidence of 25.9% $\geq$grade 2 xerostomia at 1 year in their study of 695 NPC patients treated with IMRT [13]. Our results also demonstrated that all the symptom scales declined after the start of RT and significantly improved within the first year. Salivary function seems to become stable after 1 year as the incidence of xerostomia at 13 months (25%) was similar to that at 25 months (26%).

Many investigators have reported a correlation between mean dose to the parotid glands and xerostomia, with a mixture of 3DCRT and IMRT and largely in patients with head and neck squamous cell cancers (HNSCC) [34–39]. In this study, we did not find such correlation. Possible reasons for this finding could be that all patients received bilateral neck irradiation and the dose distribution of the glands was within a relatively narrow range with only a modest number of patients in the low dose range.

A mean parotid gland dose threshold of $\leq$26 Gy was initially proposed as a planning objective for substantial sparing of the gland function by Eisbruch et al. [40]. Subsequently, the authors of the landmark QUANTEC paper concluded that severe xerostomia can be reduced if at least one parotid gland is spared with a mean dose of less than 20 Gy or if both parotid glands are spared with a mean dose of less than 25 Gy [35]. Generally, a consensus was formed that a mean dose to the parotid of less than 26–30 Gy can preserve its function substantially. In this study, the average Dmean to ipsilateral, contralateral and bilateral parotid glands was 41.5 Gy, 41.4 Gy and 41.5 Gy, respectively. Ultimately, despite the use of IMRT, none of the patients in this study met the QUANTEC criteria. This is mainly due to the major overlap of the PTV with the deep lobes of the parotid glands (Fig. 3). Moreover, overzealous effort in sparing the parotid glands can result in under-dosing part of the target volume which is at risk for disease recurrence. The parotid glands were located close to or in some cases, adjacent to various targets such as retropharyngeal lymph node, parapharyngeal extension in locally advanced tumor and site of cervical lymph node drainage. The specific location and pattern of lymphatic spread of NPC also required inclusion of both sides of the retropharyngeal and cervical nodal stations in the clinical target volume.

As a result, it is virtually impossible to meet the QUANTEC criteria for parotid glands in most cases even with IMRT and the mean dose to the parotid glands in NPC patients was consistently in excess of 30 Gy in previously reported IMRT series [4]. A prospec-

Table 3
Logistic regression for presence of moderate to severe xerostomia at 2-year post RT.

Variable (reference category)	Physician-rated xerostomia (E1)			Patient-rated dry mouth (E2)			Patient-rated sticky saliva (E3)		
	Univariate analysis	Final multivariate model		Univariate analysis	Final multivariate model		Univariate analysis	Final multivariate model	
	OR (95% CI)	OR (95% CI)	*p*-value	OR (95% CI)	OR (95% CI)	*p*-value	OR (95% CI)	OR (95% CI)	*p*-value
Age at randomisation (per year)	1.03 (0.99-1.07)			1.01 (0.97–1.05)			1.00 (0.96–1.04)		
Male (vs female)	0.85 (0.35–2.05)			0.78 (0.30–2.03)			1.66 (0.52–5.33)		
T-stage T3-4 (vs T0-2)	0.88 (0.41–1.87)			1.08 (0.50–2.34)			0.93 (0.39–2.21)		
N-stage N2-3 (vs N0-1)	0.66 (0.27–1.63)			0.60 (0.24–1.50)			0.89 (0.32–2.51)		
Overall stage IVA/IVB (vs III)	0.69 (0.31–1.56)			0.65 (0.28–1.51)			0.62 (0.23–1.70)		
WHO histologic type III (vs II)	3.45 (0.42–28.16)			2.99 (0.34–26.47)			0.95 (0.19–4.89)		
ECOG 1 (vs 0)	0.73 (0.34–1.55)			1.01 (0.46–2.20)			0.85 (0.36–2.03)		
Received induction GCP (vs no)	0.51 (0.24–1.10)*	0.50 (0.23–1.09)	0.083	0.66 (0.31–1.43)			0.50 (0.20–1.20)		
RT treatment duration (per day)	1.13 (0.90–1.41)			0.87 (0.68–1.12)			0.80 (0.57–1.12)		
Bilateral parotiod:									
Total volume (per ml)	1.00 (0.98–1.02)			1.01 (0.99–1.03)			1.00 (0.98–1.02)		
Mean dose (per Gy)	1.04 (0.97–1.12)			0.97 (0.88–1.06)			1.05 (0.94–1.17)		
% volume receiving >20 Gy (per %)	1.00 (0.95–1.06)			0.98 (0.93–1.03)			1.05 (0.97–1.13)		
% volume receiving >30 Gy (per %)	1.01 (0.98–1.04)			1.00 (0.97–1.03)			1.02 (0.99–1.06)		
% volume receiving >40 Gy (per %)	1.02 (0.99–1.05)			0.99 (0.96–1.03)			1.01 (0.97–1.06)		
% volume receiving >50 Gy (per %)	1.02 (0.99–1.06)			0.99 (0.94–1.03)			1.00 (0.95–1.06)		
% volume receiving >60 Gy (per %)	1.03 (0.99–1.06)			0.98 (0.94–1.03)			1.00 (0.95–1.06)		
% volume receiving >70 Gy (per %)	1.02 (0.96–1.09)			0.96 (0.87–1.07)			1.00 (0.90–1.12)		
Ipsilateral parotiod:									
Total volume (per ml)	1.00 (0.97–1.04)			1.02 (0.98–1.06)			1.02 (0.97–1.06)		
Mean dose (per Gy)	1.02 (0.96–1.09)			0.98 (0.91–1.06)			1.02 (0.94–1.12)		
% volume receiving >20 Gy (per %)	1.01 (0.96–1.06)			1.01 (0.96–1.05)			1.09 (0.99–1.19)*	1.09 (0.99–1.19)	0.053
% volume receiving >30 Gy (per %)	1.00 (0.98–1.03)			1.00 (0.97–1.02)			1.01 (0.99–1.04)		
% volume receiving >40 Gy (per %)	1.01 (0.99–1.04)			0.99 (0.96–1.02)			1.00 (0.97–1.04)		
% volume receiving >50 Gy (per %)	1.01 (0.98–1.04)			0.99 (0.96–1.02)			1.00 (0.96–1.04)		
% volume receiving >60 Gy (per %)	1.01 (0.99–1.04)			0.99 (0.95–1.03)			1.00 (0.95–1.04)		
% volume receiving >70 Gy (per %)	1.02 (0.97–1.07)			0.99 (0.92–1.06)			1.01 (0.93–1.09)		
Contralateral parotiod:									
Total volume (per ml)	1.01 (0.97–1.04)			1.00 (0.97–1.04)			0.99 (0.94–1.03)		
Mean dose (per Gy)	1.05 (0.98–1.12)			0.97 (0.89–1.05)			1.03 (0.94–1.14)		
% volume receiving >20 Gy (per %)	1.00 (0.95–1.04)			0.96 (0.92–1.00)*	0.96 (0.92–1.00)	0.066	1.00 (0.95–1.06)		
% volume receiving >30 Gy (per %)	1.01 (0.99–1.04)			1.00 (0.97–1.03)			1.02 (0.99–1.05)		
% volume receiving >40 Gy (per %)	1.03 (0.99–1.06)*			0.99 (0.96–1.03)			1.02 (0.98–1.06)		
% volume receiving >50 Gy (per %)	1.03 (0.99–1.06)*			0.99 (0.95–1.03)			1.01 (0.96–1.06)		
% volume receiving >60 Gy (per %)	1.03 (0.99–1.07)*	1.03 (0.99–1.07)	0.080	0.99 (0.94–1.03)			1.01 (0.96–1.06)		
% volume receiving >70 Gy (per %)	1.01 (0.95–1.08)			0.97 (0.89-1.05)			0.99 (0.91–1.09)		
Bilateral submandibular: mean dose (per Gy)	1.04 (0.93–1.16)			1.08 (0.97–1.21)			1.13 (0.99–1.29)*		
Ipsilateral submandibular: mean dose (per Gy)	1.05 (0.95–1.16)			1.06 (0.96–1.16)			1.12 (0.99–1.27)*		
Contralateral submandibular: mean dose (per Gy)	1.05 (0.94–1.18)			1.09 (0.97–1.22)			1.16 (0.99–1.35)*		
Performance of multivariate model									
Calibration (H–L test)		0.753			0.451			0.312	
Discrimination (AUC)		0.64			0.55			0.60	

OR, odds ratio; CI, confidence interval; H–L, Hosmer–Lemeshow; AUC, area under the receiver operating characteristics curve.
* $p < 0.1$ and included in multivariate model building.

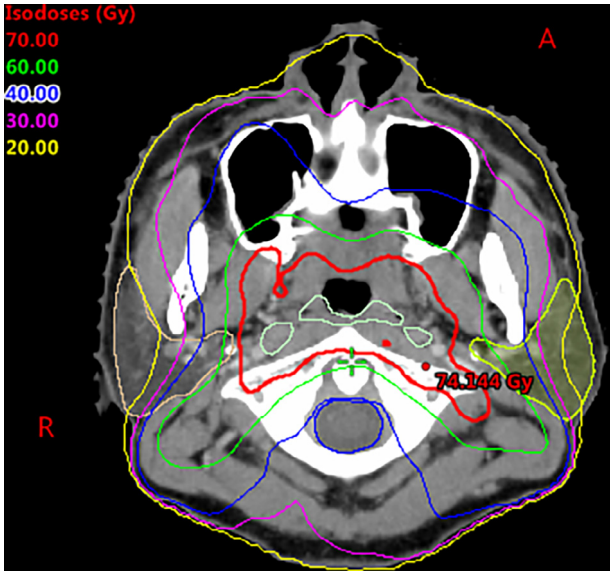


Fig. 3. Isodose distributions for IMRT plans on representatives axial image from the planning CT scan with 70 Gy isodose line in red, 60 Gy isodose line in green, 40 Gy isodose line in blue, 30 Gy isodose line in magenta and 20 Gy isodose line in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tive cohort study of 148 patients conducted by Yao et al investigated the dose distribution of organs at risk in NPC. The authors found that the Dmean of parotid glands lied within the range of 33–38 Gy [41]. Similarly, Zeng et al reported parotid gland mean dose of 31.3 Gy in 789 NPC patients treated with IMRT [16].

This study is not without its limitations. Although these data were prospectively collected, this study was limited to a large, tertiary cancer center which may affect the generalizability of the results. The evaluation of the correlation between dosimetric parameters and xerostomia was also limited by the fact that all the patients included in this study were following a standardized RT treatment plan according to a trial protocol and therefore had rather similar values for the various salivary gland DVH parameters. In addition, this study did not include patient receiving radiotherapy alone, therefore we were unable to examine the impact of chemotherapy on xerostomia. Nonetheless, several studies have helped to shed some light on this issue. Miah et al compared the incidence of $\geq$grade 2 acute and late physician-rated xerostomia between HNSCC patients treated with either IMRT or concomitant chemo-IMRT in 2 prospective studies. This study reported no significant difference in the incidence of acute (60.3% vs 64.7%, $p = 0.83$) and late (34% vs 43%, $p = 0.15$) physician-rated xerostomia with the addition of chemotherapy to IMRT [42]. The finding from a study by Zeng et al also provided additional evidence that chemotherapy was not a significant factor affecting xerostomia in NPC patients ($p = 0.211$) [16].

In summary, our study showed that a significant proportion of patients still experienced long term xerostomia with IMRT. The dose distribution of salivary glands was found to be relatively homogenous between the group of patients with and without xerostomia. Dose-effect relationships between xerostomia and the parotid glands were not observed in this study. Our results demonstrated that physicians underestimated the incidence of xerostomia when compared to patients' self-reporting. PROs should be incorporated into future studies to define endpoints that can provide direct evidence of treatment benefit.

Declaration of Competing Interest

The authors do not have any financial disclosure or conflict of interest to declare.

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