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**Oral health status of southern Chinese who received head and neck
irradiation therapy for nasopharyngeal carcinoma**

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Running title: Oral health of irradiated NPC patients

ABSTRACT

Objectives - To investigate the oral health status of patients with nasopharyngeal carcinoma (NPC) after completion of radiotherapy.

Methods - 33 NPC patients (mean age 53±10 years) who completed head and neck radiotherapy (3.6 ± 3.1 years post-operation) were examined. Dental caries, periodontal status, and oral mucosal lesions were recorded. Stimulated whole saliva (SWS) flow rate, pH, buffer capacity and carriage rate of cariogenic micro-organism were assessed. Jaw opening was measured.

Results - Xerostomia was present in all subjects, 42% had candidiasis and 21% of them had limited jaw opening. The mean number of teeth present was 22, mean DMFT was 8.0, mean number of untreated root caries lesions was 1.4. Both saliva pH and buffering capacity were low while *Streptococcus mutans* and *Lactobacillus* spp. carriage were high. 52% of the subjects did not have dental care after radiotherapy. Although few subjects expressed direct dissatisfaction, perceived level of information and post-operative dental care was insufficient.

Conclusions - Post-irradiated NPC patients constitute a high risk group for dental root caries and oral candidiasis. The carriage rate of *Streptococcus mutans* and *Lactobacillus* in this NPC patient group was the highest among findings of other similar studies. This may be related to the inadequacy in dental care after radiotherapy. Head and neck radiotherapy was not associated with periodontal disease.

INTRODUCTION

The incidence of nasopharyngeal carcinoma (NPC) is high in southern China. In the southern Chinese provinces of Guangdong, Guangxi and Fujian, rates as high as 20 per 100,000 have been reported ¹. In Hong Kong, a southern Chinese city, the age standardized incidence rates of NPC were 23 per 100,000 for males and 9 per 100,000 for females ². This cancer ranked 3rd for males and 8th for females for newly diagnosed malignant tumours in Hong Kong ². Due to the proximity of the nasopharynx to the base of the skull, surgical resection of the lesion with an acceptable margin is impossible. Radiotherapy, therefore, has always been the preferred treatment. The irradiated area would encompass the nasopharynx and adjacent tissues, including the parapharyngeal lymphatics and all of the cervical lymphatics with a 1 cm to 2 cm margin ³. This inevitably involves the stomatomasticatory complex and the major salivary glands.

Irradiation of the stomatomasticatory complex usually results in pathological changes of oral tissues. The acute mucosal reaction can vary from no reaction, through erythema with some denudation, multiple patches of denudation, to the extreme form with completed sloughing of the epithelium and a confluent fibrous membrane⁴. The mucosal condition could further be complicated by super infection with yeasts⁵. Due to the high turnover rate of the mucosa, however, acute radiation induced mucositis is usually self-limiting and gradual recovery, after completion of radiotherapy, is possible especially with the control of the candidiasis⁴.

The severity and duration of the disturbance in salivary function depends on how much salivary gland is within the irradiated area. Serous acini are more sensitive to radiation than mucinous acini, the saliva therefore becomes more glutinous. A

decrease in the amount and a change in quality of saliva can be noted within 14 days of starting external beam radiotherapy ⁶. Persistent xerostomia was reported in 40% of the NPC patients irradiated at Washington University ⁷, but has been observed in virtually all patients of other clinics ^{8,9}. The quantitative and qualitative changes of saliva could make eating and wearing of dentures extremely difficult. These salivary changes also result in important changes in the intraoral environment. Alteration in selective pressure favouring the overgrowth of *Candida albicans*, *Streptococcus mutans* and *Lactobacillus* have been reported ^{10, 11}. Reductions in the buffering capacity and pH of saliva were also noted ¹².

Radiotherapy also affects teeth especially those in the direct field of radiation. Teeth become brittle and pieces of the enamel may fracture away from teeth ¹³. A more important manifestation is 'radiation caries'. Demineralisation begins at the cervical area and sweeps across the tooth, sometimes causing amputation of the tooth crown at its neck. This is related to the alterations of the intra-oral environment secondary to salivary changes ¹³.

Radiation induced fibrotic change of tissues may affect the temporomandibular joints and muscles of mastication resulting in limited mouth opening. Trismus occurs to a significant degree in approximately 5% to 15% of irradiated NPC patients ³.

The most serious complication of radiotherapy is tissue necrosis ¹⁴. This can occur as an acute response indicating grossly excessive dosage and complete ablation of the epithelial stem cells. A more chronic response relates to the impairment of tissue perfusion and depletion of parenchymal stem cells. These would compromise the healing and defence capacity of tissues. Osteoradionecrosis is the necrosis of

bone, after radiotherapy, precipitated by infection and trauma. The occurrence of osteoradionecrosis of the jaw ranges from less than 4 per cent ¹⁴ to 13 per cent ¹⁵ of post-irradiated patients. Multiple risk factors were reported ¹⁶, e.g. dosage of radiation, oral hygiene and surgical trauma to irradiated area.

In Hong Kong as well as elsewhere, most health care professionals are aware of how to deal with oral/dental complications during and after irradiation therapy appropriately ¹⁷. However, limited allocation of public funding to oral health care for adults locally in combination with the poor general oral health awareness in the population ¹⁸ makes patient compliance with stringent recall schedules uncertain ¹⁹. Thus, not many of the NPC survivors are under appropriate post-irradiation dental care in Hong Kong.

The aims of the present study were to investigate the oral health status of a group of NPC survivors who had previously received head and neck irradiation; to describe oral physiological changes as a direct result of the irradiation and pathological conditions induced as a consequence of the oral physiological change; and to identify the treatment they received and their further treatment needs on the basis of their specific oral/dental problems.

MATERIALS AND METHODS.

The study was conducted during three weeks selected randomly at the end of 1995 in the post-radiotherapy follow-up clinic of the Department of Radiation Oncology located in the University Hospital, Queen Mary Hospital. The hospital also serves as one of the largest public hospitals on Hong Kong Island covering approximately 15% of the population of the Hong Kong Special Administrative Region and handles 100-

150 new NPC cases annually²⁰. The doctors in charge of the weekly clinic who had been briefed about the study and agreed to participate were responsible for the recruitment of the patients. All patients visiting the clinic during the sessions were approached sequentially. Thirty-three NPC patients aged between 35 to 74 years gave their consent to participate after being informed about the study corresponding to approximately 40% of the patients recalled during the selected sessions. Especially those patients who were edentulous declined to participate. Subsequent to recruitment, subjects were interviewed and examined in the Prince Philip Dental Hospital (PPDH). Demographic information, smoking habits, dental complaints, dental knowledge and dental services utilization were recorded by means of a standardized questionnaire which was pretested among patients of the same age in the PPDH reception clinic. Patient history of radiotherapy, dosage and duration of irradiation was provided by the Department of Radiation Oncology. The dental clinical examination was conducted by examiners who were dedicated for particular procedures, such as caries, periodontal conditions, saliva status etc. Jaw opening was measured, with vernier calipers, from the incisal edge of an upper central incisor to the opposing central incisor according to previous definitions^{4,21}. Subjects with less than 25 mm opening were classified as having trismus²².

Red and white patches on the oral mucosal surface, which are indicative of candidiasis, were recorded²³. Subsequent fungal culture was used to confirm the presence of candidiasis, however the detailed analysis of this aspect goes beyond the present paper. Mucositis was classified, scored and calculated as described by Spijkervet and co-workers²⁴.

Xerostomia was assessed with the xerostomia index of Jansma and co-workers¹⁷. After mouthrinsing for 30 seconds with phosphate buffered saline (pH 7.2), each subject was given a piece of sterile rubber tubing section (3 mm x 10 mm diameter) to chew for 5 minutes. The stimulated whole saliva (SWS) was voided in a sterile vial and the volume of the SWS was measured. Then, the SWS flow rate was calculated. Saliva samples were stored at 4°C and tested within 90 minutes after collection for pH and buffer capacity. pH values were measured with a Sentron® 501 Pocket FET pH meter (WA, USA). Buffer capacity was assessed using Dentobuff® strips (Espoo, Finland). Saliva samples were serially diluted and quantitative cultures for *Streptococcus mutans* and *Lactobacillus* species were performed according to Epstein et al.²⁵.

The oral hygiene of each subject was scored by the Plaque Index²⁶. The periodontal status was assessed by the Community Periodontal Index²⁷ using CPITN probes (WHO 621) on the six standard index teeth. After scaling the dentition status, dental caries, and prosthetic status were scored according to the WHO Oral Health Assessment Form²⁷. Bitewing radiographs were used to assist the diagnosis of proximal caries lesions. Care was taken to distinguish between teeth missing due to caries and due to other reasons, e.g. as part of pre-irradiation clearing. Comprehensive oral health care was subsequently provided for each patient according to clinical findings and all of them were kept under long term maintenance therapy.

Data analysis

All clinically registered information and completed questionnaires were analysed by SPSS for Windows 6.1. Differences between men and women were tested with Chi-

square test for categorical variables and with Student T-test or ANOVA for means. Relationships between selected clinical variables and radiation dose as well as time since radiation were plotted on scattergrams and tested with linear regression (regression coefficient r). In order to assess to what extent the level of oral health in the study population differed from a randomly selected population, comparisons with the Hong Kong Adult Oral Health Survey^{28,29} was performed. That study investigated 35-44 year-olds and 65-74 year-olds. Thus, for analytical and comparative purposes the present study population was subdivided in two ways: Four age groups (35-44, 45-54, 55-64, 65-74) and two age groups (35-54, 55-74). No statistically significant differences were found with regard to periodontal conditions with either method. Thus, the whole study population was analysed without age subgroups.

RESULTS

Thirty-three individuals comprising 24 men and 9 women were recruited for the study corresponding to a response rate of approximately 40%. Their mean age was 53 ± 10 years, ranging from 37 years to 72 years. They were mostly from lower socioeconomic class and the time since completion of radiotherapy was 3.6 ± 3.1 years. All of the subjects were dentate individuals. The mean total dosage given for the head and neck radiotherapy was 6750 ± 600 cGy.

Xerostomia was found in all subjects as shown in *Table I*. The majority of the subjects (64%) had xerostomia with no apparent mucosal change on the dorsal surface and lateral borders of tongue. There was no significant difference between the mean number of years since completion of radiotherapy versus xerostomia index (XI) of different categories. (XI = 1, 3.8 ± 3.1 year; XI = 2, 3.2 ± 3.9 year; XI = 3, 3.5 ± 2.7

year, Bonferroni multiple comparison, $P > 0.7$). Similarly, there was no significant correlation between SWS flow rate and time since completion of radiotherapy ($R^2 = 0.05$; $P = 0.19$). However, as shown in *Figure 1* there was a statistically significant inverse relationship between SWS flow rate and the size of the radiation dose received ($R^2 = 0.19$, $P = 0.006$), thus the higher the radiation dose the lower the flow rate.

The SWS pH from all of the subjects was low (6.4 ± 0.6) and so, too, was the buffering capacity (category low = 100%, categories medium/high = 0%). Great variation was observed regarding the quantity of *Streptococcus mutans* and *Lactobacillus* spp. identifiable from the SWS, their corresponding carriage rate was $1.4 \pm 2.0 \times 10^7$ cfu/ml SWS and $2.5 \pm 5.5 \times 10^6$ cfu/ml SWS respectively.

A total of fourteen subjects (42%) were diagnosed with mucosal candidiasis in the form of red and/or white patches, mostly located on the dorsal surface and the lateral borders of the tongue (*Table II*). No association was found between presence of intra-oral candidiasis and angular cheilitis. On the other hand, a significant difference was found between the years since completion of radiotherapy versus occurrence of candidiasis (Candidiasis, 5.0 ± 3.9 years; no candidiasis, 2.6 ± 2.0 years, ANOVA test, $P = 0.026$). No association was observed between the presence of candidiasis and the history of no regular dental treatment.

At the time of examination, the study subjects suffered from mild mucositis (mucositis score = 0.375 ± 0.402). There was no significant correlation between the years since completion of radiotherapy and mucositis score ($R^2 = 0.01$, $P = 0.791$). There was also no association between the presence of mucositis and candidiasis.

Seven out of the 33 participants had limited jaw opening of less than 25 mm (21%), mean jaw opening was 29.9 ± 8.73 mm, median was 32 mm.

There were only five subjects (15%) who were diagnosed to be caries free. The mean DMFT was 8.03 ± 6.11 which was composed of an average of 3.8 ± 3.8 decayed teeth, 2.97 ± 4.8 missing teeth, and 1.2 ± 1.8 filled teeth. Nineteen subjects (52%) displayed active root surface caries, ranging from 1 to 7 roots per person. The mean number of untreated root surface caries in this group was 1.4 ± 1.7 , and the mean number of restored root caries lesions was 1.2 ± 3.3 . No statistically significant differences were found in either crown caries or root surface caries between the younger and older age groups. Subjects with fewer teeth (1-19 teeth), however, had more missing teeth due to caries compared with subjects with 20+ teeth ($F=22.15$; $df=2$; $p<0.01$).

The Pearson product-moment correlation coefficients between bacterial counts, salivary flow, pH and dental caries prevalence are illustrated in *Table III*. Statistically significant correlations were noted between the two bacterial counts, between crown caries and root caries and between pH and salivary flow, whereas SWS flow rate did not correlate significantly with the number of Decayed-Filled Teeth. In a separate analysis shown in *Figure 2*, the number of months since completion of radiotherapy was found to be positively related to the number of Decayed-Filled Teeth.

No subject was assessed as having “healthy” periodontal conditions (CPI code 0) or having “bleeding only” (CPI code 1) as their highest score (*Table IV*). Most subjects (90.9%) had either code 2 or code 3 as their highest score. Only a relatively small proportion (9.1%) had deep pockets. With respect to oral hygiene on a per subject basis, only 0.12 sextants had no clinical plaque; 3.39 sextants and 2.03

sextants had plaque detectable with probe and readily visible plaque respectively. No sextant was assessed as having abundant plaque.

The major oral problems as perceived by the subjects themselves are presented in *Table V*. According to their own perception, all subjects had been informed of possible 'post-irradiation dry mouth' prior to their radiotherapy treatment. Reportedly, however, only haphazardly were the subjects notified of other significant oral complications of radiotherapy. Instruction on pre- and post-irradiation usage of fluoride or antiseptic mouthrinse were given to about 80% of the subjects. All the subjects recalled that they had a pre-irradiation dental check-up and that extraction of teeth with a poor prognosis was performed by hospital dentists. Conversely, after radiotherapy, only half of the examinees were called back for examination of their oral health status. 42% of the examinees did not have any comments about the quality of care at their pre-radiotherapy dental visit whereas 42% of them expressed satisfaction with the dental care provided in the post-radiotherapy period.

DISCUSSION

The design of the present study was cross-sectional. Since the determinant (radiotherapy) and the oral status are assessed at the same point in time, the study cannot distinguish whether the radiotherapy preceded the development of disease (i.e. caries, mucositis, xerostomia etc.) or whether the disease was already there. It might be desirable to conduct a longitudinal study in which observations are repeated in the same NPC patients before and after radiotherapy. Often, however, little time is available for dental or other medical procedures once the cancer is diagnosed, and the patients are always psychologically affected by the diagnosis. Thus, it could be

ethically questionable to add further clinical examinations before radiotherapy. Hence, all the NPC patients selected in this study had completed their radiotherapy. With regard to their classification as low socio-economic group special considerations must be given to the population from which the sample is drawn. It is generally accepted that genetic predisposition, environmental factors, and Epstein-Barr virus interact as causative factors for nasopharyngeal carcinoma ³⁰. Studies have indicated that specific variants of the virus have differential effects in Chinese and Caucasians ³¹⁻³³. Further studies have shown that poor living conditions, e.g. residence on fishing boats, together with special dietary habits such as preserved salted fish constitute a high risk combination for the development of this disease ^{34,35}. Thus, there would seem to be both genetic and environmental factors in the local population which would make the lower socio-economic groups specially susceptible to nasopharyngeal cancer. This situation in combination with the fact that the study was carried out in a large public medical facility may explain the socio-economic constitution of the group. The response rate is considered acceptable in a local context.

In order for the results of the study to be as comparable as possible with the results of the Hong Kong Adult Oral Health Survey conducted in 1991 which comprised middle-aged (35-44 year-olds) and elderly (65-74 year-olds) Chinese ^{28, 29}, NPC patients were selected within these two age groups. With a mean age of 53 ± 10 years the age of the participants in this study were considered sufficiently close to the two age groups to make comparisons meaningful.

Our study indicated that xerostomia (dry mouth) is the most common and inevitable consequence of radiotherapy which is in concordance with previous studies ³⁶. The inverse relationship between the salivary flow rate and the dose of irradiation

may be due to the damage of the acini gland cells¹⁴. The damaging effect seems to be permanent since the saliva flow does not recover significantly after radiation, and there is no direct relationship between saliva flow and the length of the post-radiotherapy period.

The observed SWS flow rate of less than 0.2ml/5min in almost 3/4 of the subjects is approximately 35 times lower than in a group of regular Hong Kong individuals (personal communication). The increased prevalence of oral mucosal diseases in these patients can be anticipated, since the volume of saliva together with immunoglobulin (IgA) are crucial factors in the maintenance of oral health.¹⁵ Candidiasis was the most common mucosal disease clinically seen in our subjects (42%).

Development of rampant caries in patients who develop xerostomia in later life, particularly after irradiation treatment has been documented widely³⁷. In these cases, the deterioration of oral health may be extremely rapid and dramatic²³. But in this survey, we could not demonstrate a significant relationship between saliva flow and a greater number of Decayed-Filled Teeth (crown). However, caries is a multifactorial disease, and the duration of developed xerostomia also plays an important role on caries development. This is consistent with the finding that the longer the time after radiotherapy, the higher the DF score (*Fig. 2*). Even though this group of patients is a high risk group for caries because of the decrease in saliva flow¹⁷, caries still needs time to develop. Furthermore, the protective effect of the communal water fluoridation programme in Hong Kong which has been in place more than 30 years must be considered as well.

The reduced jaw opening in approximately 1/5 of the patients may impede the ability to perform adequate oral hygiene which seems to be demonstrated by the poor oral hygiene of the patients.

The CPI findings for the NPC patients reveal that the percentage of subjects and the mean number of sextants with shallow and deep pockets are smaller than that found in healthy people in the survey of Hong Kong adult oral health in 1991²⁹. It reflects that the radiotherapy as such does not affect the periodontal tissues in this group of patients. However, the expected increase in periodontal destruction due to radiotherapy occurs largely as recession and is thus not detected by the CPI, which is based on probing depths¹⁶. This may indicate that recession should have been scored separately.

The DMFT index of our subjects was placed between the Hong Kong 35-44 year-olds and 65-74 year-old²⁸, but the Decayed component of our subjects was relatively high when compared with that of Hong Kong adults, indicating a greater need for dental services. As for the root conditions, the prevalence of root-surface caries was significantly increased compared to that of the Hong Kong adults²⁸. It has been estimated by previous studies that the root surface is around six times as soluble as enamel, and that the critical pH of around 6.2 may also be higher than that required for enamel (pH around 5.5) dissolution. This would imply that the root surface would start to dissolve much sooner than the enamel surface.¹⁵ This also indicates that the high proportion of decayed root surfaces in fact necessitates appropriate preventive and restorative care.

Possible side effects and related oral hygiene instructions were printed in a leaflet and explained to the local NPC patients before radiotherapy. Both physicians

and patients recognised dry mouth as the most common side effect, but nothing had been done to improve the situation. In practice, provision of artificial saliva to NPC patients is one of the ways to improve the situation, but the economic constraints may impede such a development³⁸. Jaw exercises during and after radiotherapy could alleviate the severity of “limited mouth opening”¹⁴. More emphasis could be put on jaw exercises before radiotherapy.

CONCLUSION

In conclusion, radiotherapy has caused many unavoidable oral complications for the NPC patients. All 33 patients examined suffered from xerostomia which places them as a high risk group for developing caries, especially root caries. Mucositis (apparently complicated by candida infection) and limited mouth opening was experienced. This hindered the oral hygiene care of the patients after radiotherapy. Both the oral health knowledge of the patients and the follow-up services provided to the patients must be considered insufficient to help them to manage the problems created by the cancer treatment.

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Table I. Xerostomia index (XI), xerostomia score, stimulated whole saliva (SWS) flow rate and pH.

XI	Description	Number (%)	SWS	
			Mean flow	pH
			(ml/min) \pm SD	mean \pm SD
0	NIL (No xerostomia)	0 (0.0)	0	0
1	Dry, with no apparent change in tongue mucosa morphology	21 (63.6)	0.04 \pm 0.04	6.6 \pm 0.4
2	Dry, atrophic tongue	7 (21.2)	0.03 \pm 0.04	6.0 \pm 0.9
3	Dry, atrophic tongue with fissure	5 (15.2)	0.03 \pm 0.03	6.4 \pm 0.5
TOTAL		33 (100.0)	0.04 \pm 0.04	6.4 \pm 0.6

**Table II. Number of subjects with candidiasis and angular cheilitis
(percentage in brackets)**

Presence of angular cheilitis	Type of Candidiasis					Total
	Tongue	Palate	Retro- molar	Tongue + palate	No can- didiasis	
Unilateral cheilitis	2 (6)	0 (0)	0 (0)	0 (0)	1 (3)	3 (9)
Bilateral cheilitis	1 (3)	0 (0)	0 (0)	0 (0)	3 (9)	4 (12)
No cheilitis	7 (21)	2 (6)	1 (3)	1 (3)	15 (45)	26 (79)
Total	10 (30)	2 (6)	1 (3)	1 (3)	19 (58)	33 (100)

$\chi^2 = 0.07$; $df=1$ (cheilitis yes/no \times candidiasis yes/no); $p = 0.979$

Table III. Correlations between bacterial counts, pH, salivary flow and caries measures

	Lactobacillus count	Streptococcus count	pH	DF-Crown	DF-Root
Streptococcus count	0.43 **				
pH	0.03	-0.30			
DF-Crown	-0.002	0.06	-0.04		
DF-Root	0.01	0.05	-0.04	0.36 *	
Salivary flow	-0.21	-0.22	-0.34 *	-0.17	-0.18

* $p < 0.05$

** $p < 0.01$

Table IV. Percentage distribution of subjects according to highest CPI score based on index teeth and age group

		Percentage of persons who have as highest score					
		0	1	2	3	4	
		No					
	Age	periodontal	Bleedin		Shallo	Deep	
	(yr)	n	disease	g only	Calculus	w	pockets
						pockets	
#This study	53±10	33	0	0	84.8	6.1	9.1
*1991	35-44	372	0	0	26	57	17
*1991	65-74	453	0	0	34	51	15

See materials and methods for explanation concerning age grouping

*1991 data for 35-44 years-old and 65-74 years-old included for comparison⁹

Table V. Proportion of responses from participants concerning their chief complaint of sequelae of irradiation and the proportion who reported that they were informed about expected irradiation side effects prior to treatment

Chief complaint	% of subjects expressing a complaint	% of subjects who reported being informed *
Dry mouth	45	100
Limited mouth opening	15	13
Caries	10	45
Tooth hypersensitivity	10	0
“Lack of strength” of remaining teeth	8	0
Toothache	6	0
Gum bleeding	3	0
Mucosal pain	3	17
Altered taste	0	60
Difficulty in swallowing	0	20
TOTAL	100	255

* Totals more than 100%, because subjects might report more than one condition

Legend of Figures

Fig. 1 Scattergram of relationship between stimulated whole saliva (SWS) flow rate and the size of the radiation dose (in cGY).

Fig. 2 Scattergram of relationship between the number of months since completion of irradiation therapy and the number of Decayed-Filled Teeth (crown caries only).

↑ Top edge

Schwarz et al: Oral health status of southern Chinese who received head and neck radiation therapy for nasopharyngeal carcinoma.

Figure 1.

↑ Top edge

Schwarz et al: Oral health status of southern Chinese who received head and neck irradiation therapy for nasopharyngeal carcinoma.

Figure 2.