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Original Article

Saliva electrolyte analysis and xerostomia-related quality of life in nasopharyngeal carcinoma patients following intensity-modulated radiation therapy

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ABSTRACT

Background and purpose: Nasopharyngeal carcinoma (NPC) is one of the most common cancers in southern China and the first-line treatment is radiotherapy. Intensity-modulated radiation therapy (IMRT) can deliver high dose to cancer and low dose to normal tissue, but xerostomia is still one of the complications after IMRT. However, how the concentration of saliva electrolytes be affected by IMRT and the effects on the quality of life are still unknown. In this prospective study, 76 NPC patients were recruited from hospitals in Hong Kong to identify the change of saliva electrolytes and xerostomia-related quality of life before and after IMRT.
Methods and materials: Saliva and questionnaire were collected before IMRT, 1 month, 3 months, 6 months and 12 months after IMRT. The concentration of saliva electrolytes was detected using inductively coupled plasma-optical emission spectroscopy (ICP-OES).
Results: Saliva flow rate significantly decreased after IMRT. Decrease in the mean value of pH was observed but the difference is not statistically significant. The concentrations of potassium, iodine, and calcium decreased and chloride concentration increased after IMRT, while the concentrations of sodium, magnesium, copper or zinc were kept at the same level before and after treatment. Xerostomia-related quality of life was adversely affected by IMRT, but partially recovered after 1 year.
Conclusions: Our study revealed the change of saliva electrolytes and xerostomia-related quality of life in patients undergone IMRT for NPC.

Nasopharyngeal carcinoma (NPC), also known as the "Canton tumor", is one of the most common cancers in southern China. In Hong Kong, the Hong Kong Cancer Registry has noted that NPC was the 6th most common cancer in males with 599 new cases and an incidence rate of 17.7 in 100,000 in 2016. The mortality of NPC ranked 8th in male and 10th in both sexes [1]. The first-line treatment for nasopharyngeal cancer is radiation therapy. Xerostomia is a common, debilitating complication of radiation therapy for nasopharyngeal carcinoma [2]. The type and severity of side effects are directly related to radiation dosimetry, including total dose, fraction size, duration of treatment and the volume of tissue irradiated. Prevalence of xerostomia has been reported to be 73.5–93% [3,4]. The reduced saliva flow after radiotherapy makes the patients more susceptible to oral diseases and dental caries. Furthermore, patients will experience dry mouth which causes difficulty in speech and swallowing, adversely affecting oral functions. This significantly impairs quality of life, which further compromises nutritional intake and continuity of cancer treatment. Though there are several palliative treatments for xerostomia, none of those is definite or curative [5]. New techniques have been developed in recent years to focus radiation beams to the target tissue and avoid unnecessary irradiation of salivary gland tissue. One such technique is the intensity-modulated radiation therapy (IMRT). IMRT delivers dose distributions with partial sparing of the parotid gland tissue by administering a high dose to the part of the parotid gland positioned close to the tumor, while the rest of the gland receives low or no dose at all [6]. The IMRT is

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considered to be superior to conventional radiotherapy in terms of dosimetry and preservation of salivary gland function [7]. However, studies on the treatment of nasopharyngeal and oropharyngeal tumors with IMRT have shown that the preservation of parotid gland function is only partly achieved [8,9]. It has been reported that both saliva rate and quality of saliva reduced after IMRT [10]. We hypothesized that the concentration of electrolytes in saliva was changed after IMRT and quality of life was negatively affected due to xerostomia.

Human saliva consists of 99.5% water, and the other 0.5% includes electrolytes, mucus, glycoproteins, enzymes and antibacterial compounds such as secretory IgA and lysozyme. There are major salivary glands, including parotid, submandibular and sublingual glands, in charge of more than 90% saliva production, while the remaining is produced by the minor salivary glands [6]. Based on previous studies, radiotherapy may reduce saliva secretion and protein production. Stiubea et al. showed significantly increased concentration of sodium with an essentially unchanged concentration of potassium, calcium, magnesium and phosphate in an animal study [11]. Valdez et al. showed an increased content of chloride after radiotherapy [12]. However, for most of the ions in saliva, the change of concentration after radiotherapy especially in the form of IMRT is yet to be determined. In the present study, the inductively coupled plasma-optical emission spectroscopy (ICP-OES) was used to measure the concentration of saliva electrolyte in NPC patients before and after IMRT. The ICP-OES allows determination of elements with atomic mass ranging from 7 to 250 (Li to U), except inert elements (such as He, Ne, Ar, Kr, Xe, Rn).

Xerostomia is mainly a subjective symptom [13]. The Xerostomia Questionnaire is a patient-reported xerostomia-specific tool, which has been tested for its validity and reliability at the University of Michigan and has been widely used in clinical trials. The Xerostomia Related Quality of Life-Scale (XeQoLS) that was used in the investigation is a validated 15-question survey. The original version of this tool is in English. Recently, a Chinese version has been validated [14]. It is believed that the patients' perspective will help to understand the mechanisms that underlie the loss of salivary function and therefore offer a valuable contribution to clinical management of radiation-induced xerostomia, which currently relies largely on palliative therapies.

Previously a study showed salivary anionic changes after conventional radiotherapy for NPC, while the effects on quality of life were not revealed [15]. In this study, we aim to analyse the concentration of saliva electrolytes of NPC patients before and after IMRT, and to evaluate the influence of radiation-induced Xerostomia on quality of life of these patients.

Material & methods

Participants

This was a prospective study. 76 NPC patients from Queen Mary Hospital and Prince of Wales Hospital in Hong Kong treated with IMRT were recruited prospectively. Saliva was collected from these patients at 5 time intervals: before radiotherapy, 1 month after therapy, 3 months, 6 months and 12 months after therapy. The study was approved by the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster and the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee. Each subject was asked to sign an informed consent before participation.

Patients' socio-demographic information and medical-related characteristics were collected. Associated variables included age, gender, years of education, occupational status, marital status, annual family income, cancer stage, radiation dose, radiation dosages to major salivary glands, chemotherapy, dental hygiene, and co-morbidity.

Inclusion criteria:

1. Patients with a newly diagnosed histopathologically confirmed NPC;
2. Patients scheduled for IMRT;
3. Southern Chinese population, age older than 20 years;
4. Patients voluntarily participated in the study and signed the informed consent.

Exclusion criteria:

1. Patient had precious removal of any parotid or submandibular glands;
2. Previous cancer history;
3. Previous chemotherapy or radiotherapy history;
4. Pregnancy.

We also recruited 20 healthy people as a control group. Inclusion criteria: older than 20 years, no cancer history, no major medical history such as diabetes, no periodontal disease, and no medications taken. The socio-demographic information and medical-related characteristics were collected. 3.5–5 ml of saliva was collected from each participant for one time.

Collection of saliva

For accurate sample collection, subjects were requested to refrain from activities such as eating, drinking, tooth-brushing, cigarette smoking for at least 1 h prior to the collection of samples in sterile bottles. Subjects rinsed mouth with 20 ml of distilled water for 1 min for two times, and waited for at least 10 min after rinsing to avoid dilution of the saliva sample. 2% citric acid was used on the dorsum of tongue to stimulate saliva secretion. The subjects was instructed to let the saliva accumulate in the mouth and spit it out into the sterile bottles. The saliva collection lasted for 10 mins. While collecting saliva samples, stimulated salivary flow rate (mL/min) and pH were also measured using H135 Minilab Pocket pH Meters (Hach, USA). The saliva samples were stored in ice box and carried to the laboratory within 60 min.

Determination of salivary electrolyte concentration using ICP-OES

The salivary electrolyte concentration was determined by ICP-OES (Spectro Arcos, Kleve, Germany). 0.1 mL of saliva was diluted by 4.9 mL 2% (w/v) nitric acid to detect the concentration. The standard curves of sodium, potassium, magnesium, calcium, chloride and iodine ions were made by standard solution (Sigma-Aldrich, St. Louis, MO, USA), which run every time before detection. The concentration of the electrolyte was calculated through linear regression of the standard solution.

Quality of life questionnaire

XeQoLS is based on the earlier studies including the European Organization for Research and Treatment of Cancer Quality of Life Head and Neck and other earlier investigations with specific oral-pharyngeal cancer quality of life scales. The XeQoLS measures the impact of salivary gland dysfunction and xerostomia on the four domains of oral health-related quality of life including physical functioning, personal/psychological functioning, social functioning, and pain/discomfort. Each domain score is calculated by averaging the values of all the respective items. A total average XeQoLS score is also calculated. The domain and total average scores ranged from 0 to 4, with a higher score indicating greater adverse impact on daily life. The questionnaire was done at the same time with saliva collection during each visit.

Statistics

The related-samples Friedman's Two-way analysis of variance tests was used to evaluate the outcome of saliva pH value, flow rate, electrolytes concentration, and scores of QoL. $P < 0.05$ was considered statistically significant.

Results

A total of 76 NPC patients treated with IMRT were recruited. The mean age of the patients was 53 years, ranging from 25 to 83 years old (SD = 11.401). 76.3% of the patients were male, and 23.7% were female. This corresponds to the male/female ratio of NPC incidence (2.9:1) in Hong Kong [16]. 25.3% of patients were current smokers, which was much higher than the percentage of 10.5% reported for the general population in Hong Kong [17]. Drinking was reported in 4.0% of the patients.

Seventy-six percent of the patients were diagnosed as advanced stages (stage III and IV) NPC. The treatment planning system used was Eclipse from Varian. All patient were treated with IMRT using 6 MV photon with 9 evenly distributed fields. The most common prescribed dose to the high risk planning target volume (PTV1) including the primary NP tumor and enlarged nodes was 70 Gy and the prescribed dose to the intermediate risk planning target volume (PTV2) was 66 Gy in 33 fractions using simultaneous boost. The high risk PTV was generated from GTV primary or enlarged LNs with 5 mm margin and the intermediate risk PTV covered subclinical spread of disease around the primary and involved neck levels. Elective nodal irradiation equivalent to the low risk PTV in the reference would be given to uninvolved nodal regions in the neck. The dose constraint for bilateral parotid gland was set at mean dose of 26 Gy but priority was given to the PTVs [18]. In most cases, the medial part of bilateral parotid gland will be included within PTV2. The mean dose to right parotid gland ranges from 26.2 Gy to 50.8 Gy, with an average value of 36.3 Gy. While the mean dose to left parotid ranges from 30.1 Gy to 67.8 Gy, with an average value of 38.1 Gy.

Eighty-four present of the patients (84%) underwent chemotherapy. The standard chemotherapy was concurrent chemoradiotherapy using cisplatin for stage III, IV cases and for high risk stage II patients who presented with unilateral neck node(s) that were 3 cm or more in diameter or multiple unilateral neck nodes not involving the SCF. Adjuvant chemotherapy and induction chemotherapy was administered according to practice of individual center and individual patient's need. The tumor and treatment information of 75 patients (one patient was excluded due to incomplete medical record) is shown in Table 1.

Table 1
Demographic and clinical characteristics.

Characteristics	Patients (%)
Sex (n = 76)	
Male	58 (76.3)
Female	18 (23.7)
Smoking (n = 75)	
Yes	19 (25.3)
No	56 (74.7)
Drinking (n = 75)	
Yes	3 (4.0)
No	72 (96.0)
Stage	
I/II	18 (24%)
III/IV	57 (76%)
Chemotherapy	
Yes	63 (84%)
No	12 (16%)
Concurrent	63 (84%)
Induction	8 (10.7%)
Adjuvant	26 (34.7%)

Concurrent, induction and adjuvant shall under 'yes'.

There was no significant difference between the normal control and the baseline of the patients. The results of pH value and flow rate in patients are illustrated in Table 2 and Fig. 1. Significant decrease in saliva flow rate was observed after radiation therapy ($p < 0.000$), from a mean value of 0.57 mL/min to less than 0.1 mL/min. No significant recovery was observed during 1 year follow-up. Decrease in the mean value of pH was observed after radiotherapy although the difference was not statistically significant ($p = 0.086$), which was consistent with the previous research on conventional radiotherapy [15].

One month after radiation therapy, severe xerostomia was observed in patients and difficulty was encountered in collecting enough amount of saliva for ICP-OES analysis. Therefore, the electrolytes measured at 3 month after IMRT was used as the first follow-up. The results of electrolyte concentration are shown in Table 3 and Fig. 1. Potassium concentration decreased significantly at 3, 6, and 12 months after radiotherapy compared to the baseline. Significant decrease in iodine concentration was observed at 3 and 6 months follow-up, while no significant difference between baseline and 12 months ($p < 0.000$). The concentration of calcium decreased significantly at 3 months, but no significant difference was detected at 6 and 12 months. Interestingly, the concentration of chloride was increased at 6 and 12 months after IMRT. No significant change was observed in concentration of sodium, magnesium, copper or zinc.

The results of XeQoLS are shown in Fig. 2. Significant individual variance was observed in terms of the perception of dry mouth. However, when compared with the pre-radiotherapy value, significant changes were observed in all 14 questions indicating the QoL of patients was affected in all aspects in the questionnaire, including selection of food, eating, speaking, dental awareness, mucosa discomfort, social life and interpersonal relationships. It was worth mentioning that compared to 1 month post-radiotherapy, some aspects showed significant improvement during follow-up at 6 month and/or 12 months, e.g. item 2 mucosa discomfort, 4 social life, 5 eating, 9 enjoyment of life, 10 interference of daily activities, 12 taste sensation, and 13 overall QoL.

Discussion

Our study investigated the saliva flow rate, electrolytes and xerostomia-related quality of life in patients undergone IMRT for NPC. Saliva flow rate and concentrations of potassium, iodine, and calcium decreased after radiotherapy, while concentrations of sodium, magnesium, copper or zinc showed no significant difference. Interestingly, the concentration of chloride increased after IMRT. Xerostomia-related quality of life significantly decreased after IMRT, but partially recovered 1 year after treatment.

The decreased saliva flow rate and pH value could increase the risk of rampant dental caries in patients undergone IMRT for NPC. Oral cavity serves as a habitat for various kinds of bacteria including acidogenic bacteria such as streptococcus mutans and lactobacilli. The dietary sugars from food fragments provide substance for the fermentation of bacteria, producing organic acids such as lactic, acetic and formic acids, thus leading to drop in pH value on the tooth surface [19]. When pH drops below the critical value

Table 2
Results of pH value and flow rate (mean ± SD).

	Baseline (BL)	1 month	3 month	6 month	12 month	Group P value	Multiple comparison
pH	7.2669 (0.86233)	6.3921 (0.90476)	5.914 (0.7937)	6.1361 (0.8408)	6.4625 (0.87437)	0.086	NS
Flow rate	0.57 (1.16)	0.06 (0.15)	0.06 (0.15)	0.05 (0.05)	0.10 (0.27)	0.000	BL > 1 M, 3 M, 6 M, 12 M

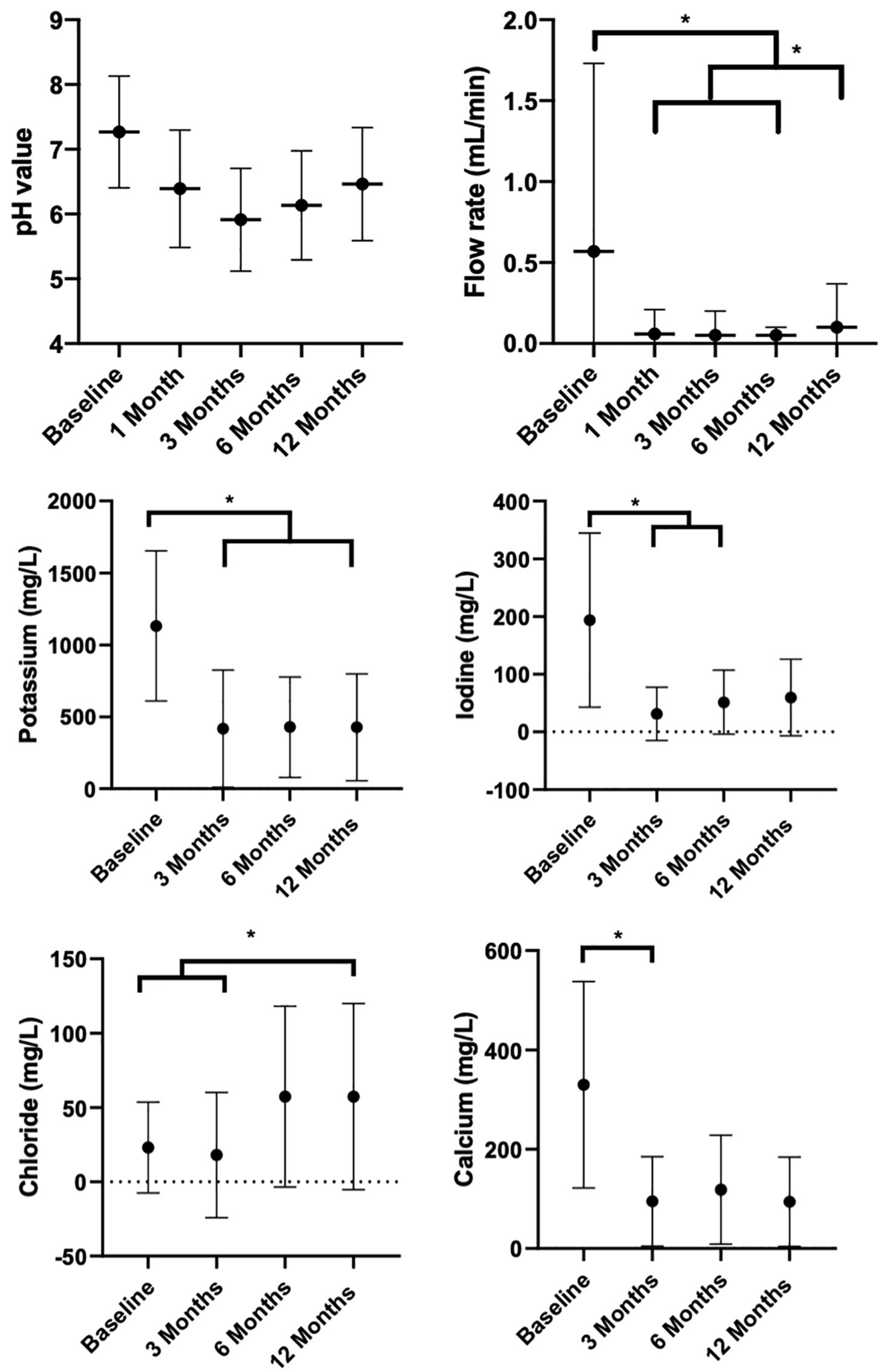

Fig. 1. Results of pH value, flow rate and saliva electrolytes. The error bar represents the standard deviation of the experiment. *:$p < 0.05$.

of approximately 5.5, solubility of calcium hydroxyapatite crystals greatly increases, leading to demineralization of tooth substance and formation of cavities [20]. Saliva helps defend against this process by two mechanisms. Saliva actively flushes away food fragments, diminishing bacteria from fermentation substance. And its neutral pH value and buffering ions such as HCO_3^- help resist the

Table 3
Results of saliva electrolytes.

	Baseline (BL)		3 month		6 month		12 month		Group *P* value	Multiple comparison
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Na	618.85	334.13	458.59	417.89	425.91	356.74	369.54	336.01	0.103	NS
K	1132.04	521.93	418.24	407.61	428.36	349.26	427.39	371.26	0.002	3 M, 6 M < BL
I	193.95	150.86	31.43	46.34	51.57	55.64	59.60	66.66	0.000	3 M < 12 M, BL; 6 M < BL
Cl	23.15	30.65	18.04	42.27	57.42	60.90	57.44	62.69	0.002	3 M, BL < 12 M
Ca	330.08	207.64	95.01	90.08	118.62	109.89	94.12	90.12	0.048	3 M < BL
Mg	160.83	146.23	121.68	121.61	87.89	82.79	74.92	70.61	0.506	NS
Cu	1.64	0.37	1.72	0.31	1.98	1.82	1.62	0.12	0.615	NS
Zn	0.03	0.15	0.00	0.00	0.02	0.11	0.02	0.15	0.572	NS

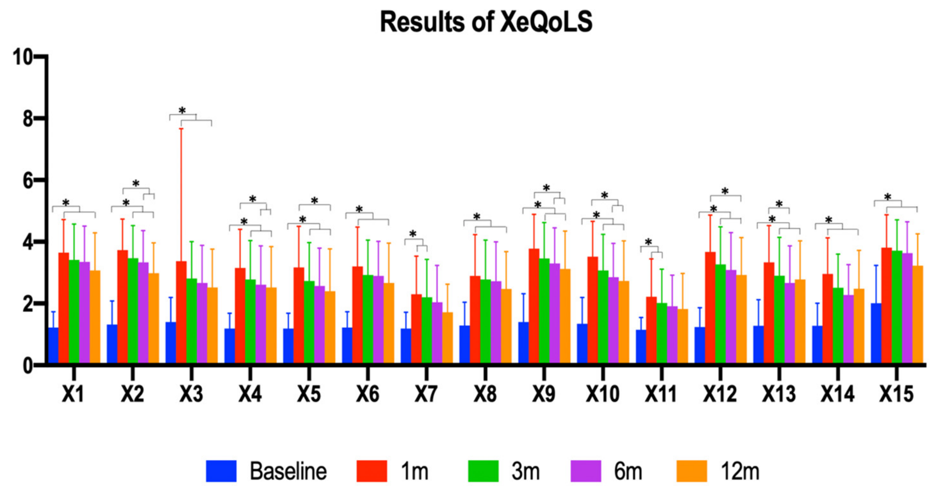

Fig. 2. Results of XeQoLS. The error bars represent the standard deviation of the scores. *:$p < 0.05$. X1: My mouth/throat dryness limits the kinds or amounts of food I eat. X2: My mouth/throat dryness causes discomfort. X3: My mouth/throat dryness causes a lot of worry or concern. X4: My mouth/throat dryness keeps me from socializing. X5: My mouth/throat dryness makes me uncomfortable when eating in front of other people. X6: My mouth/throat dryness makes me uncomfortable speaking in front of other people. X7: My mouth/throat dryness makes me nervous. X8: My mouth/throat dryness makes me concern about the looks of my teeth and mouth. X9: My mouth/throat dryness keeps me from enjoying life. X10: My mouth/throat dryness interferes with my daily activities. X11: My mouth/throat dryness interferes with my intimate relationships. X12: My mouth/throat dryness has a bad effect on tasting food. X13: My mouth/throat dryness reduces my general aspects of life. X14: My mouth/throat dryness affects all aspects of my life. X15: If you were to spend the rest of your life with your month/throat dryness just the way it is now, how would you feel about this?. Physical functioning: X1, X6, X10, X12. Pain/discomfort: X2, X3, X7, X9. Personal/psychological functioning: X8, X13, X14, X15. Social functioning: X4, X5, X11.

drop in pH and facilitate the quick restoration of normal pH after food intake, reducing the time when teeth are under acid challenge. Our results showed that in patients undergone IMRT for NPC, both mechanisms were impaired, resulting in higher risk of rampant caries.

Saliva contains various ions, such as sodium, potassium, calcium, magnesium, chloride, bicarbonate and phosphate, etc [21]. These ions act as a buffer, maintaining the acidity of the mouth, usually with a pH of 6.2–7.4. This prevents dissolution of minerals in dental hard tissues [22]. Saliva is hypotonic in nature, and the relatively low concentration of sodium, chloride, glucose and urea makes the dissolution of substances and thus taste sensation possible [23]. Saliva electrolyte can be influenced by gender, age, diet, medications and diseases [24]. The concentration of most electrolytes also can be influenced by salivary flow rate [25]. The final product of saliva is formed in two stages. The first stage is the secretion of NaCl-rich, plasma-like isotonic primary saliva by salivary acinar cells, and then primary saliva is modified by reabsorbing most of the NaCl and secreting $KHCO_3$ when passing through the secretory ductal system, resulting in the final hypotonic saliva [26]. Radiation causes major damage to both acini and secretory duct epithelial cells [12].

The underlying mechanisms for the alteration of saliva electrolytes identified in our study may be multifaceted and complex. First, the decreased concentrations of potassium, iodine and calcium could be a result of radiation induced damage of plasma membrane and the related ion channels in acinar cells. This was consistent with our previous findings that membrane stabilization agent had a protective effect on the secretory function of salivary glands during radiotherapy [27,28]. Second, the reduced concentrations of the three electrolytes might be due to the decreased salivary flow rate. When the primary isotonic saliva passed through the salivary ducts at a lower flow rate after IMRT, electrolytes were reabsorbed thoroughly, ending up with a lower concentration. Third, the reason for increased chloride and decreased potassium could be related to radiation induced damage of ductal system. The reabsorption of NaCl secreted by acinar cells is the main function of ductal system to produce the hypotonic saliva. Potassium is mainly secreted by ductal cells in the second stage of saliva secretion, mostly by the intralobular ducts, although extralobular ducts also support potassium secretion [26]. Accordingly, radiation induced damage of the chloride and potassium channels in the ductal system will lead to impaired function of chloride reabsorption and potassium secretion, leading to increased chloride and decreased potassium. Since saliva secretion is a complicated process involving multiple electrolyte channels and their interaction, these clinical findings warrant further in-depth mechanism studies.

The change of electrolytes concentrations would have different impacts on oral functions. Saliva has a much higher potassium concentration than plasma. Low salivary concentration of potassium might lead to low intracellular potassium level of taste bud, resulting in easier depolarization of calcium channel, which further affects calcium influx and release of neurotransmitters for the taste of bitter and sour. This may partially explain the taste alteration of patients after radiation therapy. Iodide in saliva can serve as an antioxidant, apoptosis-inductor and tumor suppressor [29]. Decreased level of iodide in the long run may increase the risk of oral and salivary gland diseases. And importantly, decreased concentration of calcium ion leads to less effective remineralization of teeth, contributing to rampant caries of patients after radiotherapy.

In terms of XeQoL, psychosocial and functional impacts were greatest in the early period. There was significant improvement at post-radiotherapy 6 and 12 months when compared with 1 month, while no significant improvement in flow rate and electrolyte concentration was observed. This means the QoL is more of a subjective feeling of the patients and not directly related with the actual saliva flow rate and component. It may be affected by patient expectation, coping strategies, and changes in the way how a patient evaluates overall well-being and satisfaction over time. The increase in QoL may be attributed to patients getting used to the dry mouth condition and utilizing different methods to alleviate the problems such as frequent rinsing of mouth and adequate fluid intake. This provides medical professionals with possible strategies to improve the QoL of patients after radiotherapy, such as pre-treatment psychological preparation for the dry mouth and providing timely counselling and coping strategies after the radiation therapy. The aim is to help the patients to adjust their expectations, understand salivary gland hypofunction and xerostomia, and learn how to live with it.

There are certain limitations of our study. Whole saliva was used for analysis instead of single gland saliva. This was limited by the total volume of saliva after radiation therapy. For some of the patients, saliva was scarce after radiation therapy even with acid stimulation. Technically, only by collecting the whole saliva, we were able to obtain enough saliva for analyses of pH and electrolytes. Therefore, our results can only apply to whole saliva instead of single gland saliva. And it was for the same reason that stimulated whole saliva (SWS) was used instead of unstimulated whole saliva (UWS), although UWS may be more directly related to daily perception of dry mouth. In terms of SWS, percentage contribution of saliva component is different under different stimulations. In this study, the only stimulating agent used was citric acid. However, this cannot totally mimic the stimulation caused by eating and chewing, which also involves other factors such as smell and taste taking part in stimulating saliva flow. The results of this study can reflect the function level of salivary glands after IMRT but it may not be completely correlated to the SWS secreted during eating.

In conclusion, severe xerostomia was observed in many patients after IMRT. The concentration of potassium, iodine, and calcium decreased but chloride concentration increased after IMRT, while the concentration of sodium, magnesium, copper or zinc were kept at the same level before and after treatment. Patients' XeQoLS was adversely affected by IMRT, but partially recovered after 1 year.

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Competing interest

The authors declare no potential conflicts of interest.

Author contribution

X.M. Lan contributed to conception, design, data acquisition and interpretation, performed all statistical analyses, drafted the manuscript; J. J. Pu contributed to data acquisition and interpretation, drafted and critically revised the manuscript; K. C. W. Wong, W. Qiao, W.F. Yang and S. Pang contributed to data acquisition; J.Y. K. Chan and D.L.W. Kwong contributed to design and data acquisition, critically revised the manuscript; Y.X. Su, contributed to conception, design, and data interpretation, critically revised the manuscript. All authors approved the final manuscript for publication.

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