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Assessment of radiation-induced salivary gland change in nasopharyngeal carcinoma: Correlation between clinical xerostomia grade and contrast-enhanced CT density change

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Background : *Radiation-induced xerostomia is the most common complication in patients with nasopharyngeal carcinoma (NPC) after radiation therapy (RT).*

Objective : *To correlate salivary dysfunction as assessed by clinical xerostomia grade with change in computed tomography (CT) density of the salivary glands on contrast-enhanced CT in patients with NPC treated with RT.*

Methods : *Seventeen patients with NPC, who had contrast-enhanced CT before and after radiation therapy (70 - 75 Gy) were assessed retrospectively. CT density change was calculated using difference in attenuation (Δ attenuation) and ratio of attenuation (Δ ratio). The ratio of attenuation was: parotid or submandibular attenuation (HUs) / ipsilateral paraspinal muscle attenuation (HUs). The mean Δ ratio of bilateral parotid glands and submandibular glands in each patient was statistically correlated with clinical xerostomia grade. Mean percentage change in attenuation and ratio for all salivary glands were used as a CT index and ratio index and compared with clinical xerostomia grade.*

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Results : *Attenuation (HUs) and ratio of attenuation in the parotid and submandibular glands after radiation significantly increased from pre-radiation (P <0.001). There was no significant correlation between Δ ratio and clinical xerostomia grade in parotid and submandibular glands at any of the 3 follow-up points. There was no significant difference between CT index and ratio index among the xerostomia grade 0, grade 1, and grade 2 groups.*

Conclusions : *Contrast-enhanced CT can detect increase in attenuation of the parotid and submandibular glands in NPC treated with RT, but there was no significant correlation between CT density change and severity of clinical xerostomia grade.*

Keywords : *Xerostomia, nasopharyngeal carcinoma, radiation, CT attenuation.*

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เหตุผลของการทำวิจัย : *ผู้ป่วยหลังฉายรังสีส่วนศีรษะและลำคอจะพบภาวะน้ำลายแห้งเป็นผลข้างเคียงได้บ่อย และการอักเสบของต่อมน้ำลายสามารถตรวจพบได้จากการทำเอกซเรย์คอมพิวเตอร์*

วัตถุประสงค์ : *ศึกษาความสัมพันธ์ของความรุนแรงของภาวะน้ำลายแห้งหลังฉายรังสีในผู้ป่วยมะเร็งหลังโพรงจมูกกับการเปลี่ยนแปลงค่า CT attenuation ในภาพเอกซเรย์คอมพิวเตอร์หลังฉีดสารทึบรังสี*

วัสดุและวิธีการ : *ผู้ป่วย 17 ราย ซึ่งได้รับการฉายรังสีขนาด 70 - 75 Gy ได้รับการคำนวณค่า CT attenuation ของต่อมน้ำลายก่อนและหลังฉายรังสี เพื่อหาค่าเฉลี่ยของความเปลี่ยนแปลง และสัดส่วนการเปลี่ยนแปลงเทียบกับกล้ามเนื้อคอระหว่างต่อมน้ำลายพาโรติดทั้งสองข้าง และต่อมน้ำลายใต้คางทั้งสองข้าง รวมถึงอัตราการเปลี่ยนแปลงรวมของต่อมน้ำลายทั้ง 4 ต่อม และนำมาเปรียบเทียบกับระดับความรุนแรงของภาวะน้ำลายแห้ง*

ผลการศึกษา : *CT attenuation ของต่อมน้ำลายพาโรติดและต่อมน้ำลายใต้คางหลังฉายรังสีมีค่าสูงกว่าก่อนฉายรังสี อย่างมีนัยสำคัญ ($P < 0.001$) ค่าเฉลี่ยของความเปลี่ยนแปลง และสัดส่วนการเปลี่ยนแปลง รวมถึงอัตราการเปลี่ยนแปลง CT attenuation รวมทั้ง 4 ต่อมไม่มีความสัมพันธ์กับความรุนแรงของภาวะน้ำลายแห้ง*

สรุป : *การศึกษานี้พบว่ามีความแตกต่างของ CT attenuation ของต่อมน้ำลายพาโรติดและต่อมน้ำลายใต้คางก่อนและหลังฉายรังสีอย่างมีนัยสำคัญ แต่ไม่พบว่ามีความสัมพันธ์กับความรุนแรงของภาวะน้ำลายแห้ง*

คำสำคัญ : *ภาวะปากแห้งน้ำลายน้อย, การฉายรังสี, เอกซเรย์คอมพิวเตอร์.*

Radiation therapy (RT) is the standard treatment for local or limited regional nasopharyngeal cancer (NPC).[1] However, RT of the nasopharyngeal region results in both acute and long-term complications that affect normal tissues. Radiation-induced xerostomia is the most common complication in patients with NPC after RT [2, 3], because most of the salivary glands are included in the radiation fields. Xerostomia is defined as dry mouth caused by insufficient or cessation of saliva production in the mouth. Persistent xerostomia causes difficulties in mastication and swallowing, as well as increasing the risk of dental problems – all of which results in poor long-term quality of life in patients.[4]

According to Bronstein AD, *et al.*[5], the RT results in increased attenuation of the parotid and/or submandibular glands on subsequent contrast-enhanced computed tomography (CT) imaging. This change might be associated with salivary gland dysfunction and xerostomia. However, no previous study has investigated the association between CT density changes and clinical impact on clinical xerostomia grade.

In this study, we aimed to correlate salivary dysfunction as assessed by clinical xerostomia grade with change in CT density of the salivary glands on contrast-enhanced CT in patients with NPC that were treated with RT. Knowledge about this relationship may be useful for predicting severity of xerostomia after RT.

Materials and Methods

Patients

Inclusion criteria were: patients with pathologically proven NPC that were treated by RT from 1st January 2009 to 31 December 2013 study period. All patients underwent contrast-enhanced CT scan and were referred to the Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital for definitive radiation therapy (RT) or concurrent chemoradiation (CCRT) with a radiation dose of 70 - 75 Gy. All patients received contrast-enhanced CT scan 2 - 4 months after completing RT, with subsequent follow-up visits at the hospital.

Patients who had distant metastasis or who received palliative radiation dose were not included. Patients with known salivary diseases, including Sjogren’s syndrome, chronic sialolithiasis, sialadenitis, and/or sialosis or history of salivary gland surgery were also excluded.

Seventeen NPC patients were included. Eleven patients were men (age range: 40 - 64 years, mean age: 54 years) and six were women (age range: 33 - 80 years, mean age: 57 years). Patient and tumor staging characteristics are shown in Table 1.

CT studies

Contrast-enhanced CT scans were performed before and after RT in all patients. CT scans were acquired on a Somatom Sensation 16 - row multi-detector computed tomography (MDCT) scanner (Siemens AG Medical Solutions, Erlangen, Germany) or an Aquilion One 320-slice MDCT scanner (Toshiba Medical Systems, Tokyo, Japan). CT images were obtained using nasopharynx protocol with the following parameters: tube voltage: 120 kV; tube current: 280 - 400 mA (automatically adjusted for patient body build); gantry rotation time: 0.5 seconds (Somatom) or 0.75 seconds (Aquilion One); and, detector collimation: 1.5 mm. Contiguous 3-mm-thick-section axial images were reconstructed. All CT studies were performed with contrast enhancement. Post-contrast images were acquired using 75 ml (Aquilion One) or 100 ml (Somatom) IV administration of nonionic contrast material. An automated power injector at a flow rate of 3ml/sec was used, with 40-second (Somatom) or 45-second (Aquilion One) delay scanning after contrast injection. Attenuations of each parotid gland, submandibular gland, and adjacent muscle were calculated in Hounsfield units (HUs) using the region of interest (ROI) tool on PACS (Synapse®). ROIs of approximately 9 - 12mm^2 were drawn in the central region of the bilateral parotid glands, submandibular glands, and paraspinal muscles in the post-contrast phase as shown in Figure 1.

In order to limit factors that could influence differences in attenuation among patients, we compared the attenuation of salivary glands with the ipsilateral paraspinal muscle in each patient [ratio of attenuation = attenuation of parotid or submandibular glands (HUs)/attenuation of paraspinal muscle (HUs)]. Mean attenuation and ratio of the bilateral parotid glands and submandibular glands in each patient obtained on CT before and after RT were calculated for statistical analysis. CT attenuation change (Δ attenuation) and ratio of attenuation change (Δ ratio) from the previously mentioned mean value were then calculated. The symbol Δ was used to indicate the difference after RT.

Percentage of attenuation change for each gland was calculated using the following formula: post-treatment attenuation - pre-treatment attenuation /pre-treatment attenuation $\times$ 100. Ratio of attenuation change for each gland was calculated using the following formula: post-treatment ratio-pre-treatment ratio/pre-treatment ratio $\times$ 100. The mean of the above mentioned percentage attenuation and ratio change for all salivary glands was then calculated and used as a CT index and ratio index for the salivary glands.

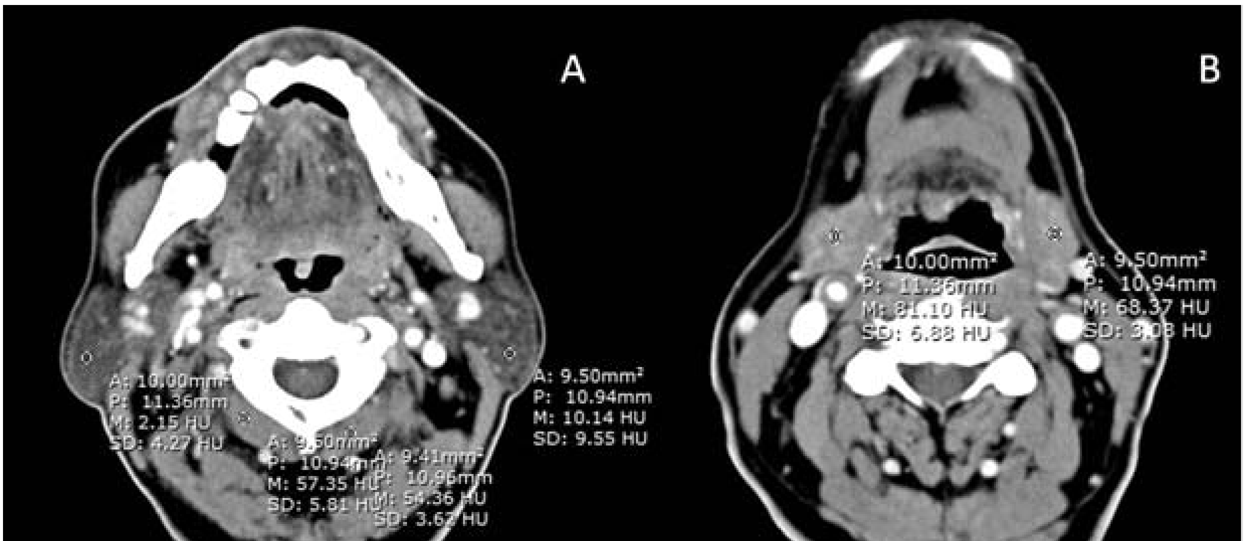

Figure 1. A case of 64 years old male with NPC stage T3N1M0 on first CT follow-up after 35 fractions of total dose 74 Gy shows (A) ROIs placement in bilateral parotid glands and paraspinal muscles and (B) bilateral submandibular glands.

Attenuation of CT images was measured by authors, both of whom were blinded to clinical xerostomia grade.

Clinical xerostomia grading

Patients were evaluated for clinical xerostomia grade by one experienced radiotherapist using the head neck tumor flow sheet at each follow-up visit. The xerostomia grades were defined, as follows; grade 0 = none; grade 1 = symptomatic; grade 2 = altered eating; and, grade 3 = requiring NG/IV/TPN. Patients were evaluated at 2 - 4 months after completion of RT and then at every follow-up visit together with nasopharynx CT.

Statistical analysis

SPSS version 17 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Wilcoxon signed ranks test was used to evaluate changes in CT attenuations (HUs) and ratio of attenuation between before and after RT. Correlation between Δ ratio of salivary glands and clinical xerostomia grade was assessed by Spearman's rho correlation method. Comparisons of Δ attenuation and Δ ratio of bilateral parotid and submandibular glands, and CT index and ratio index among clinical xerostomia grade groups was analyzed using Kruskal-Wallis H test. A *P*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. In addition to the routine radiation treatment, 2 of 17 patients received neck boost treatment, one received 1.5 Gy at the right neck, and one received 3 Gy at the left neck. No significant difference in mean dose was observed between the right and left parotid glands in any patients.

Ten of 17 patients received a 2^{nd} CT follow-up scan and 6 patients received a 3^{rd} CT follow-up scan. Duration between 1^{st} and 2^{nd} CT follow-up scan and 2^{nd} and 3^{rd} CT follow-up scan varied (3 months to 1.5 years and 9 months to 1.5 years, respectively).

Association between CT density change and xerostomia grade

To evaluate response of treatment, CT scans of the nasopharynx were acquired for all patients 2 - 4 months after completion of radiation therapy. Mean duration of CT follow up after last radiation treatment was 94 days (range: 77 - 117).

Contrast-enhanced attenuation of parotid glands before radiation ranged from -20.3 to 79.78 HUs (mean: 25.38), with a ratio of -0.33 to 1.12 (mean: 0.38). Contrast-enhanced attenuation of parotid glands at the 1^{st} CT follow-up after radiation ranged from 8.62 to 121.12 HUs (mean: 59.79), with a ratio of 0.6 to 1.70 (mean: 0.93).

Contrast-enhanced attenuation of submandibular glands before radiation ranged from 31.91 to 134.87 HUs (mean: 87.48), with a ratio of 0.56 to 1.93 (mean: 1.35). Contrast-enhanced attenuation of submandibular glands at the 1^{st} CT follow-up after radiation ranged from 77.05 to 168.12 HUs (mean: 115.89), with a ratio of 1.35 to 2.39 (mean: 1.80).

Attenuation (HUs) and ratio of attenuation in the parotid and submandibular glands increased significantly from pre- to post-radiation (P <0.001;

Wilcoxon signed ranks test). However, there was no significant difference in attenuations among the 1st, 2nd, and 3rd follow-up visits.

At the 1st follow-up after radiation, the Δ ratio of parotid attenuation ranged from -0.09 to 1.41, (mean: 0.55), whereas the Δ ratio of submandibular attenuation ranged from -0.13 to 1.20 (mean: 0.44).

No significant correlation was observed between the Δ ratio and clinical xerostomia grade in the parotid and submandibular glands at any of the 1st, 2nd, or 3rd follow-ups after completion of RT treatment (Table 2).

Table 1. Patient and tumor staging characteristics.

Characteristics	
Patient number (n)	17
Age (years)	Mean 55.47 (33 - 80)
Sex (n)	
- Male	11
- Female	6
T classification (n)	
- T1	4
- T2	7
- T3	4
- T4	2
N classification (n)	
- N1	7
- N2	9
- N3	1
Radiation techniques (n)	
- IMRT	3
- VMAT	14
Total dose (n)	
- 70 Gy	13
- 70 Gy +boost radiation at neck	2
- 74 Gy	2
Number of fraction (n)	
- 33 Fractions	12
- 35 Fractions	5
Duration of CT follow-up after last radiation (days)	Mean 94 (77 - 117)

Table 2. Correlation between the Δ ratio and clinical xerostomia grade in the parotid and submandibular glands at any of the 1st, 2nd, or 3rd follow-ups after completion of RT treatment.

Mean Δ attenuation ratio	**Xerostomia grade**	***P* value**
1st F/U (n = 17)		
- Parotid gland	R = 0.429	NS (>0.05)
- Submandibular gland	R = 0.312	NS
2nd F/U (n = 10)		
- Parotid gland	R = 0.247	NS
- Submandibular gland	R = 0.492	NS
3rd F/U (n = 6)		
- Parotid gland	R = 0.393	NS
- Submandibular gland	R = 0.655	NS

Xerostomia grade in patients at 1st follow-up after completion of RT was grade 0 in 1 patient; grade 1 in 6 patients; grade 2 in 10 patients; and, grade 3 in 0 patients. There was no significant difference in Δ attenuation or Δ ratio for bilateral parotid and submandibular glands among the xerostomia grade 0, 1, and 2 groups (Figure 2). No significant differences between CT index and ratio index among clinical xerostomia grades were identified.

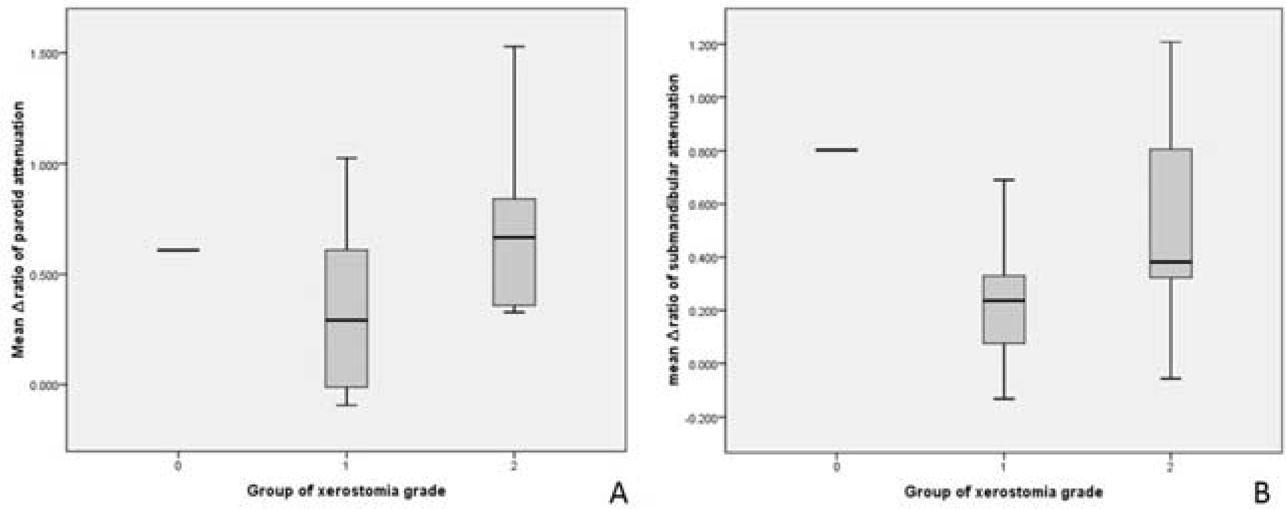

Figure 2. Mean Δ ratio of attenuation of (A) parotid glands and (B) submandibular glands on the 1st follow-up show no significant difference among xerostomia grade 0, 1 and 2 groups (*P* >0.05)

Discussion

Radiation therapy is a standard treatment modality for local or limited regional nasopharyngeal cancer.[1] Accidental damage to the major salivary glands during treatment causes severe reduction in salivary output and subsequent xerostomia.[6] Radiation-induced xerostomia starts early during treatment. There is a decrease in salivary flow of about 50 - 60% in the first week of radiation, with salivary flow diminishing to about 20% of normal after 7 weeks of RT.[7] After completion of radiation therapy in patients with nasopharyngeal cancer, CT is a frequently used follow-up method within 3 - 6 months for comparative baseline study.[8]

Bronstein, *et al.* reported that increased CT density was related to a high dose of glandular irradiation (>45 Gy) and that both the parotid and submandibular glands showed a similar degree of increased CT density post-radiotherapy, but that chemotherapy did not cause increased salivary gland density. They proposed that increased density may be due to contrast medium being stored in the expanded extracellular space resulting from a loss of acinar cells after radiotherapy.[5] Gossner J, *et al.* found that the density of the submandibular gland showed a time-dependent change, with an increase in median density in about 19% of patients in first follow-up CT scans at 1 - 2 months after completing RT. Median density decreased slightly in about 5% of patients compared with pre-therapeutic CT scan 4 - 6 months after completed RT, and they strongly decreased in about 55% of patients at follow-up examinations >1 year after completion of radiotherapy. They postulated that the time-dependent change was consistent with the timing of pathological changes in acute inflammatory reaction, followed by late fibrosis.[9]

In this study, we found significant increase in attenuation (HUs) of the parotid gland and submandibular gland from pre-radiation to post-radiation (P <0.001), but no significant difference was observed for attenuations among each of the 3 follow-up visits and no time-dependent change. In addition to instrument measurement, we used visual inspection to evaluate the size and attenuation of the salivary glands. We found that all the parotid and submandibular glands showed heterogeneous increased enhancement and most of them (94% of parotid glands and 88% of submandibular glands) had decreased in size. This is consistent with previous studies that reported decreased size of the parotid glands. Wu VW, *et al*. reported that post-radiation parotid glands were significantly smaller than their pre-radiation size as measured from CT images.[10] Lee C, *et al.* found a decrease in parotid gland volume at a rate of 0.6 - 0.7% volume loss per day during radiotherapy for head and neck cancers, with a median parotid volume loss at the end of treatment of 21.3%.[11]

Our study shows variable baseline CT attenuation of salivary glands before radiation, ranging from -20.3 to 79.78 for parotid glands and from 31.91 to 134.87 for submandibular glands. Min-Suk Heo, *et al*. reported a significant decrease in the CT number of parotid and submandibular glands with age, presuming an age-dependent increase in adipose tissue content in salivary glands.[12] This, however, is not consistent with our results, which found no correlation between age and baseline attenuation for either of the two types of glands.

No previous studies have examined the relationship between CT density of the salivary glands and clinical xerostomia grade in post-radiation NPC patients. In the present study, we found that no significant correlation exists between CT density change (Δ attenuation and Δ ratio) and clinical xerostomia grade in the parotid glands and submandibular glands at any follow-up point. It should also be noted that no patient with grade 3 xerostomia was analyzed in this study. In addition, the standard error (SE) was high due to the small number of samples, variance of attenuation and heterogeneity of salivary glands, and different durations of CT follow-up in each patient. Another possible explanation is multifactorial causes, such as drugs or systemic illness that may affect salivary flow in addition to post-radiation xerostomia.

Our study has several mentionable limitations. First and owing to our study's retrospective design, selection bias was unavoidable. Second, the study population in this study was quite small and no patients had grade 3 xerostomia. Next, there was heterogeneous enhancement of salivary glands in each patient after radiation, so variance of attenuation occurred. We endeavored to mitigate this heterogeneity by measuring each parotid gland, submandibular gland, and paraspinal muscle three times, from which we then calculated the mean. Another limitation involved variation in CT follow-up durations after RT which may have affected the attenuation of the salivary glands. Lastly, clinical xerostomia grades were subjectively evaluated. Xerostomia grading was based primarily on the severity of symptoms described by the patient.

Conclusion

Contrast-enhanced CT of the neck can detect increase in attenuation of the parotid and submandibular glands in nasopharyngeal carcinoma treated with radiation therapy, but there was no significant correlation between CT density change and severity of clinical xerostomia grade at any follow-up point in this study.

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