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Evaluation of radiation-induced changes to parotid glands following conventional radiotherapy in patients with nasopharygneal carcinoma

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Objectives: Xerostomia is a common post-radiotherapy (post-RT) complication in nasopharyngeal carcinoma (NPC) patients. This study evaluated the relation of post-RT parotid gland changes with the dose received.
Methods: Data from 18 NPC patients treated by radiotherapy between 1997 and 2001 were collected. Parotid gland volumes were measured and compared between their pre-RT and post-RT CT images; both sets of CT were conducted with the same scanning protocol. Doppler ultrasound was used to assess the haemodynamic condition of the glands after radiotherapy. Doppler ultrasound results were compared against 18 age-matched normal participants. A questionnaire was used to evaluate the patients' comments of xerostomia condition. Radiotherapy treatment plans of the participants were retrieved from the Eclipse treatment planning system from which the radiation doses delivered to the parotid glands were estimated. The correlations of parotid gland doses and the post-RT changes were evaluated.
Results: The post-RT parotid glands were significantly smaller ($p<0.001$) than the pre-RT ones. They also demonstrated lower vascular velocity, resistive and pulsatility indices ($p<0.05$) than normal participants. The degree of volume shrinkage and subjective severity of xerostomia demonstrated dose dependence, but such dependence was not definite in the haemodynamic changes.
Conclusion: It was possible to predict the gland volume change and subjective severity of xerostomia based on the dose to the parotid glands for NPC patients. However, such prediction was not effective for the vascular changes. The damage to the gland was long lasting and had significant effects on the patients' quality of life.

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Xerostomia is one of the commonest radiation-induced complications in nasopharyngeal carcinoma (NPC) patients after a radical course of radiotherapy [1, 2]. Persistent xerostomia, which is due to the damage of the parotid glands, causes difficulties in mastication and swallowing and enhances the risks of dental problems; these subsequently degrade the quality of life in long-term survivors [3, 4].

With the recent advancements in radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), highly conformal dose distributions are possible and the sparing of parotid gland can be made more effective. However, conventional radiotherapy protocol for NPC is still used in some centres, and the treatment protocol is to employ lateral opposing beams to the face and upper neck plus an anterior beam to cover the lower neck. This inevitably irradiates the parotid glands to a mean dose of over 45 Gy, with the medial portion receiving as high as 60 Gy [5, 6].

Up to now, the mechanism of parotid gland damage and saliva reduction due to radiation is largely unknown. It is postulated that the saliva secretion of the parotid glands is related to the changes in morphology and vascular condition as a result of radiation therapy [7]. CT is a useful imaging tool for monitoring the response of radiation therapy by providing morphological information of the head and neck structures, including the parotid glands. For the assessment of post-radiotherapy (post-RT) vascular changes of parotid glands, there has been a report of dose-dependent increases in the extracellular extravascular space (EES) and decreases in vascular permeability using MRI [8]. However, the variation of haemodynamics in post-RT intraparotid vessels, which is useful for better understanding of the physiological changes of the parotid glands, is still unclear. Doppler ultrasonography is effective in the evaluation of the gland haemodynamics such as the blood flow velocity and resistive index, which are useful parameters in the assessment of the vasculature of the parotid gland [7]. Our study hypothesised that high-dose radiation to the parotid gland would destroy the acini and granules, which would alter the pressure on the blood vessels and result in changes of the blood velocity. More importantly, there is scant information about the relationships between these parameters with the radiation dose delivered to the glands. The knowledge of these relationships can provide useful references for the prediction of the severity of

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xerostomia after radiotherapy, and better understanding of how the complication will affect the quality of life in long-term survivors.

The objectives of this study are to assess the change of volume, blood flow velocity and vascular resistance of the post-RT parotid gland and evaluate their correlations with the radiation dose received and the subjective assessment of the severity of xerostomia from NPC patients.

Methods and materials

18 NPC patients (11 men and 7 women, age range 41–63 years, mean age 51.0 years) treated by conventional two-dimensional external beam radiotherapy between 1997 and 2001 were recruited (patient group). Radiotherapy consisted of two phases. Phase I treatment started with two large lateral opposing faciocervical fields covering the base of the skull upper cervical lymphatics *en bloc* to 40 Gy. The lower neck was irradiated with an anterior cervical field to 40 Gy. Phase II treatment used a 3-field technique with one anterior and 2 wedged lateral opposing facial fields for another 28 Gy (Figure 1). The neck was treated with a separate anterior cervical field and midline shield for another 26 Gy. Both phases used 6 MV photons and involved the irradiation of both parotid glands. The total prescribed dose to the tumour was 66–68 Gy delivered in 2 Gy daily fractions. An additional parapharyngeal boost dose (10 Gy) was given using a 6 MV photon posterior oblique field (Figure 2) if there was parapharyngeal extension of disease at diagnosis [9]. All patients were treated with radiotherapy alone and completed treatment for more than 3 years (3 years, n=7; 4 years, n=6; 7 years, n=3; 8 years, n=2) with no sign of recurrence at the time of participation in the present study. In addition, all patients did not have any known salivary gland disease before radiotherapy.

CT scan images were used to estimate the volume of the parotid glands. 2 sets of CT scans were performed on the 18 participants, 1 before radiotherapy and the other 1 at about 2–3 years after radiotherapy, which was a routine protocol for NPC patient follow-up in local departments. Both sets of CT were performed with contrast following the routine head and neck protocol, with slice thickness of 3 mm at the levels covering the parotid glands. After the retrieval of CT images from the database, the volumes of the gland before and after radiotherapy were generated from the Eclipse treatment planning system (Varian Oncology Systems, Palo Alto, CA) by delineating the parotid glands on the corresponding CT slices by the same investigator. The percentage gland volume change (dV) was used to indicate the differences between the pre-RT and post-RT volumes. A paired t-test was used to study the significance of their differences. The correlation between dV and the total mean parotid gland dose was evaluated by the Pearson correlation test.

Ultrasound examination of the parotid glands of the participants was performed in 2008, about 8–11 years after completion of radiotherapy. The examinations were carried out by the same operator, who was blinded to the radiotherapy protocols received by the participants, with a 12–5 MHz linear transducer (Philips HDI 5000, Bothell, WA). For each parotid gland, the blood flow velocity (peak systolic velocity (PSV) and end diastolic velocity (EDV)) and vascular resistance (resistive index (RI) and pulsatility index (PI)) were measured using the power Doppler and spectral Doppler sonography. PSV and EDV were indicators of blood flow velocity during the systole and diastole phases of the cardiac cycle, respectively, whereas RI and PI were indicators of the pressure exerted on the blood vessels. The settings of the power Doppler ultrasound were standardised for high sensitivity, with a low wall filter to allow detection of vessels with low blood flow. Pulsed repetition frequency

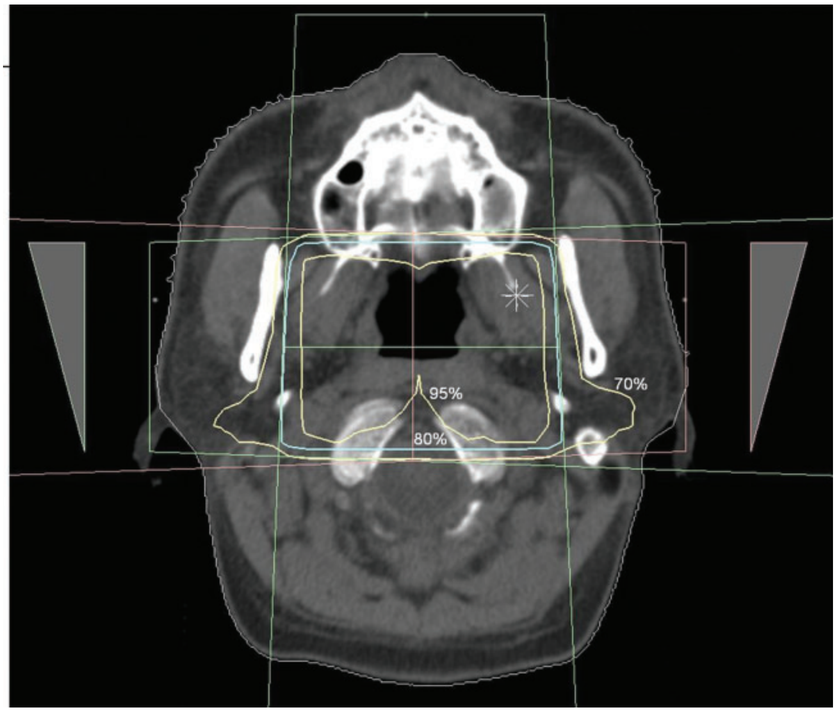

Figure 1. Dose distribution of the Phase II three-field technique at the principal plane. The entire nasopharynx is enclosed by the 95% isodose level. The medial portions of the parotid glands receive over 70% of the isodose level.

Figure 2. Field orientation and dose distribution of the posterior oblique faciocervical field for the boost treatment of the parapharyngeal region. The prescribed dose is at the 90% isodose level, which encompasses a considerable portion of the parotid gland.

(PRF) was 700 Hz, and medium persistence was used. On spectral Doppler sonography, the sample volume was standardised for 1 mm, a low wall filter was used and the PRF was adjusted until the spectral waveforms were demonstrated without aliasing. Angle correction was 60° or below. Measurements were obtained at random locations of three vessels that consistently demonstrated three consecutive Doppler spectral waveforms (Figure 3). For each parotid gland, the mean PSV, EDV, RI and PI were calculated.

To evaluate changes in the haemodynamics of the parotid gland after radiotherapy, another 18 healthy participants (normal group), who were age (±3 years) and gender matched with the patients, and with no history of salivary gland disease and radiotherapy or surgery in the head and neck region, were also recruited. All healthy participants received ultrasound examination of the parotid glands according to the standardised scanning protocol as for the patient group. This was based on the assumption that healthy participants with the same age and gender would demonstrate similar haemodynamics in the parotid gland, and deviations of the ultrasound findings in the patient group would indicate changes due to the radiation effect. The haemodynamic results of both patients and normal participants were recorded and compared using a paired *t*-test. The differences of PSV, EDV, RI and PI between the participants in the patient group and the matched normal participants (dPSV, dEDV, dRI, dPI) were calculated by subtracting the patient group readings from that of the normal group. Correlations between the d-parameters and the total mean parotid gland doses were evaluated by the Pearson correlation test. All participants in the patient group and healthy participant group had the study procedures explained and written consent was obtained before the ultrasound examination.

To estimate the doses received by the parotid glands, the participants' localisation radiographs, treatment plans retrieved from the Eclipse treatment planning system (Varian Oncology Systems), treatment records and prescriptions were collected. For each phase of treatment (including the two phases ± parapharyngeal boost), the mean doses to the parotid glands were calculated by correlating the dose distributions with the anatomical information in the CT images. Their estimated total mean doses were calculated by conducting plan summation of all phases of radiotherapy treatment using the treatment planning system.

In addition, all participants of the patient group were required to complete a structured and validated questionnaire adapted from Zimmerman et al [10]. The questionnaire consisted of five questions and was used to assess the condition of xerostomia by collecting the patients' comments on its severity in terms of its impact on their daily life including (1) difficulty in swallowing and mastication, (2) difficulty with speech, (3) interruption of sleep, (4) discomfort of mouth and (5) dryness of mouth at the time of this study. A continuous scale from 0 to 10 was used to assess the severity of individual conditions, with "0" implying the least severe condition and "10" the most severe condition. Apart from the individual question scores, an overall "impact factor"

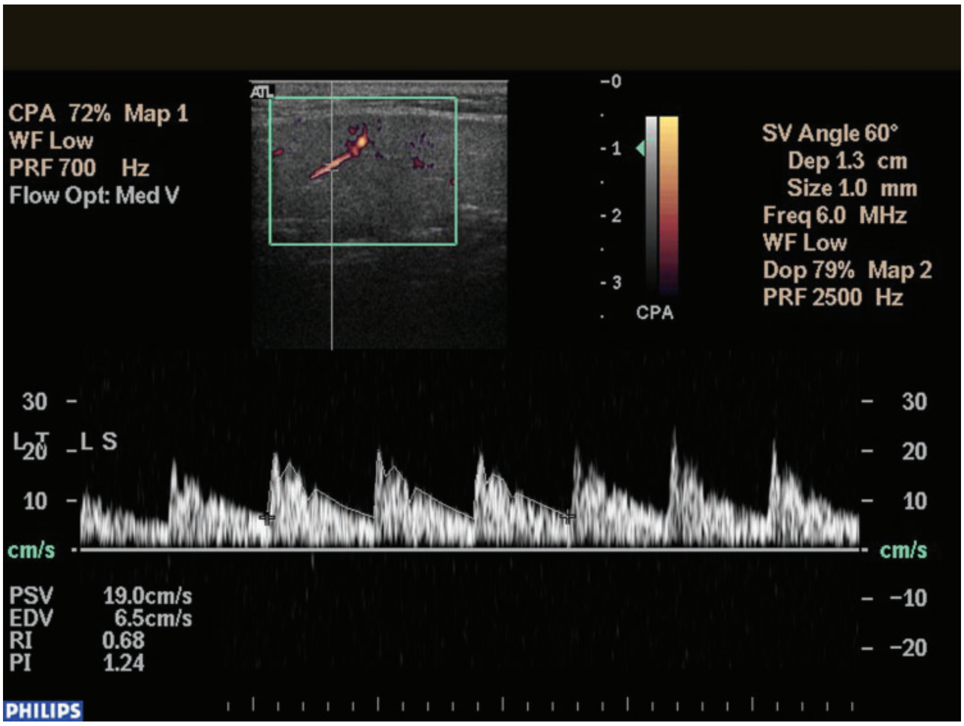

Figure 3. Spectral Doppler sonogram showing the measurement of blood flow velocity (peak systolic velocity (PSV) and end diastolic velocity (EDV)) and vascular resistance (resistive index (RI)) of a normal parotid gland. Note the average of the measurements is obtained from three consecutive waveforms.

(IF), which was also calculated by taking the average scores of the five questions, was used to indicate the patient's subjective xerostomia severity. In addition, each patient was also asked to give a subjective assessment on the percentage of salivary function at the time of assessment compared with their salivary function before radiation treatment (residue percentage (RP)). The IF and RP were also checked against the total mean parotid gland doses for correlation using the Pearson correlation test.

This study was approved by the Human Subject Ethics Subcommittee of the Department of Health Technology and Informatics of the Hong Kong Polytechnic University. All participants signed a consent form prior to the study.

Results

In addition to the routine radiotherapy course, 11 out of the 18 patients received the parapharyngeal boost treatment, which increased the dose to the ipsilateral parotid gland. The total maximum and mean doses received by the parotid glands ranged from 38.1 Gy to 64.4 Gy.

The post-RT parotid gland volumes in all patients were smaller than that of the pre-RT glands. The mean percentage

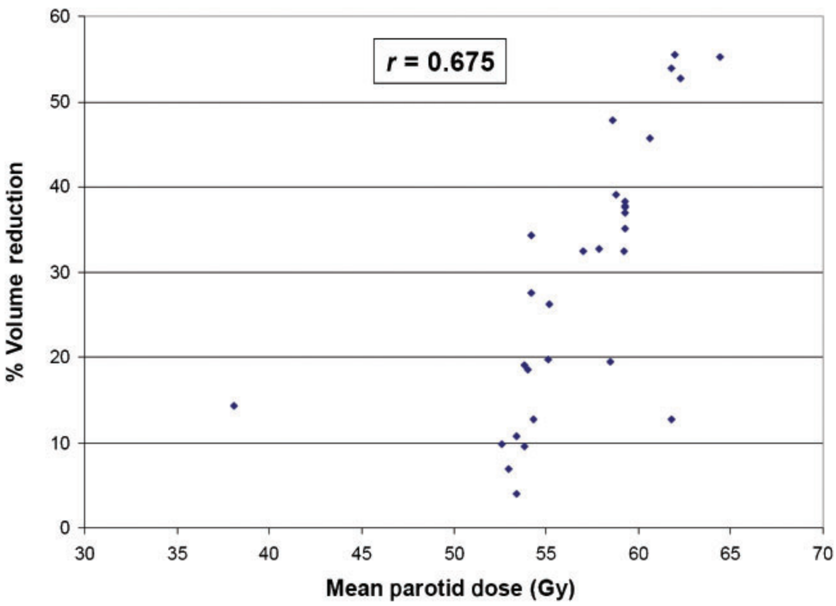

Figure 4. Scatter plot of the post-radiotherapy percentage volume reduction in parotid gland (dV) against the total mean parotid gland dose.

Table 1. Comparison of the Doppler ultrasound study on the haemodynamic parameters of the parotid glands between the patient group and normal group

	Patient group (n=36)		Normal group (n=36)		Paired t-test p-value
	Mean	SD	Mean	SD	
PSV (cm s^{-1})	8.14	$\pm$2.56	14.71	$\pm$6.13	0.001
EDV (cm s^{-1})	3.06	$\pm$0.96	3.92	$\pm$0.67	0.007
RI	0.65	$\pm$0.07	0.73	$\pm$0.09	0.003
PI	1.09	$\pm$0.18	1.51	$\pm$0.48	0.004

PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistive index; PI, pulsatility index; SD, standard deviation.

volume difference (dV) of all the 36 parotid glands, taking into account the left and right sides, was extremely significant (paired t-test, $p<0.001$). The overall mean volume reduction was 12.2$\pm$7.2 cm^3, which was about 35% of the gland volume before radiotherapy. The degree of volume reduction showed high correlations with the total mean doses received by the parotid gland (Figure 4).

36 parotid glands from the patient group and healthy participant group were scanned by ultrasound. In the ultrasound examinations, the mean values of PSV, EDV, RI and PI of normal participants were significantly higher than that of the post-RT patients (Table 1) ($p<0.05$). However, the differences in these four parameters between the patients and matched normal participants did not show correlation with the total mean dose received by the parotid glands (Figure 5a–d).

The scores for individual questions in the questionnaire from the patient group are shown in Figure 6. The impacts on swallowing and mastication were relatively greater, whereas the interruption of sleep was less severe. Besides, the overall IF of the 18 participants in the patient group ranged from 2.18 to 6.34, with a mean value of 4.40

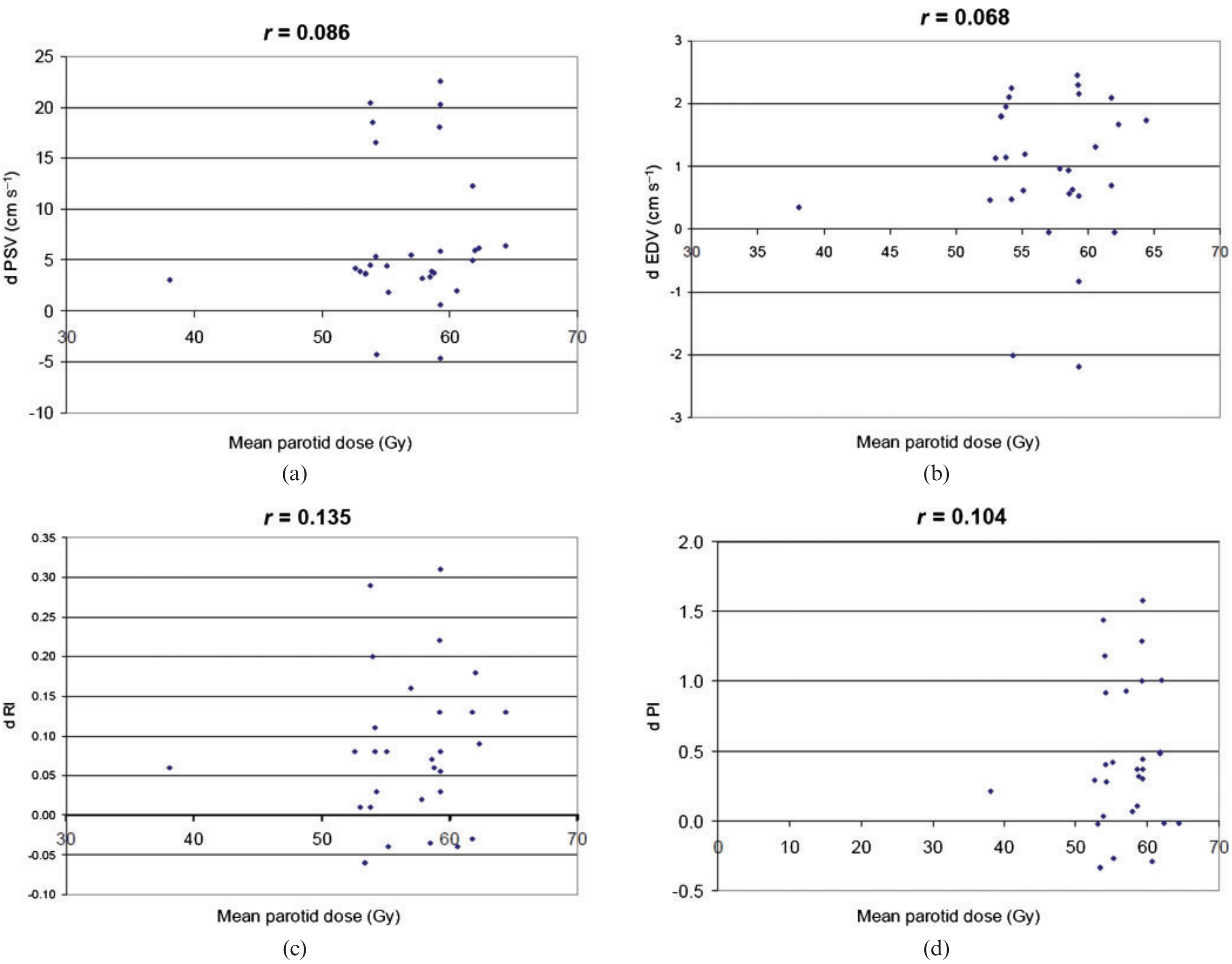

Figure 5. (a–d) Scatter plots showing the differences of the haemodynamic parameters between participants in the patient group and normal group against the total mean parotid gland doses: (a) dPSV (peak systolic velocity), (b) dEDV (end diastolic velocity), (c) dRI (resistive index) and (d) dPI (pulsatility index).

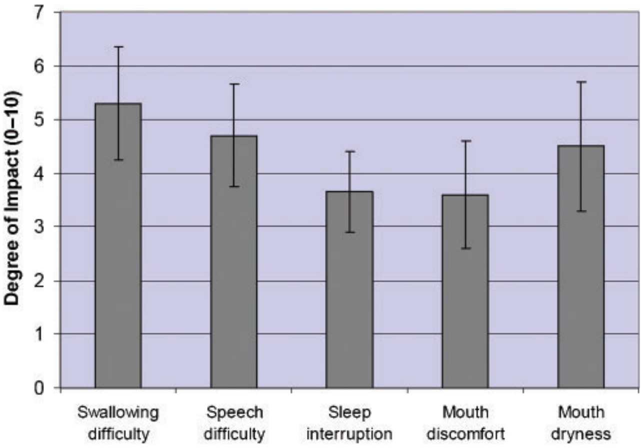

Figure 6. A histogram showing the summary results from the xerostomia questionnaire on the post-RT (radiotherapy) patients.

(Table 2). The range of residue percentage (RP) was from 20.0% to 60.0%, with a mean of 39.0%. The IF showed positive correlation with the mean parotid gland dose (r=0.614) whereas the RP showed a negative correlation (r=−0.869).

Discussion

Post-RT parotid glands demonstrated loss of gland parenchyma and acinar cell atrophy [11, 12], which was responsible, in part, for the more heterogeneous, variable hyperechocity that appeared in the ultrasound scan [7] and gland volume shrinkage in CT images.

The post-RT parotid glands demonstrated an average of 35% volume reduction compared with normal glands, as measured from the CT images, with the differences being extremely significant ($p<0.001$). More important, the magnitude of shrinkage (dV) was associated with the total mean doses delivered to the glands. The findings were in line with the studies by Wang et al [13] and Teshima et al [14], who reported that the gland volume reductions correlated significantly with the mean dose. This revealed the fact that a higher radiation dose to the parotid gland would cause greater loss and atrophy of acinar cells, which subsequently leads to shrinkage in the gland. The atrophy of the acinar cells was also believed to be the main cause of impaired salivary secretion leading to xerostomia.

The Doppler results showed that radiation treatment had an impact on the haemodynamics of the parotid gland. The PSV, EDV, RI and PI were significantly higher in normal glands. This implied that blood flow was faster and there was greater pressure experienced by the vessels in the normal glands than those of the post-RT glands. The higher blood velocity in the normal parotid gland was because the blood vessels of normal glands were surrounded by the more densely packed secretory acini and granules, which were less easy to dilate and pulsate (similar to stiff vessels) during systole and diastole, and therefore resulted in higher PSV and EDV. In contrast, the post-RT parotid glands suffered from the loss of acini and granules [11, 12, 15]. This led to the reduction of compression pressure exerted on the vessels by fewer acini and granules, and resulted in a relatively lower RI and PI. In addition, it was also speculated that the lower blood flow velocity and vascular resistance in post-RT parotid glands was due to their less organised vascular architecture. This resulted in the increase in arterial venous shunting across the capillary bed, which had less parenchymal tissue through which to percolate. Since the patients and normal subjects were age and gender matched, the confounding effect of these two factors on the Doppler findings would be considered minimal, and the differences in the blood flow velocity and vascular resistance between the two groups were likely to be due to the effect of radiation therapy. However, the differences in PSV, EDV, RI and PI between the normal and post-RT glands were not dose dependent, as their values did not demonstrate significant correlations with the magnitude of dose received by the glands. This could be due to the relatively small sample size, which was a limitation of this study. This implied that it was not easy to predict the magnitude of vascular changes in the parotid glands purely based on the total dose received.

The results of the questionnaires further proved that there were subjective impacts of xerostomia on the NPC survivors after radiotherapy. At the time of the assessment, when the patients had completed their radiation treatment for more than 3 years, the mouth dryness still persisted and the difficulty in mastication and swallowing remained the greatest problem, followed by the difficulty with speech. This echoed the fact that the radiation-induced gland damage was long lasting for the dose levels experienced by the 18 subjects in this study. The findings were in line with Nagler et al [16], who reported that parotid glands irradiated with 60 Gy or above would lead to permanent damage to acinar cells. The results of this study also showed that complete recovery of the salivary condition was not likely for these dose levels, as all subjects expressed that their salivary function was only about 40% of the normal state. An important finding in the present study was that the patients' subjective assessment of the impact of xerostomia showed some degree of dependence on the mean dose received by the parotid glands. In addition, the subjective recovery of the saliva function demonstrated an inverse function with the mean dose received. Despite

Table 2. Results of the xerostomia questionnaire on the subjects of the patient group

	Maximum	Minimum	Mean	SD	Correlation with mean parotid dose (r value)
IF	6.34	2.18	4.40	±1.37	0.614
RP (%)	60.0	20.0	39.0	±11.7	−0.869

IF, overall impact factor (average scores of the five questions); RP, residue percentage (the subjective assessment of the percentage of salivary function remaining at the time of assessment compared with that before radiotherapy); SD, standard deviation.

the fact that recovery from radiation-induced xerostomia was dependent on a variety of factors, including the patient's general condition and length of time after radiation treatment [17], the total mean dose received proved to be influential to the patient's quality of life in this study.

The general results of this preliminary study indicated that the change in volume of the parotid gland and level of xerostomia in the survivors were dose dependent. However, this study was only performed on patients treated with conventional techniques, with the mean dose levels to the parotid glands all above the tolerance of the organ. This was the main reason all patients showed some degree of gland damage and xerostomia. With the evidence that the severity of some side effects is dependent on the dose magnitude to the parotid gland, this justifies the use of techniques such as intensity modulated radiotherapy, which can further reduce the dose to the parotid, as important to further minimise the complications.

Conclusion

Radiation-induced xerostomia is a major cause of morbidity among NPC patients after conventional radiation therapy. There were definite impacts on the size reduction and change in the blood flow of the parotid glands due to radiation. It was possible to predict the gland volume change and severity of xerostomia based on the total dose received by the parotid glands. However, such prediction was not effective for vascular changes. The damage to the gland was long lasting and had significant influence on the quality of life for post-RT patients. Therefore, maintaining a low dose to the parotid gland should be considered in radiotherapy treatment planning.

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