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Original Paper

Increased Incidence of Tongue Cancer after Primary Radiotherapy for Nasopharyngeal Carcinoma—the Possibility of Radiation Carcinogenesis

P.M.L. Teo,[1] A.T.C. Chan,[1] S.F. Leung,[1] R.M.C. Chau,[1] P.K.W. Yu,[1] W.W.K. King[2] and P.J. Johnson[1]

[1]Department of Clinical Oncology; and [2]Department of Surgery, Prince of Wales Hospital, Shatin, Hong Kong, China

The aim of this study was to define the risk of tongue and other aerodigestive tract cancers developing after primary radiation therapy for nasopharyngeal carcinoma (NPC). A cohort of 903 patients with non-disseminated NPC given radical radiotherapy between 1984 and 1989 was studied for the incidence of tongue cancer and other malignancies during follow-up. A contemporary cohort of 87 patients with tongue cancer, without a history of NPC, was studied for demographic data, cigarette smoking and alcohol consumption habits. These were then compared with all the NPC patients and with the NPC patients who later developed tongue cancers. There was a significantly increased number of tongue cancers following radiotherapy for NPC. The risk of developing tongue cancer after radiotherapy for NPC was 0.13% per patient per year. There was no increase in the number of other malignancies. The association between NPC and tongue cancer was that of a non-random temporal sequence with tongue cancers following NPC but not in the reverse order. The demographic data and smoking and alcohol consumption history of the 7 NPC patients who subsequently developed tongue cancer were significantly different from the *de novo* tongue cancer patient population. The absence of common aetiological factors between NPC and tongue cancer and the non-random sequence of tongue cancers occurring after NPC suggests that these seven tongue cancers could be radiation induced. The estimated radiation dose received by the part of the tongue developing cancer was substantial and significantly higher than the dose to the cancer-free tongue. An increase of tongue cancers after radiotherapy for NPC is reported and arguments are made in support of the hypothesis that these were radiation-induced malignancies. We suggest a decrease in the volume of tongue included within the planning target volume of NPC in the absence of oropharyngeal and/or parapharyngeal infiltration. Awareness of the association should make early diagnosis of this likely radiation-induced cancer possible.

Key words: NPC, tongue cancer, radiation-induced malignancy
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INTRODUCTION

NASOPHARYNGEAL CARCINOMA (NPC) is a common head and neck (H&N) malignancy in southern China [1–4]. Unlike other H&N cancers, the peak incidence for NPC is 40–50 years [1–4]. The predisposing factors for NPC are also unique. It is strongly associated with Epstein–Barr virus [1, 3], certain carcinogenic diets, such as salted fish and mui-choi (a type of Chinese salt-preserved vegetable) [1, 5, 6], and certain ethnic groups such as southern Chinese and Eskimos [1]. It is not, however, associated with the habit of drinking alcohol and only weakly associated with cigarette smoking [7]. In addition, certain cytogenetic abnormalities [2] and loss of heterozygosity on chromosomes 3 [8] and 11 [9] have been related more frequently to the occurrence of NPC than other H&N and aerodigestive tract cancers. Mucosal field-

Correspondence to P.M.L. Teo, e-mail: anthonytcchan@cuhk.edu.hk
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cancerisation [10] leads to the occurrence of multiple H&N cancers [11, 12] and H&N cancers are associated with oesophageal and bronchal cancers [11, 13]. For H&N cancer there have been no reports of radiation-induced cancers arising within the radiation field. The Radiation Therapy Oncology Group has reported the lack of association between NPC and second malignancies [14]. However, our recent experience suggests that there may, in our NPC population, be an increased incidence of tongue cancer. The aim of this study was to define the risk of second aerodigestive tract cancers in patients with NPC who underwent radical radiotherapy.

PATIENTS AND MATERIALS

Between 1984 and 1989, 903 patients with newly diagnosed NPC (non-disseminated disease) were given radical radiotherapy (62.5 Gy in 6 weeks) to the nasopharynx and cervical nodes. Parapharyngeal tumour infiltration ($n = 288$) was boosted with additional external beam radiotherapy (PPB; 20 Gy) [4] and local residual tumours ($n = 115$) detected at 4–6 weeks postradiotherapy (62.5 Gy) were treated with intracavitary brachytherapy (ICT; 24 Gy over three fractions) [4]. During the same period (1984–1989), there were 87 newly diagnosed *de novo* tongue cancers (i.e. without a history of NPC). The two groups of patients were studied separately for their age and sex distributions, smoking and alcohol drinking habits, survival and the incidence of second malignancies.

In the 903 patients with NPC, the incidence rate of second malignancy was calculated from first presentation to death or last follow-up using the subject-years method [15]. The annual cancer incidence rates reported in the Hong Kong Cancer Registry 1992 were used to calculate the expected incidence rates of the various malignancies in the 903 patients. The age- and sex-adjusted rates were standardised to the Hong Kong population in 1992. A test of the null hypothesis that the patients with NPC had an incidence rate of each (second) malignancy similar to that of the age- and sex-matched Hong Kong population was then performed, comparing the observed rate and the expected rate. In addition, the expected numbers of second malignancies in each gender were calculated using the sex-specific annual incidence rates in the Cancer Registry. The actuarial incidence rate of tongue cancers subsequent to the diagnosis of NPC was plotted against time using the Kaplan–Meier method and the cumulative incidence at 5 years and the annual percentage risk of developing tongue cancer were also calculated.

The 7 patients with NPC who subsequently developed tongue cancer were compared with the 896 patients with NPC who did not, for the stage of disease, the sex ratio and the rates of administration of PPB, ICT and adjuvant chemotherapy, using Fisher's exact test. Data from the Cancer Registry were also used to calculate the expected number of cases of NPC in the 87 patients with *de novo* tongue cancer, employing the subject-years method [15]. The 87 patients with *de novo* tongue cancer were compared with the 7 patients with NPC who later developed tongue cancer, for the distribution of age, sex and stage of the tongue cancer by the non-parametric test or Fisher's exact test where appropriate. All *P* values were two-sided.

Primary radical radiotherapy for NPC [1, 4] consisted of two phases. For the initial phase, the lateral opposing faciocervical fields delivered a central dose of 40 Gy/20 fractions/4 weeks (Figure 1a). However, since the oral tongue was routinely shielded (Figure 1a), only the tongue base was irradiated to a substantial dose. For the latter phase of radiotherapy with a three-field technique that encompasses the

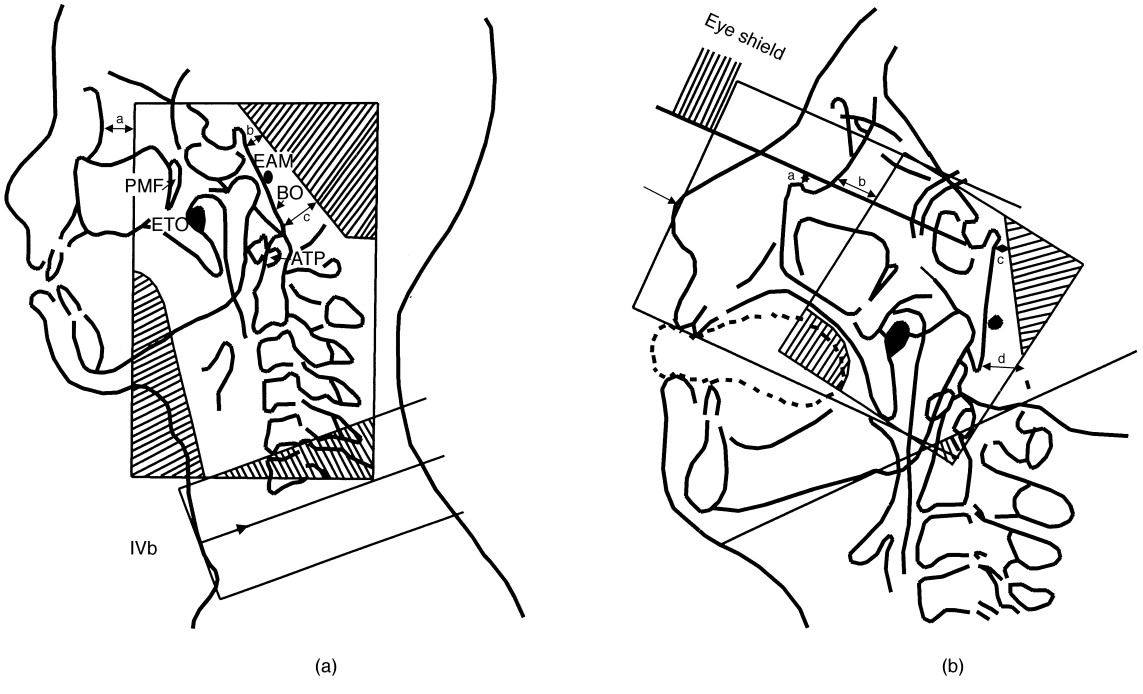

Figure 1. (a) Diagram showing the positions of the lateral faciocervical and the lower cervico-supraclavicular fossa fields with shielded areas shaded during the initial phase (40 Gy) of Ho's radiotherapy technique for nasopharyngeal carcinoma (NPC). PMF, pterygomaxillary fissure; ETO, Eustachian tubal orifice; EAM, external auditary meatus; BO, basiocciput; ATP, atlantoid transverse process end-on; (a)1.5 cm; (b) 0.75 cm (c) 1.5 cm. (b) Diagram showing the positions of the lateral and anterior facial fields and the upper margin of the anterior cervical beam with the shielded area shaded during the second phase (22.5 Gy) of Ho's radiotherapy technique for nasopharyngeal carcinoma (NPC). (a) 0.5 cm; (b) 1.5 cm; (c) 0.75 cm, and (d) 1.5 cm.

nasopharynx and adjacent soft tissues (Figure 1b), treating to another 22.5 Gy/nine fractions/2.5 weeks, the oral tongue was also shielded from the lateral facial fields. However, once again the tongue base (its surface and inferior/hypopharyngeal portion) was largely outside the tongue shields which were deliberately placed at some distance from the ventral surface of the soft palate for fear of shielding the tumour.

The radiation dose to the tongue, the junction between the tongue and tongue base, and the tongue base itself was calculated by applying the Cadplan prospectively in 10 other patients of similar disease stage using identical primary radiotherapy techniques [1, 4]. The 7 patients with NPC developing tongue cancers could not be planned with Cadplan in retrospect because 4 of the 7 had died from the tongue cancer and the remaining 3 were reluctant to be subjected to repeated computed tomography scanning while immobilised. However, since the radiotherapy plan was standardised for NPC of the same T-stage [1, 4], the radiation dose to the nasopharynx and surrounding structures could be regarded as approximately comparable between different patients, notwithstanding minor differences due to body contour and tissue thickness. In addition, although *in vivo* thermoluminescent dosimetry (TLD) could not be carried out in the 7 patients in retrospect, an attempt to reproduce the radiotherapy on a phantom was made using the treatment specifications for each case. The radiation dose (TLD) was measured at the dorsum and lateral surfaces of the oral tongue and the tongue base. Assuming comparability of the pattern of radiation dose distribution between the different portions of the tongue after the same primary radiotherapy technique for NPC, the location of the seven tongue cancers was related to the radiation dose as estimated from the Cadplan calculations (which showed the maximum, minimum and range of dose) and the TLD measurements (which depicted a single point dose within the tongue cancer volume), in an attempt to establish the relationship between the radiation dose and the genesis of the tongue cancer.

RESULTS

At the time of this analysis, the median follow-up of the NPC patients, calculated from the time of diagnosis, was 5.75 years (range 0.07–10.2 years). There were 50 patients lost to follow-up, but these were included in the survival and risk analyses. 485 patients were alive without evidence of relapse or metastasis, 333 had succumbed to NPC between 0.08 and 9.43 years after radical radiotherapy and 23 were alive with active disease.

The male to female ratio of the 903 patients with NPC and the 87 patients with *de novo* tongue cancer were 2.94:1 and 2.22:1, respectively. The patients with NPC were significantly younger than the patients with *de novo* tongue cancer, with a median age of 45 (range 13–79) and 57 (range 26–95) years, respectively ($P = 0.0001$). There were also significantly less cigarette smokers and alcohol drinkers among the patients with NPC than among the patients with *de novo* tongue cancer ($P = 0.034$).

Table 1. *Number of second malignancies in* 903 *nasopharyngeal carcinoma (NPC) patients*

Type of second carcinoma	Number		*P* value
	Expected	Actual	
Tongue	0.20	7	< 0.001
Larynx	0.53	1	0.519
Bronchus	5.63	6	0.881
Oesophagus	1.04	1	0.968
Liver	3.12	2	0.525
Rectum	1.20	1	0.850
Stomach	1.43	1	0.719

A total of 19 patients developed second malignancies after the diagnosis of NPC. There were no synchronous double primary lesions. Tongue cancer, which occurred in 7 patients, was the commonest second malignancy, and was significantly more frequent than expected (Table 1). The incidence of other second malignancies was not significantly different from that expected in a sex- and age-matched local population (Table 1). When the actuarial incidence of tongue cancer after NPC was plotted against time, the risk of developing tongue cancer was 0.13% per patient per year (Figure 2). The cumulative incidence of tongue cancer at 5 years after the diagnosis of NPC was 0.3 (95% confidence interval − 0.12%–0.72%). Moreover, a significant increase in incidence of tongue cancer associated with NPC was seen in both sexes, the expected numbers of tongue cancer being 0.16 and 0.04, respectively, and the observed numbers being 2 and 5, respectively ($P < 0.001$ for males and females).

The seven tongue cancers were well- or moderately well-differentiated epidermoid carcinoma and diagnosed in the absence of NPC recurrence. Demographic data, smoking and alcohol drinking habits, the stage and histology of the tongue cancer, the location of the seven tongue cancers and the primary NPC radiation dose to the part of the tongue developing cancer, are presented in Table 2. The mean interval between NPC radiotherapy and the development of tongue cancer was 71.9 months (range 21–91).

From the Cadplan calculations, a mean of 50% of the tongue volume, mainly the tongue base and the part of the oral tongue immediately anterior to the tongue base, received 20–43 Gy during the initial phase of radiotherapy (Figure 1a). During the second phase of radiotherapy (Figure 1b), an average of 20% of the tongue volume (mainly the tongue base) received 19–26.8 Gy. The dose–volume histogram (DVH) of the tongue (Figure 3a,b) also confirmed that a substantial radiation dose was delivered to a significant

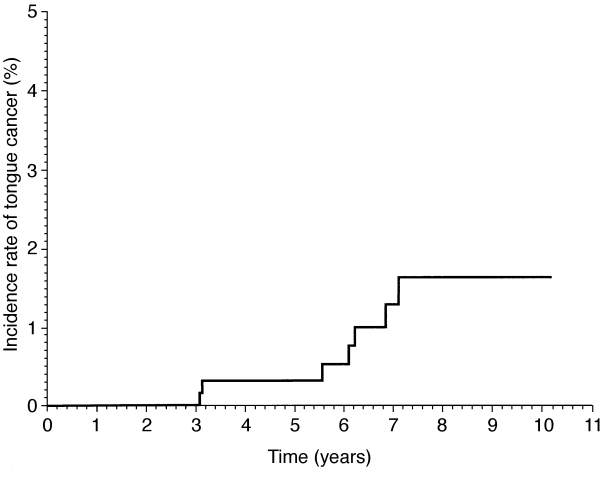

Figure 2. Actuarial incidence rate of developing tongue cancer against time after diagnosis of nasopharyngeal carcinoma (NPC).

Table 2. Characteristics of the 7 patients who developed tongue cancer after nasopharyngeal carcinoma (NPC)

No.	Sex/ age	Smoker/ alcoholic	Interval between completion of RT for NPC and diagnosis of tongue cancer (months)	Size/location of tongue cancer	Primary NPC radiation dose to the part of the tongue developing cancer		Stage of tongue cancer
					Dose estimated with Cadplan median (range) Gy	Dose estimated with TLD measurement (Gy)	
1.	F/29	Non-smoker*/ non-alcoholic†	21	3 cm, left junction between oral tongue and tongue base	58.4 (48.0–68.8)	66.5	III T_2N1Mo
2.	M/34	Smoker and drug addict/non-alcoholic	91	5 cm, midline tongue base	60.4 (49.0–71.8)	62.6	IV T4N3bMo
3.	F/23	Non-smoker/ non-alcoholic	84	2 cm, left junction between oral tongue and tongue base	67.2 (60.1–74.3)	69.0	IV T4N1Mo
4.	F/42	Non-smoker/ non-alcoholic	82	3 cm, right tongue base	75.2 (61.6–88.8)	80.6	II T_2NoMo
5.	F/67	Non-smoker/ non-alcoholic	60	3 cm, midline tongue base	58.4 (48.0–68.8)	65.3	IIIT3NoMo
6.	F/58	Non-smoker/ non-alcoholic	87	4 cm, right lateral surface of oral tongue	30.7 (15.9–45.4)	47.4	IV T4NoMo
7.	M/56	Smoker/ non-alcoholic	78	2 cm, midline junction between oral tongue and tongue base	68.3 (63.6–73.0)	67.8	IIT2NoMo

*Non-smoker was defined as someone who had no history of smoking cigarettes, pipes or cigars. †Non-alcoholic was defined as someone who had no regular/habitual intake of alcohol and whose daily alcohol intake, if any, was estimated to be less than that contained in one can of beer (350 ml). RT, radiotherapy; TLD, thermoluminescent dosimetry.

percentage of the tongue volume. For the parapharyngeal boost [4], nearly the entire tongue received 13–20 Gy. Therefore, more than 20% of the tongue volume received 42–89.8 Gy during radiotherapy with Ho's technique [1, 4] and the highest dose (> 60 Gy) was always delivered to the tongue base and to the oral tongue immediately anterior to the tongue base. The TLD measurements for estimation of the radiation dose to the part of the tongue developing cancer fell within the dose range estimated by the Cadplan calculations, with only one exception, thus confirming the dose distribution to the tongue as calculated by the Cadplan. The tongue cancers occurred mostly at the tongue base or the junction between the oral tongue and the tongue base (Table 2) which corresponded to the high-dose region.

In contrast, the expected number of patients having NPC among the 87 patients with *de novo* tongue cancer was 0.17 and there was no significant difference between the expected number (0.17) and the observed number (0). Although the stage distribution was comparable between the *de novo* tongue cancers and the tongue cancers developing after NPC, the mean age and the sex ratio were significantly different (Table 3).

Table 3. Comparison between the de novo *tongue cancers and the tongue cancers developing after nasopharyngeal carcinoma (NPC)*

Parameter	NPC history	*P* value
Age (years)		
57 (median)	No	0.0001 (Non-parametric test)
45 (median)	Yes	
Sex		
M/F = 60/27	No	0.043 (Fisher's exact test)
M/F = 2/5	Yes	
Stage		
I II III IV	No	0.818 (Fisher's exact test)
13 23 16 27		
0 2 2 3	Yes	

DISCUSSION

There are two possible explanations for the development of tongue cancers following radical radiotherapy for patients with NPC. Either the tongue cancer developed as a radiation-induced malignancy or the two cancers shared common risk factors. In the following discussion, we will argue that the latter explanation is unlikely and that, by exclusion, radiation carcinogenesis is the most likely explanation.

NPC is unique among H&N cancers in its predisposing factors which include ethnic origin [1], exposure in early childhood to carcinogens during the weaning period [1, 5, 6], ingestion or inhalation of other carcinogens such as mui-choi, other preserved food, and cigarette smoke [5–7], certain cytogenetic abnormalities [2, 8, 9] and infection by the Epstein–Barr virus [1, 3]. NPC is only weakly associated with cigarette smoking [7] and is not associated with alcohol intake. Moreover, NPC is not associated with mucosal field-cancerisation [10] as may be the case in multiple aero-digestive tract malignancies. Indeed, the unique predisposing factors in NPC are the likely cause for its lack of increased second malignancies of the aerodigestive tract, most of which are caused by cigarette smoking and alcohol consumption. Therefore, from a review of the literature, NPC and tongue cancer do not share risk factors.

While seven tongue cancers were diagnosed after NPC, there was not a single case of NPC diagnosed after tongue cancer. This further argues against the two cancers sharing common oncogenetic factors or carcinogens. Had this been the case, we should have expected a significant increase in patients having NPC following tongue cancers. Moreover, among the 7 patients who developed tongue cancers after NPC, there were 5 females with only 2 smokers and none with a history of excessive alcohol intake (Table 2). These 7 patients were also significantly younger than the 87 patients with *de novo* tongue cancers (without a history of NPC) (Table 3). Thus, our data suggest the operation of different aetiological factors between NPC and tongue cancer and

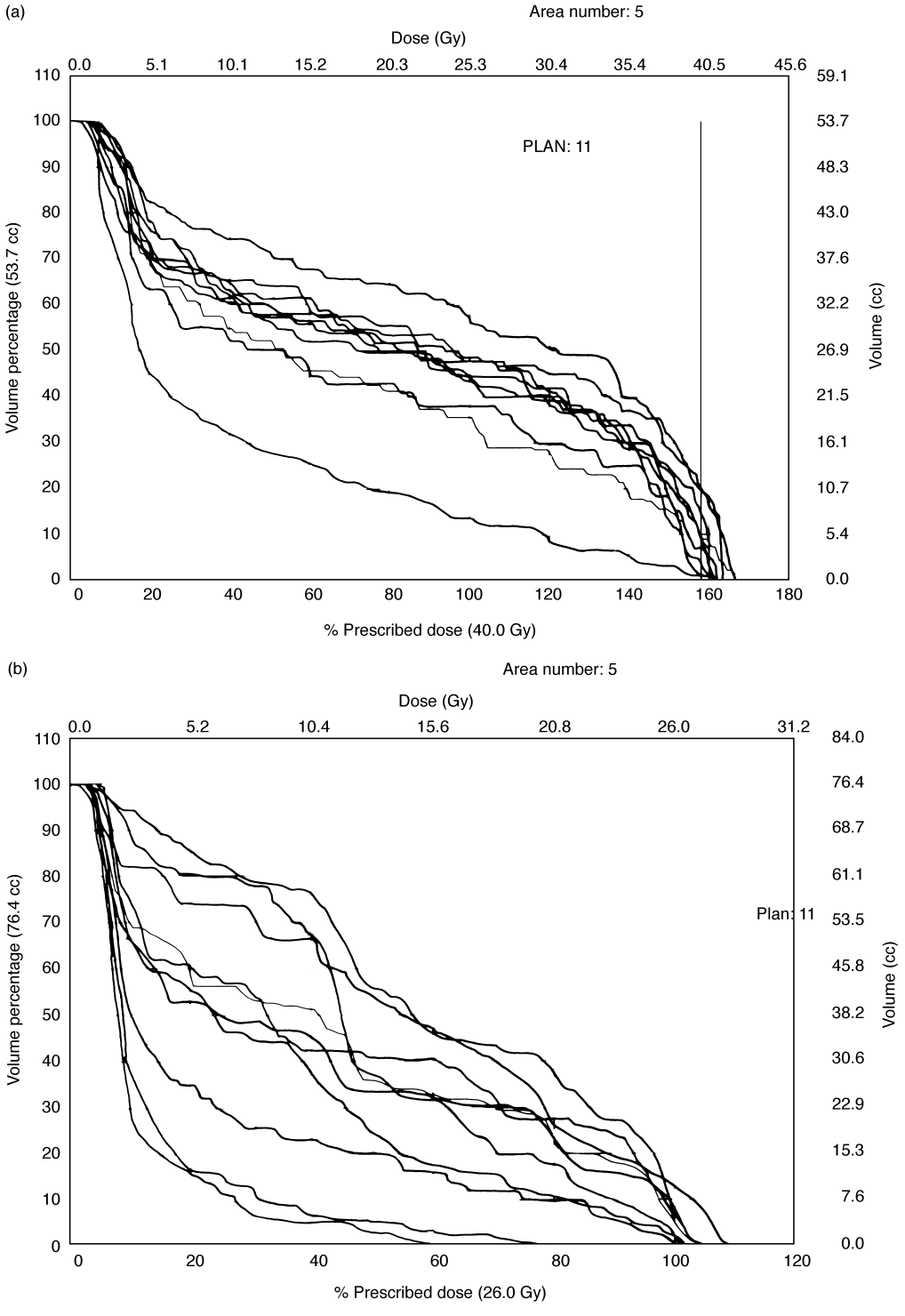

Figure 3. Dose–volume histogram (DVH) of the tongue during (a) phase I and (b) phase II of the radiotherapy for nasopharyngeal carcinoma (NPC).

between the tongue cancer arising *de novo* and the tongue cancer arising after NPC. We believe, therefore, that the increased incidence of tongue cancers after NPC is most likely the result of the primary radiotherapy.

The carcinogenic effects of ionising irradiation have been described in atomic bomb survivors and patients who received radiotherapy. In atomic bomb survivors, radiation-induced cancers include leukaemia, multiple myeloma and cancers of the lung, thyroid, breast, stomach, colon, oesophagus and urinary tract. The relative risk for leukaemia peaked at 5–10 years whilst the relative risk for the development of other cancers increased each year [16]. However, there is no definite evidence of an increase of H&N cancer as a result of the atomic bomb radiation [17].

Therapeutic radiation-induced leukaemias become apparent within 2–4 years, peaking at approximately 6–8 years and decreasing to normal levels at approximately 25 years. Solid cancers typically occur more than 10 years after treatment

but with large variations [18–21]. The most well-documented secondary cancers occur in Hodgkin's disease. In the Stanford study of 1507 patients with Hodgkin's disease, 83 second cancers occurred more than 1 year after diagnosis and the mean 15 year actuarial risk of all second cancers was $17.6 \pm 3.1\%$ of which $13.2 \pm 3.1\%$ were due to solid tumours [20]. The data suggest that the risk of solid tumours continues to increase with time. The most common second tumour was lung cancer in these patients. Cancers of the stomach, bone and soft tissue also arose within the field of radiation, whereas other tumours including non-Hodgkin's lymphoma, melanoma and squamous cell carcinoma of the skin occurred in excess in the patients treated with chemotherapy [20]. Squamous cell carcinoma of the H&N has also been reported to arise in previously irradiated fields of patients with Hodgkin's disease [22]. The numbers in different centres are small but it is postulated that, with longer follow-up, there will be more cases reported. However, in primary H&N cancers, there is no conclusive evidence that the risk of a second primary cancer is different in patients treated with surgery, radiation therapy or surgery plus radiation therapy [23]. In the UCLA series of 2151 patients with primary H&N cancers, the overall ratio of development of second cancers of the H&N was in excess of 2.5 per 1000 person-years at risk. The frequency was no greater in the patients treated with radiation than in the patients treated only by surgery and it was concluded that the risk of radiation-induced cancer should not be a factor influencing clinical decision making in the management of H&N cancers [23, 24].

Hence, the finding in the present study of the development of 7 cases of tongue cancer after NPC, which we argue were radiation-induced malignancies as a result of primary NPC radiotherapy, is the first in the literature of radiation-induced secondary epidermoid cancers arising within the radiation field for a primary H&N cancer. Although the latency period between NPC radiotherapy and the development of tongue cancer (71.9 months, range 21–91 months, Table 2) was substantially shorter than the typical latency period for the development of radiation-induced malignancies [18–22], it does fall within the wide range of latency periods after radiation exposure for the development of solid tumours [18, 20–22, 25, 26]. It should be emphasised that in most reports [17–22] of a long latency period between radiation exposure to the occurrence of the radiation-induced solid tumours, the radiation dose had been low to moderate (mostly between 5 and 50 Gy). For example, the radiation-induced solid tumours in the Stanford series [20] occurred after mediastinal/para-aortic nodal irradiation which delivered a radiation dose not exceeding the prescribed dose of 40–44 Gy to the sites where the secondary malignancies later developed. In contrast, the tongue cancers in our series had arisen after a significantly higher radiation dose (to the tongue base and the oral tongue immediately anterior to the tongue base), which was estimated to be above 60 Gy by the TLD measurement in 6 of the 7 cases (Table 2).

An inverse relationship between the radiation dose and the latency period for the development of the radiation-induced sarcomas had been suggested by Laskin and colleagues [26]. Cahan and associates [25] reported that radiation-induced sarcomas seldom occurred after moderate doses and that a substantial dose of 3000 rads (30 Gy) was required. These two reports suggest both a dose–latency period relationship and a dose–incidence rate relationship at least, for radiation-induced sarcomas. Although the dose–latency period and dose–incidence rate relationships for radiation carcinogenesis have not been clearly defined for the various histological types of radiation-induced malignancies, it appears, from our present experience, that a substantial radiation dose (Table 2) is associated with a significant risk of development of epidermoid carcinoma of the tongue during the first decade after the radiation exposure. Whether the low radiation dose delivered to the rest of the tongue which is protected by tongue shields (Figure 1) will also be associated with a significant risk of carcinogenesis after a longer latency period cannot be assessed from the present study.

Although radiation-induced tongue cancer is an uncommon complication of primary radiotherapy for NPC, its incidence may increase with longer follow-up and as survival improves. The poor treatment results of the tongue cancers may, at least in part, be explained by their advanced stages—two stage III and three stage IV (Table 2). Therefore, efforts should be directed towards reduction of the incidence of radiation-induced tongue cancer and early diagnosis of the disease where it arises. To reduce the disease incidence, it is important that during modern radiotherapy, planning with three-dimensional conformal methods, the tongue should be spared as much as possible from high-dose irradiation in the absence of oropharyngeal and/or parapharyngeal involvement by NPC. The posterolateral oblique photon boost, recommended for conventional two-dimensional radiotherapy for parapharyngeal involvements [4], should include a shield whenever appropriate to decrease the dose to the tongue without compromising the tumour dose. To facilitate early diagnosis of the radiation-induced malignancy, a high index of suspicion has to be inculcated among the radiation oncologists so that the patient's complaint about 'a foreign body sensation in the back of the mouth' should be given due respect and the patient should be subject to a thorough examination with special attention to the tongue base.

In conclusion, we report a significant increase in tongue cancers after NPC which we have reasons to believe were radiation-induced malignancies. We have also suggested ways in which the morbidity and mortality of this unusual radiation complication can be minimised. However, the study was motivated by the casual observation of a seemingly high incidence of tongue cancer in the present data, and could be regarded as a 'data-driven' analysis in which bias could be introduced. Therefore, confirmatory evidence from other centres is deemed necessary to substantiate this hypothesis.

1. Ho JHC. An epidemiologic and clinical study of nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1978, **4**, 183–198.
2. Huang DP, Ho JHC, Chan WK, Lau WH, Lui M. Cytogenetics of undifferentiated nasopharyngeal carcinoma xenografts from southern Chinese. *Int J Cancer* 1989, **43**, 936–939.
3. Lung ML, Lam WP, Sham J, *et al.* Detection and prevalence of the "f" variant of Epstein–Barr virus in Southern China. *Virology* 1991, **185**(1), 67–71.
4. Teo PML, Lee WY, Yu P. The prognostic significance of parapharyngeal tumour involvement in nasopharyngeal carcinoma. *Radiother Oncol* 1996, **39**, 209–221.
5. Shanmugaratnam K, Tye CY, Goh EH, Chia KB. *Etiological Factors in Nasopharyngeal Carcinoma: a Hospital-based, Retrospective, Case–Control, Questionnaire Study*. IARC Scientific Publication No. 20. Lyon, IARC, 1978, 19–212.
6. Armstrong RW, Armstrong MJ, Yu MC, Henderson B. Salted fish and inhalants as risk factors in nasopharyngeal carcinoma in Malaysian Chinese. *Cancer Res* 1983, **43**, 2967–2970.

7. Mabuchi K, Bross DS, Kessler II. Cigarette smoking and nasopharyngeal carcinoma. *Cancer* 1985, **55**, 2874–2876.
8. Huang DP, Lo KW, Choi PHK, *et al.* Loss of heterozygosity on the short arm of chromosome 3 in nasopharyngeal carcinoma. *Cancer Genet Cytogenet* 1991, **54**, 91–99.
9. Hui AB, Lo KW, Leung SF, *et al.* Loss of heterozygosity on the long arm of chromosome 11 in nasopharyngeal carcinoma. *Cancer Res* 1996, **56**(14), 3225–3229.
10. Waridel F, Estreicher A, Bron L, *et al.* Field cancerisation and polyclonal p53 mutation in the upper aero-digestive tract. *Oncogene* 1997, **14**(2), 163–169.
11. Licciardello JT, Spitz MR, Hong WK. Multiple primary cancer in patients with cancer of the head and neck: second cancer of the head and neck, oesophagus, and lung. *Int J Radiat Oncol Biol Phys* 1989, **17**(3), 467–476.
12. Shikhani AH, Matanoski GM, Jones MM, Kashima HK, Johns ME. Multiple primary malignancies in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 1986, **112**(11), 1172–1179.
13. Yellin A, Hill LR, Benfield JR. Bronchogenic carcinoma associated with upper aerodigestive cancers. *J Thorac Cardiovasc Surg* 1986, **91**(5), 674–683.
14. Cooper JS, Scott C, Marcial V, *et al.* The relationship of nasopharyngeal carcinomas and second independent malignancies based on the Radiation Therapy Oncology Group experience. *Cancer* 1991, **67**(6), 1673–1677.
15. Armitage P, Berry G. *Statistical Methods in Medical Research*, 2nd edn. Oxford, Blackwell, 1987.
16. Preston DL, Kato H, Kopecky KJ. Studies of the mortality of A-bomb survivors. *Radiat Res* 1987, **111**, 151–178.
17. Pinkston JA, Wakabayashi T, Yamamoto T. Cancer of the head and neck in atomic bomb survivors: Hiroshima and Nagasaki 1957–1976. *Cancer* 1981, **48**, 2172–2178.
18. Boice JD. Cancer following medical irradiation. *Cancer* 1981, **47**, 1081–1090.
19. Fisher B, Rockette H, Fisher ER. Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiation: the NSABP experience. *J Clin Oncol* 1985, **3**, 1640–1658.
20. Tucker MA, Coleman NC, Cox RS. Risk of secondary malignancies following Hodgkin's disease after 15 years. *N Engl J Med* 1988, **318**, 76–81.
21. Valagussa P, Santoro A, Bellani-Fossati F. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. *J Clin Oncol* 1986, **4**, 830–837.
22. Wallner KE, Leibel SA, Wara WM. Squamous cell carcinoma of the head and neck after radiation therapy for Hodgkin's disease: a report of two cases and a review of the literature. *Cancer* 1985, **56**, 1052–1055.
23. Parker RG, Enstrom JE. Second primary cancers of the head and neck following treatment of initial primary head and neck cancers. *Int J Radiat Oncol Biol Phys* 1988, **14**, 561–564.
24. Parker RG. Radiation-induced cancer as a factor in clinical decision making. *Int J Radiat Oncol Biol Phys* 1990, **18**, 993–1000.
25. Cahan WG, Woodard HQ, Higinbotham NL, Steward FW, Coley BL. Sarcoma arising in irradiated bone—report of eleven cases. *Cancer* 1948, **5**, 3–29.
26. Laskin WB, Silverman TA, Enzinger FM. Postradiation soft tissue sarcomas—an analysis of 53 cases. *Cancer* 1988, **62**, 2330–2340.

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