

Pilot Study Using Technetium-99m Pertechnetate Sequential Radionuclide-Sialography to Assess Salivary Gland Function in Nasopharyngeal Cancer Patients on Radiation Therapy

K S Ng,*^{MBBS}, F X Sundram,**^{FAMS, MSc (Nucl Med), DMRT (Lond)}, H S Khoo Tan,***^{MBBS, FRCR}, S Somanesan,****^{BSc (Hons)},
B Chung,^{+MHSM}, F Gao,^{++MSc}, D Machin,^{+++PhD}

Abstract

Introduction: Nasopharyngeal carcinoma (NPC) is mainly treated by radiation therapy. A common complication of radiotherapy is xerostomia. Direct measurements of the amount of saliva produced using suction cups and volumetric assessments are cumbersome and time-consuming. Sequential radionuclide sialography is a reproducible and convenient method of measuring salivary function. **Materials and Methods:** Patients with newly diagnosed NPC underwent a pilot study using technetium-99m pertechnetate sequential radionuclide sialography to assess their salivary function before and at 3 months post radiation therapy. From the sialography, time activity curves were obtained for analysis of salivary function. The shape of the time activity curve with citric acid stimulation was classified into 4 types according to the degree of radiation-induced dysfunction. **Results:** All 14 patients had worse ($P < 0.005$) time activity curves for both parotids and submandibular glands after radiation therapy. All patients with abnormal curves before radiation therapy presented type IV (non-functioning) curve after radiation therapy. A ratio of pre- and post-stimulation counts allowed for quantification of the degree of stimulatory response. We found a significant decrease in R_c before and after radiation therapy for all salivary glands ($P < 0.001$). The salivary gland to background ratio, which is a reflection of the degree of salivary gland functional uptake, also had a significant reduction after radiation. **Conclusion:** It is feasible to use technetium-99m pertechnetate in the measurement of salivary gland function in nasopharyngeal cancer patients treated with radiation therapy.

Ann Acad Med Singapore 2003; 32:455-60

Key words: Radionuclide-scintigraphy, Stimulatory response, Submandibular glands, Time activity curves, Xerostomia

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy occurring worldwide with particularly high frequencies in the Far East. The incidence is highest in Hong Kong followed by Singaporean Chinese. NPC is treated mainly by radiation therapy.¹ A common complication of radiotherapy in head and neck cancers, including nasopharyngeal cancer, is xerostomia. This is because the salivary glands, often included in the radiation fields, are sensitive to radiation damage. The reduction in salivation then leads to problems such as oral cavity infection, dental caries and poor intake of food. Such

patients are, therefore, more susceptible to xerostomia. Attempts to alleviate this situation have included artificial saliva preparation, lemon drops and mouth gargles, but none have proven effective or widely accepted by patients. There have been reports on the reduction of xerostomia using pilocarpine.²⁻⁴ This cholinergic agonist is classified as a sialogogue as it can stimulate salivary gland secretion. Other potential effects include urinary frequency, bronchospasm, hypotension, cardiac arrhythmia and increased lacrimation and perspiration.

In evaluating the severity of xerostomia, a simple, reliable and reproducible method of measuring salivary gland

* Medical Officer

** Head and Senior Consultant

**** Radiation Physicist

Department of Nuclear Medicine

Singapore General Hospital

*** Senior Consultant

Department of Therapeutic Radiology

+ Senior Radiation Therapist

++ Biostatistician, Clinical Trials and Epidemiology Science

National Cancer Centre, Singapore

+++ Professor

Clinical Trials Research Unit

University of Sheffield, United Kingdom

Address for Reprints: Dr Felix Sundram, Department of Nuclear Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

function is required. Direct measurements of the amount of saliva produced using suction cups and volumetric assessments are often cumbersome and time-consuming, requiring samples to be collected over several hours.²⁻⁶ A more reproducible and convenient method of salivary function measurement is sequential radionuclide sialography, using technetium-99m pertechnetate.^{7,8} In this technique, the radioactive tracer is injected intravenously into the patient and, subsequently, the technetium-99m pertechnetate is excreted in the saliva. By measuring the amount of radioactivity over a period of time in the major salivary glands, that is, the parotid and submandibular glands, the functional capacity of the gland can be evaluated. Similarly, by measuring the amount of tracer in the oral cavity, the rate of excretion of saliva into the oral cavity can be determined. Pre- and post-radiotherapy assessments can be further used to evaluate the progression of xerostomia, thereby offering guide to therapy.

The aims of this pilot study were twofold. First, it assessed the feasibility of using technetium-99m pertechnetate to measure salivary gland function in a group of nasopharyngeal cancer patients treated with radiation therapy. Second, it aims to ascertain the magnitude of change in salivary gland function before and after radical radiotherapy for NPC.

Materials and Methods

Newly diagnosed early and late stage nasopharyngeal cancer patients were assessed for salivary gland function, immediately before and 3 months after radical radiotherapy to the head and neck. These patients were selected during consultation clinics after the diagnosis was made. Only patients who met the eligibility criteria were recruited into the study. The eligibility criteria were: 1) aged between 20 and 60 years old; 2) previously untreated and histologically proven undifferentiated NPC; 3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 4) no past history of salivary gland surgery or abnormality; 5) not planned for chemotherapy; 6) no other previously diagnosed cancer; 7) no previous radiation therapy to the head and neck region; and 8) informed consent.

At each assessment, the patient received an intravenous dose of 5 mCi of technetium-99m pertechnetate. The parotid and submandibular regions were scanned with a gamma camera in an anteroposterior position, with the patient lying supine. We used a dual detector gamma camera, ADAC (Philips, Milpitas, California, USA), with the energy window set at 140 ± 20 keV, which is the energy window for technetium-99m. Images were obtained in a 64 x 64 matrix at a frame rate of 1 minute per frame. Sequential dynamic images were obtained every 3 to 5 minutes (Fig. 1). After 30 minutes, 0.5 mL of 10% solution of citric acid was syringed onto the anterior dorsal surface of the tongue

to stimulate the salivary gland, using a small tube placed in the patient's mouth. The patient's head was not moved during the procedure to ensure accurate recording by the gamma camera.

Regions of interest were placed over the parotids, submandibular glands and oral cavity. The activity detected in the regions of interest was measured and plotted for 30 minutes. This time activity curve represents the total functional viability of the gland. The general shape of the curve was then classified according to post-stimulation response patterns.

To measure the degree of stimulatory response (Rc), a ratio was obtained from the time activity curve as follows:

$$Rc = a/b \text{ (} a \geq b \text{) or } b/a \text{ (} a < b \text{),}$$

where *a* is the pre-stimulation counts per minute (cpm) before acid stimulation and *b* is the post-stimulation cpm measured at the time of maximum response.

A correction was done for the background activity by subtracting the counts over a similar area of the brain from the counts of the salivary gland under investigation. The maximum peak activity (Cmax) was obtained from the initial 30 minutes of the time activity curve by calculating the maximum counts averaged per unit area (64 x 64 matrix) of the salivary gland. This was corrected for the background (B) count to obtain the activity score over this period. This activity score, represented by the (salivary) S/B ratio, is calculated by the formula (Cmax - B)/B. This ratio indicates the radionuclide uptake capacity of the salivary gland. Hence, it is a reflection of the degree of salivary gland function.

The amount of salivary secretion into the oral cavity was determined by 5 minutes' radioactivity counts pre- and post-stimulation with citric acid. Before the stimulation, the patient was asked to swallow first, and then hold whatever saliva in the mouth, for the next 5 minutes. The gamma camera was then moved to a lateral skull position and radio-opaque markers placed to indicate the radiation fields on the skin. Thus, the volume of parotid gland and submandibular gland in the radiation field (Fig. 2) was ascertained. A percentage of irradiated and unirradiated salivary gland was calculated by determining the area of salivary gland within and beyond the radiation fields. The patients' intended treatment for NPC was at no time affected by this study. The field of radiation that the patient received was determined by the stage of the NPC.

McNemar test was used to determine the activity curves before and after radiation therapy.⁹ The average Rc pre- and post-radiation and S/B ratio were tested using Wilcoxon signed-rank test.⁹ The 95% confidence intervals (CI) for the differences in the means were calculated.

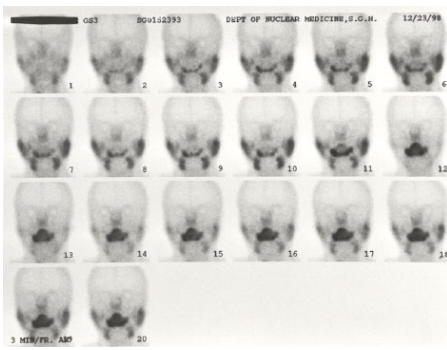


Fig. 1. Sequential dynamic images obtained after injection of 5mCi of technetium-99m pertechnetate in the anteroposterior position.

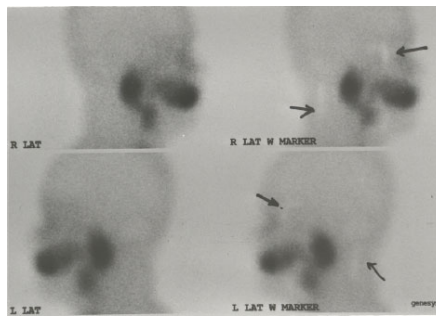


Fig. 2. Lateral images of the parotid and submandibular glands with radio-opaque markers (arrow) placed to indicate radiation fields on the skin.

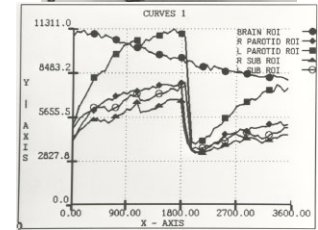
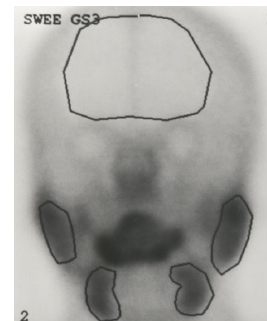
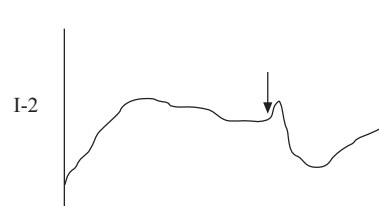
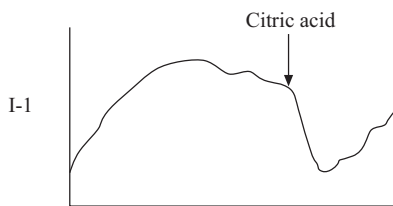
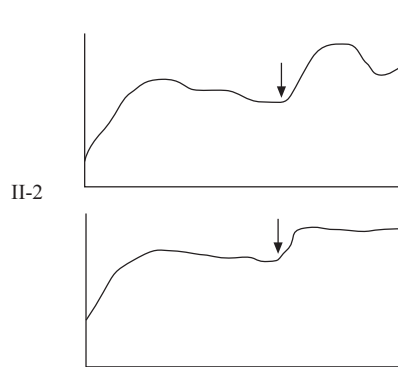
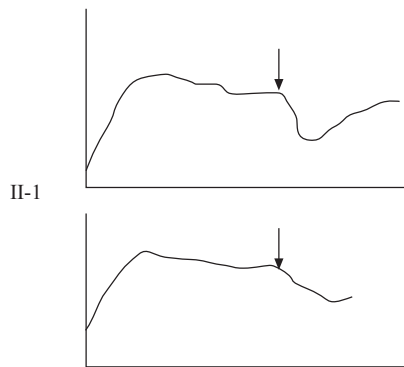


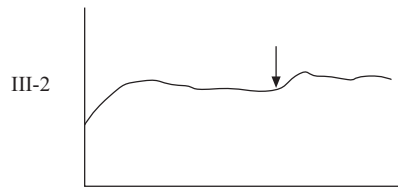
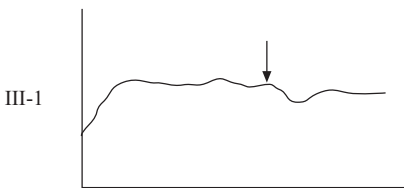
Fig. 4. Scanned image and time activity curves obtained post-stimulation response pattern with 10% citric acid.



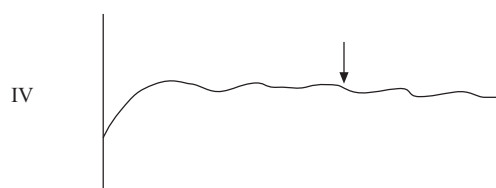
Type I curve. (Normal / Slight impairment) Prominent fall in post stimulation counts.



Type II curves. (Mild to moderate impairment) Moderate fall in counts or prolonged fall.



Type III curve. (Severe impairment) Minimal change in counts.



Type IV curve. (Non-functioning gland) No change in counts with stimulation.

Fig. 3. Classification of the types of the time activity curves regarding salivary response patterns under citric acid stimulation.

Results

Patients

Ten early and 10 late stage NPC patients who were newly diagnosed were recruited for the study. A total of 20 patients with NPC were assessed before radiotherapy for salivary function between 1998 and 2001. However, 1 patient died, 1 was later placed on chemoradiation therapy trial, 1 developed metastasis and 3 patients refused post-radiation therapy scan. Hence, a total of 14 patients had post-radiation therapy assessment 3 months after the initiation of therapy. This report is based on these 14 patients.

Of the 14 patients, 1 had 80% of both parotids irradiated, 2 had their submandibular glands spared and 1 had 50% of both submandibular glands irradiated.

Classification of the Type of the Time-activity-curve

The general shape of the time activity curve was classified according to post-stimulation response patterns and further classified according to changes in post-stimulation counts (Figs. 3 and 4). In type I curves, the post-stimulation counts drop significantly as there is prompt tracer secretion into the oral cavity. This indicates normal or minimally impaired function. Type II curves show a smaller and more prolonged fall in counts than type I curves and reflect mild to moderate salivary gland dysfunction. Type III curves show minimal change after stimulation and indicate severe impairment. Type IV curves show a plateau, that is, no response to citric acid stimulation. Types I, II and III curves were sub-classified into I-2, II-2 and III-2 when an increase in gland activity was demonstrated after stimulation, but with delayed flow or excretion of saliva (obstructive pattern). The type of the stimulus-response pattern was classified from I to IV. As shown in Table I, type I curves were observed mostly in the parotid and submandibular glands before radiation therapy. Abnormal curves before radiation therapy could be due to prior salivary gland disease, which was asymptomatic or not detected. There was no normal curve after radiation therapy and more than half of the patients had type IV curves. All patients with abnormal curves before radiation therapy showed type IV curves after therapy. In testing the different pre- and post-radiation therapy, types III and IV curves were grouped together. This was because the number of patients studied was small and 6 patients did not have post-radiation scans due to reasons mentioned earlier.

The distribution of types of curves pre- and post-radiation for early and late stage patients is shown in Table II. Four early stage patients had normal salivary glands before radiation therapy. However, 3 months after treatment, their salivary glands showed mild to severe impairment and some did not function. Of the 10 late stage patients, 8

TABLE I: CLASSIFICATION OF TIME ACTIVITY CURVES BEFORE AND AFTER RADIATION THERAPY (RT) (n = 14)

Site	Pre-RT	Post-RT			P value
		Type II	Type III	Type IV	
Right parotid	Type I (13) Type II (1)	2	3	8 1	0.003
Left parotid	Type I (12) Type II (2)	2	2	8 2	0.003
Right submandibular gland	Type I (12) Type II (1) Type III (1)	3	4	5 1 1	0.005
Left submandibular gland	Type I (12) Type II (2)	4	1	7 2	0.003

TABLE II: CLASSIFICATION OF TIME ACTIVITY CURVES BEFORE AND AFTER RADIATION THERAPY (RT)

Site	Pre-RT	Post-RT		
		Type II	Type III	Type IV
Early stage patients (n = 4)				
Right parotid	Type I (4)	1	1	2
Left parotid	Type I (4)	1	1	2
Right submandibular gland	Type I (4)	2	1	1
Left submandibular gland	Type I (4)	2	1	1
Late stage patients (n = 10)				
Right parotid	Type I (9)	1	2	6
	Type II (1)			1
Left parotid	Type I (8)	1	1	6
	Type II (2)			2
Right submandibular gland	Type I (8)	1	3	4
	Type II (1)			1
	Type III (1)			1
Left submandibular gland	Type I (8)	2		6
	Type II (2)			2

developed non-functioning salivary glands after radiation therapy. Of the 40 salivary glands in these 10 patients, 72.5% had type IV curve after radiation therapy.

The Stimulatory Response Ratio (Rc)

The mean $\pm$ standard deviation of Rc for the parotid and submandibular glands before and after radiation therapy are shown in Table III. The *P* values for the change in Rc before and after radiation therapy for all the salivary glands were ≤ 0.001 for the right parotid and both submandibular glands, and 0.0008 for the left parotid gland. This indicates a significant decrease in the ability of salivary glands to respond to acid stimulation post-radiation therapy.

TABLE III: MEAN $\pm$ SD OF Rc AND S/B RATIO BEFORE AND AFTER RT (n = 14)

Site	Pre-RT Mean $\pm$ SD	Post-RT Mean $\pm$ SD	95% CI	P value
Rc				
Right parotid	2.28 $\pm$ 0.60	1.15 $\pm$ 0.15	(0.76, 1.49)	0.0006
Left parotid	2.81 $\pm$ 1.30	1.17 $\pm$ 0.24	(0.82, 2.45)	0.0004
Right submandibular gland	1.76 $\pm$ 0.44	1.09 $\pm$ 0.08	(0.41, 0.94)	0.0001
Left submandibular gland	1.69 $\pm$ 0.38	1.11 $\pm$ 0.08	(0.34, 0.82)	0.0004
S/B ratio				
Right parotid	0.59 $\pm$ 0.24	0.40 $\pm$ 0.28	(0.00, 0.39)	0.03
Left parotid	0.58 $\pm$ 0.20	0.46 $\pm$ 0.26	(0.06, 0.30)	0.15
Right submandibular gland	0.64 $\pm$ 0.18	0.37 $\pm$ 0.34	(0.08, 0.46)	0.009
Left submandibular gland	0.59 $\pm$ 0.24	0.35 $\pm$ 0.30	(0.08, 0.40)	0.007

CI: confidence interval; Rc: stimulatory response; RT: radiation therapy; S/B: salivary/background; SD: standard deviation

The S/B ratio

Table III shows the mean $\pm$ SD of S/B ratio for the parotid and submandibular glands before and after radiation therapy. The S/B ratio showed a significant reduction after radiation ($P \leq 0.03$) for all salivary glands except the left parotid ($P = 0.15$).

Activity in the Oral Cavity

The mean of the differences between the salivary activity within the oral cavity pre- and post-radiation is 8.4×10^4 counts (before and after stimulation), with a confidence interval of 1.3×10^4 and 15.5×10^4 ($P = 0.002$) (Table IV). There was a real difference in the amount of salivary activity within the oral cavity after radiation therapy.

Discussion

Various methods to assess salivary gland function have been reported. The most reliable, reproducible and safe method is sequential radionuclide sialography using technetium-99m pertechnetate.⁸ In this pilot study, the results obtained for assessing salivary gland function were comparable with other reports using the same method. The time activity curves, obtained using technetium-99m pertechnetate sialography, are useful for this purpose. The use of other radionuclides, such as ^{131}I , is also feasible.^{7,10} However, such tracers have lethal "b" emissions, which cause radiation damage to the thyroid tissue and long half-lives. These properties limit their use in clinical investigations.

The classification of time activity curves, with respect to stimulus-response patterns, is a simple and easy way to estimate salivary function.⁷ It gives an overall qualitative assessment of salivary function. The Rc value and S/B ratio derived from time activity curves enable a more quantitative assessment of the salivary glands. The results from this pilot study show that, besides comparing the change in type

TABLE IV: MEAN OF SALIVARY ACTIVITY WITHIN THE ORAL CAVITY 5 MINUTES BEFORE AND AFTER STIMULATION WITH CITRIC ACID

Variable	Pre-RT	Post-RT
Before stimulation	83018.41	83745.01
After stimulation	168792.82	85529.67
Difference before and after stimulation	85774.41	1784.65

RT: radiation therapy

of curve due to radiation therapy, the values of Rc and S/B ratios can also be included in the assessment of salivary function.

The process of secretion of saliva is complicated and involves neural regulation and stimulation, serous and mucus production and the transportation of the saliva into the oral cavity.¹¹ Radiation therapy affects salivary glands by damaging both the acinar cells of the glands and causing fibrosis to the neural and vascular supply of the glands. Fibrosis of the ductal cells and surrounding tissue oedema also reduces the transportation of saliva from the glands to the oral cavity.¹²

Thus, the time activity curve gives a good estimate of the entire process of salivary secretion. The presence of obstructive type and non-functioning type curves post-radiation indicates that radiation affects both ductal and acinar cells. Our data also show that between the 2 types of salivary glands, the parotid glands appear to be more susceptible to radiation damage, which is in agreement with morphological studies on radiation effects in man and animals.

The changes noted in the Rc values reflect radiation injury to the neural cells responsible for gland stimulation and vascular supply to the glands. Such a change might also be due to post-radiation fibrosis of ductal cells reducing transportation of saliva. The S/B ratios, on the other hand,

primarily reflect the degree of radiation injury to the acinar cells. The S/B ratios of all the glands were affected in our study, except the left parotid. This could be due to the fact that the change in the left parotid was small and that the power of the study with 14 subjects was inadequate.

Reduced saliva in the buccal cavity is the end result of post-radiation therapy changes noted in the time activity curve, Rc values and S/B ratio. These collective changes are reflected by salivary activity within the oral cavity. Our study has shown that radiation therapy would significantly reduce the amount of total saliva secreted into the oral cavity.

We have also shown that the analysis of salivary function using sequential radionuclide sialography with technetium-99m pertechnetate could be further extended to patients with NPC. These patients are highly likely to suffer from xerostomia, as shown by the results of our study. The usefulness of sequential radionuclide sialography with technetium-99m pertechnetate extends beyond diagnosis of the complication of xerostomia from radiation therapy; it could enable evaluation of future potential treatments or preventive methods and their efficacies.

However, we did use other means of measuring salivary secretion, such as volumetric assessment using suction cups, in this pilot study. Nor did we interview the patients on their subjective functional status. Questions directed at the patients' intake of food, whether they needed medication or how often they needed to drink to wet their mouths could be asked, which would give a fairly general idea of the severity of xerostomia.¹³

Future studies aimed at finding the correlation of salivary function between sequential radionuclide sialography with technetium-99m pertechnetate and volumetric or subjective assessment, as well as specific drug(s) therapy for xerostomia, should be performed using the same protocol and methods employed in this pilot study.

Acknowledgements

The authors acknowledge the following:

1. Singapore Radiological Society;
2. National Medical Research Council;

3. Nasopharyngeal Carcinoma work group, National Cancer Centre, Singapore, including Drs V K Sethi, Chua Eu Jin, Chua Eu Ting, Joseph Wee, Fong Kam Weng, Lee Khai Mun, Lee Kim Siang and Terence Tan; and
4. Singapore General Hospital, Department of Nuclear Medicine physicians Drs Gilbert Keng Han Weng, David Ng Chee Eng and Wong Wai Yin.

REFERENCES

1. Chong V F H, Tsao S Y, editors. Nasopharyngeal carcinoma. Chapters 1, 2 & 10. Singapore: Armour, 1997.
2. Fox P C, Atkinson J C, Macynski A A, Wolff A, Kung D S, Valdez I H, et al. Pilocarpine treatment of salivary gland hypofunction and dry mouth (xerostomia). *Arch Intern Med* 1991; 151:1149-52.
3. Greenspan D, Daniels T E. Effectiveness of pilocarpine in postradiation xerostomia. *Cancer* 1987; 59:1123-5.
4. Valdez I H, Wolff A, Atkinson J C, Macynski A A, Fox P C. Use of pilocarpine during head and neck radiation therapy to reduce xerostomia and salivary dysfunction. *Cancer* 1993; 71:1848-51.
5. Mira J G, Wescott W B, Starcke E N, Shannon I L. Some factors influencing salivary function when treating with radiotherapy. *Int J Radiat Oncol Biol Phys* 1981; 7:535-41.
6. Mossman K L. Quantitative radiation dose-response relationships for normal tissues in man. II. Response of the salivary glands during radiotherapy. *Radiat Res* 1983; 95:392-8.
7. Tsujii H, Furudate M, Irie G. Effects of radiotherapy on the salivary gland as measured by 99mTcO₄⁻ (Japanese). *Nippon Igaku Hoshasen Gakkai Zasshi* 1980; 40:485-93.
8. Tsujii H. Quantitative dose-response analysis of salivary function following radiotherapy using sequential RI-sialography. *Int J Radiat Oncol Biol Phys* 1985; 11:1603-12.
9. Altman D G, Machin D, Bryant T N, Gardner M J. Statistics with confidence. 2nd ed. London: British Medical Journal, 2002.
10. Harden R M, Alexander W D, Shimmins J, Russell R I. Quantitative uptake measurements of 99mTc in salivary glands and stomach and concentration of 99mTc, 132I and 82Br in gastric juice and saliva. *Strahlentherapie (Sonderb)* 1968; 67:77-87.
11. Guyton, Hall. Textbook of medical physiology. USA: WB Saunders, 1996:817-9.
12. Cotran R S, Kumar V, Collins T. Robbins pathologic basis of disease. USA: WB Saunders, 1999:424-7.
13. Warde P, Kroll B, O'Sullivan B, Aslanidis J, Tew-George E, Waldron J, et al. A phase II study of Biotene in the treatment of postradiation xerostomia in patients with head and neck cancer. *Support Care Cancer* 2000; 8:203-8.