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RADIATION-INDUCED CRANIAL NERVE PALSY: A CROSS-SECTIONAL STUDY OF NASOPHARYNGEAL CANCER PATIENTS AFTER DEFINITIVE RADIOTHERAPY

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Purpose: To address the characteristics and the causative factors of radiation-induced cranial nerve palsy (CNP) in nasopharyngeal carcinoma (NPC) patients with an extensive period of followed-up.

Patients and Methods: A total of 317 consecutive and nonselected patients treated with definitive external-beam radiotherapy between November 1962 and February 1995 participated in this study. The median doses to the nasopharynx and upper neck were 71 Gy (range, 55–86 Gy) and 61 Gy (range, 34–72 Gy), respectively. Conventional fractionation was used in 287 patients (90.5%). Forty-five patients (14.2%) received chemotherapy.

Results: The median follow-up was 11.4 years (range, 5.1–38.0 years). Ninety-eight patients (30.9%) developed CNP, with a median latent period of 7.6 years (range, 0.3–34 years). Patients had a higher rate of CNP (81 cases, 25.5%) in lower-group cranial nerves compared with upper group (44 cases, 13.9%) ($\chi^2 = 34.444$, $p < 0.001$). Fifty-nine cases experienced CNP in more than one cranial nerve. Twenty-two of 27 cases (68.8%) of intragroup CNP and 11 of 32 cases (40.7%) of intergroup CNP occurred synchronously ($\chi^2 = 4.661$, $p = 0.031$). The cumulative incidences of CNP were 10.4%, 22.4%, 35.5%, and 44.5% at 5, 10, 15, and 20 years, respectively. Multivariate analyses revealed that CNP at diagnosis, chemotherapy, total radiation dose to the nasopharynx, and upper neck fibrosis were independent risk factors for developing radiation-induced CNP.

Conclusion: Radiation-induced fibrosis may play an important role in radiation-induced CNP. The incidence of CNP after definitive radiotherapy for NPC remains high after long-term follow-up and is dose and fractionation dependent. © 2011 Elsevier Inc.

Nasopharyngeal carcinoma, Radiotherapy, Radiation-induced cranial nerve palsy.

INTRODUCTION

Radiotherapy is one of the most commonly used and effective cancer treatment modalities. However, radiation-induced adverse effects are common, especially at high doses (1). The long-term complications secondary to radiotherapy are usually permanent. Among all known long-term adverse effects, radiation-induced peripheral neuropathy, especially involving cranial nerves, is one of the least studied and least understood complications of radiotherapy. Although uncommon, cranial nerve palsy (CNP) is frequently debilitating; it can severely affect patients' quality of life and can even be life-threatening (2, 3). However, characteristics of radiation-induced CNP in the treatment of head-and-neck malignancies are largely unknown. The relatively low incidence of radiation-induced CNP makes a randomized, controlled, prospective study of this topic difficult. Furthermore, the potential long latent period before the onset of CNP after radiotherapy reduces the feasibility of a prospective cohort study. The aim of this cross-sectional study is to address the characteristics and causative factors of radiation-induced CNP in a large group of patients with nasopharyngeal carcinoma (NPC) who were definitively irradiated and followed for an extensive period of time.

PATIENTS AND METHODS

Patients

Between February 2000 and February 2002, 317 consecutive and nonselected patients previously treated with definitive radiotherapy for NPC before February 1995 were followed up at the Cancer Center of Fudan University and enrolled in this cross-sectional study. No patients declined participation. This cross-sectional study was designed to identify and study patients who developed CNP during long-term follow-up. Patients who were reirradiated for recurrent disease were excluded in this analysis. Patients' history was carefully reviewed. Reclassification of T category according to the 1997 American Joint Committee on Cancer staging system was not performed owing to the extensive period of time when patients were

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treated. The nodal classification in some patients was based on physical examination. Table 1 summarizes the patient characteristics.

Treatment methods

All patients received definitive external-beam radiotherapy with either ^{60}Co or megavoltage linear accelerators between November 1962 and February 1995. The standard definitive doses to the primary tumor and lymph nodes were 70 Gy and 66 Gy, respectively, with conventional fractionation. Any residual lesion in either the nasopharynx or neck received a boost dose. The institutional treatment techniques used for patients in the study have evolved during the past 3 decades. Two main techniques (Techniques A and B) of external-beam radiotherapy were used for definitive treatment of localized NPC.

The treatment technique for Technique A has been described in detail previously (4). Briefly, it is divided into two phases. In the initial phase, the skull base, nasopharynx, and upper neck were treated *en bloc* by two lateral-opposing faciocervical portals to 36–40 Gy, whereas the lower neck was treated with a separate upper portal with midline shield and subclavicular lung shields. In the second phase, the skull base and nasopharynx were irradiated by a three-field arrangement (two lateral fields and one upper facial field) to avoid excessive irradiation to the spinal cord, with an enlarging upper beam used to cover the whole neck. The midline structures and the lung apices were shielded from the upper cervical portal as in phase one. The radiotherapy of Technique B used the same three fields as in part two of Technique A to radically dose the skull base and nasopharynx, whereas the entire neck was treated separately by a large neck field. Two hundred fifty-five patients (80.4%) were treated with Technique B, and 62 patients (19.6%) were treated with Technique A.

The median doses to the nasopharynx and upper neck were 71 Gy (range, 55–86 Gy) and 61 Gy (range, 34–72 Gy), respectively. Conventional fractionation radiotherapy was used for 287 patients (90.5%), whereas hyperfractionation radiation or later-course accelerated hyperfractionation radiation was used for 30 patients (9.5%). High-dose-rate brachytherapy with ^{192}Ir was used in 24 patients, either as part of definitive treatment or as a boost for residual disease in the nasopharynx. Forty-five patients (14.2%) also received chemotherapy with various regimens.

Diagnosis of cranial nerve palsy

The criteria for diagnosis of CNP were previously described by Lin *et al*. (2). Briefly, a diagnosis of radiation-induced CNP was based on the patient's detailed history and physical examination. The possibility of recurrence-induced CNP was ruled out using MRI or CT scans and nasopharyngoscopy, as well as biopsy if necessary before the diagnosis of radiation-induced CNP could be made. Additionally, careful follow-up for at least 12 months was required before the diagnosis of radiation-induced CNP was made. For purposes of analysis, cranial nerves were divided into upper cranial nerves (II–VI) and lower cranial nerves (IX–XII), as described by Chang *et al*. (5). Because of its anatomic position, cranial nerve VII was not included in either upper or lower group of cranial nerves and was analyzed separately. The vestibulocochlear nerve (VIII) was not included in this analysis because hearing difficulty is frequently associated with many other pathologies of the auditory system, including aging. According to the 1995 LENT-SOMA (Late Effects of Normal Tissue – Subjective, Objective, Management and Analytic) criteria (6), the incidence of Grade ≥2 newly developed CNP was recorded for each nerve.

Table 1. Patient characteristics

Characteristic	*n*	%
Gender		
Male	212	66.9
Female	105	33.1
Age (y)		
≤50	254	80.1
>50	63	19.9
N classification		
N0	90	28.4
N1–3	227	71.6
Chemotherapy		
Yes	45	14.2
No	272	85.8
Radiation technique		
Technique A	62	19.6
Technique B	255	80.4
Total dose to nasopharynx (Gy)		
≤70	139	43.8
>70	178	56.2
Fractionation		
Conventional	287	90.5
Hyperfractionated	30	9.5
Brachytherapy		
Yes	24	7.6
No	293	92.4
Total dose to neck (Gy)		
≤60	146	46.1
>60	171	53.9

Statistics

Cumulative risk of all radiation-induced CNP from the date of initial radiotherapy was estimated by the Kaplan-Meier method. Differences in cumulative risk between groups were based on the log–rank test. The Cox proportional hazards regression model was utilized to estimate the relative risk (RR) of the development of CNP. All reported p values are two-sided and considered statistically significant if <0.05.

RESULTS

The median follow-up for all 317 patients was 11.4 years (range, 5.1–38.0 years). One hundred fifteen patients (36.3%), 137 (43.2%), and 65 (20.5%) were observed for 5–10 years, 10–20 years, and >20 years, respectively.

Characteristics of cranial nerve palsy

Ninety-eight of 317 patients (30.9%) experienced radiation-induced CNP during follow-up. One case of cranial nerve VII symptom that occurred at 18 months after completion but recovered spontaneously within 3 months was not included as a CNP case. Patients had a higher rate of lower CNP (81 cases, 25.5%) than upper CNP (44 cases, 13.9%) ($\chi^2 = 34.444$, $p < 0.001$). The median time to the development of CNP after radiation was 7.6 years (range, 0.3–34 years), 8.0 years (range, 0.3–26 years), and 7.9 years (range, 0.5–34 years) for the whole, upper, and lower groups, respectively. The average annual rates of developing CNP were 2.2%, 1.0%, and 1.8% for the whole, upper, and lower groups, respectively. The cumulative incidences of CNP

were 10.4%, 22.4%, 35.5%, and 44.5% at 5, 10, 15, and 20 years, respectively (Fig. 1). The results demonstrate that among all patients who developed CNP, approximately 10% of patients developed CNP during every 5 years of follow-up. The cumulative incidences of lower CNP were 5.7%, 17.4%, 27.1%, and 37.3% at 5, 10, 15, and 20 years, respectively; and those of the upper CNP were 5.4%, 10.1%, 17.4%, and 19.4% at 5, 10, 15, and 20 years, respectively.

Fifty-nine patients experienced CNP in more than one nerve: 27 patients developed symptoms in both upper and lower cranial nerve groups (intergroup), and 32 patients developed symptoms in more than one cranial nerve in either group (intragroup). For patients with involvement of two or more nerves, multiple CNPs occurring within 6 months of each other were defined as synchronous CNP. Twenty-two patients (68.8%) with intragroup CNP had multiple CNPs that occurred synchronously, whereas 11 patients (40.7%) with intergroup CNP had multiple CNPs that occurred synchronously, ($\chi^2 = 4.661$, $p = 0.031$). No CNP was observed in cranial nerve VII except for the one case that occurred at 18 months after radiotherapy but spontaneously resolved within 3 months, as mentioned above.

Significant causative factors

The severity of fibrosis in the upper neck of each patient was graded at the time of follow-up according to LENT-SOMA criteria (6). Fifty-four (17%) patients presented with severe fibrosis (Grade 3 or 4) in the upper neck. These patients had a 26.1% 5-year cumulative incidence and a 46.0% 10-year cumulative incidence of CNP, compared with 7.2% and 17.3%, respectively, in patients with Grade 0–2 fibrosis (Fig. 2) ($p < 0.001$). Severe neck fibrosis was associated with an approximately two-fold risk of developing CNP as compared with patients with Grade 0–2 fibrosis (RR = 1.807; 95% confidence interval, 1.440–2.266; $p < 0.001$) (Table 2).

Multivariate analyses revealed that CNP at diagnosis, chemotherapy, total radiation dose to the nasopharynx, and upper neck fibrosis were independent risk factors for developing radiation-induced CNP (Table 2). Subgroup analysis revealed that CNP at diagnosis and fractionation dose were independent risk factors for developing radiation-induced CNP in the upper cranial nerve group (Table 3). Radiation technique, total dose to the nasopharynx, and upper neck fibrosis were independent risk factors for developing radiation-induced CNP in the lower group (Table 4).

DISCUSSION

Cranial nerve palsy after definitive radiotherapy for NPC is rare and has an extended latent period. Because of its prolonged course and rarity, little is known about its characteristics. This cross-sectional study is the first of its kind to analyze the characteristics and causative factors of CNP in a large patient population with extended follow-up. Multivariate analyses revealed that muscle fibrosis of the neck, total

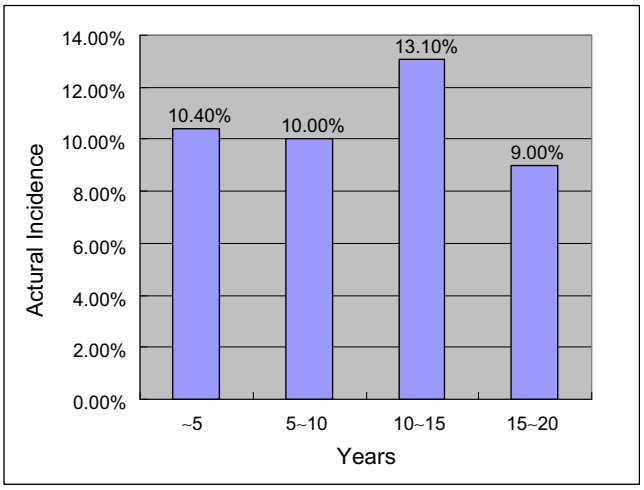

Fig. 1. Actual incidences of cranial nerve palsy.

radiation dose to the nasopharynx, hyperfractionation technique, use of chemotherapy, and CNP at diagnosis are significant risk factors for developing CNP after radiotherapy. Specifically, symptomatic CNP at the time of diagnosis and dose of radiation to the primary disease were significantly associated with the development of CNP in cranial nerves II–VI; and radiation technique (thus higher neck dose due to potential overlap of the superior/inferior fields), total dose to the primary disease, and upper neck fibrosis were significantly associated with radiation-induced CNP in cranial nerves IX–XII.

As treatment outcomes improve, long-term side effects are expected to be seen more frequently, especially with conventional radiotherapy techniques. We consider this study design and results important because a large number of patients with long-term follow-up were accrued, which allowed for analyses of factors related to the development of this rare side effect. The factors associated with the development of CNP can

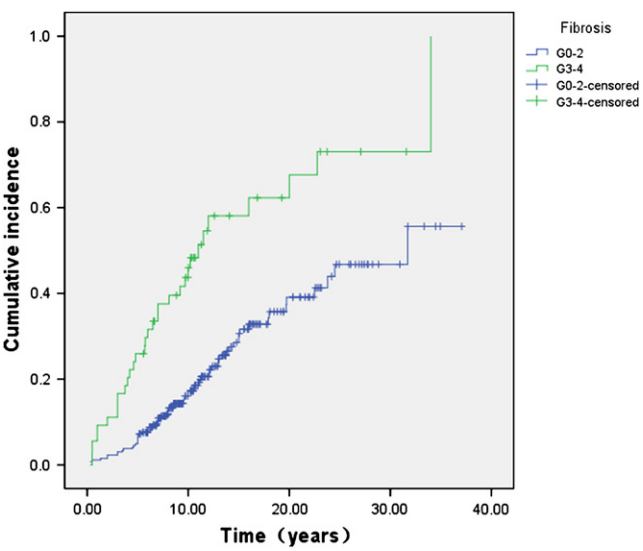

Fig. 2. Cumulative incidence of radiation-induced cranial nerve palsy in patients with G0–2 or G3–4 fibrosis.

Table 2. *P* values from log–rank test and Cox model for CNP

Factor	Log–rank test (*p*)	Cox model		
		RR	95% CI	*p*
Gender	0.517	0.945	0.610–1.463	0.799
Age	0.267	0.540	0.286–1.018	0.057
CNP at diagnosis	0.018	2.093	1.138–3.850	0.018*
N classification	0.280	1.378	0.768–2.471	0.283
Chemotherapy	0.142	1.422	1.056–1.914	0.021*
Radiation technique	0.310	1.798	0.888–3.639	0.103
Total dose to nasopharynx	0.012	1.961	1.187–3.238	0.009*
Brachytherapy	0.426	1.117	0.394–3.170	0.835
Fractionation dose	0.248	1.989	0.922–4.292	0.080
Total dose to neck	0.784	0.805	0.465–1.394	0.440
Neck fibrosis	0.000	1.807	1.440–2.266	0.000*

Abbreviations: CNP = cranial nerve palsy; RR = relative risk; CI = confidence interval.
* Statistically significant ($p < 0.05$)

Table 4. *P* value from log–rank test and Cox model for lower CNP

Factor	Log–rank test (*p*)	Cox model		
		RR	95% CI	*p*
Gender	0.884	0.908	0.566–1.457	0.690
Age	0.711	0.621	0.316–1.220	0.167
CNP at diagnosis	0.959	1.019	0.453–2.296	0.963
N classification	0.609	1.019	0.535–1.943	0.954
Chemotherapy	0.254	1.388	0.993–1.942	0.055
Radiation technique	0.049	3.400	1.324–8.734	0.011*
Total dose to nasopharynx	0.000	3.088	1.730–5.513	0.000*
Brachytherapy	0.399	0.755	0.231–2.473	0.643
Fractionation dose	0.204	2.071	0.902–4.751	0.086
Total dose to neck	0.343	0.970	0.522–1.801	0.922
Neck fibrosis	0.000	1.938	1.521–2.470	0.000*

Abbreviations as in Table 2.
* Statistically significant ($p < 0.05$)

be used to distinguish tumor recurrence from treatment-induced neurologic sequelae.

Our results indicate that neck muscle fibrosis is a significantly associated with the development of CNP after definitive radiotherapy for NPC ($p < 0.001$), especially in the nerves that course through the neck muscles, and may be a causative factor for CNP. Patients with severe fibrosis in the upper neck (Grade 3–4) had an approximately two-fold greater risk of developing CNP (RR = 1.807) compared with those with Grade 0–2 fibrosis. A number of smaller studies have reported that fibrosis may be an important factor in the development of radiation-induced CNP and another type of radiation-induced peripheral neuropathy, brachial plexopathy (2, 7–10). The relationship of brachial plexopathy and fibrosis was demonstrated by an autopsy series of 2 patients with breast cancer who were suffering from brachial plexopathy after postoperative radiation. In that report, Stoll and Andrews (8) found marked fibrosis surrounding the nerve trunk, with fibrous infiltration and replacement of nerve fibers. Results from other studies demonstrated fibrosis surrounding the brachial plexus on MRI (9, 10). With regard to CNP, Lin *et al.* (2) found that 12 of 19 patients with radiation-induced lower CNP had marked neck fibrosis. Our study, in conjunction with results from the aforementioned reports, reveals that direct nerve damage by radiotherapy may not be the only causative factor for CNP at therapeutic dose for NPC. Rather, muscle fibrosis secondary to radiotherapy may be a more important factor leading to radiation-induced CNP. The courses of the cranial nerves in the lower group are surrounded by neck muscles. When these muscles become fibrotic because of radiotherapy, we can conjecture that the nerves may become entrapped or otherwise damaged by fibrosis. Additionally, fibrosis may lead to injury of vessels supplying the nerves. Our results demonstrate the importance of avoiding excess radiation to muscle and soft tissue.

Table 3. *P* values from log–rank test and Cox model for upper CNP

Factor	Log–rank test (*p*)	Cox model		
		RR	95% CI	*p*
Gender	0.172	0.723	0.356–1.467	0.369
Age	0.966	0.993	0.428–2.301	0.987
CNP at diagnosis	0.000	3.612	1.675–7.786	0.001*
N classification	0.652	1.717	0.742–3.973	0.207
Chemotherapy	0.249	1.362	0.891–2.083	0.153
Radiation technique	0.579	0.905	0.354–2.314	0.834
Total dose to nasopharynx	0.788	1.099	0.536–2.255	0.796
Brachytherapy	0.265	2.308	0.779–6.840	0.131
Fractionation dose	0.087	2.912	1.072–7.913	0.036*
Total dose to neck	0.562	0.658	0.287–1.509	0.323

Abbreviations as in Table 2.
* Statistically significant ($p < 0.05$).

Total radiation dose to the nasopharynx over 70 Gy was an important risk factor for CNP in our study (RR = 1.961, $p = 0.009$). Specifically, the total dose of radiation to the lower, but not upper, cranial nerves was identified as a significant prognostic factor leading to the development of CNP (RR = 3.088, $p < 0.001$). This gives additional support to the idea that radiation dose of approximately 70 Gy alone may be safe for the nerves, but the dose may lead to muscle fibrosis, which in turn leads to CNP. Both upper and lower cranial nerves, at least part of them, usually receive a similar radiation dose in conventional radiation. However, the nerves of the lower group were more likely to develop CNP. Additional evidence of total radiation dose affecting lower cranial nerves is seen in a study by Teo *et al.* (11, 12). They report that radiation-induced cranial nerve IX–XII palsy occurred almost exclusively on the side of parapharyngeal tumor infiltration that required boosting. In a study by King *et al.* (3), 6 of the 7 patients who required a boost dose of radiation to the parapharyngeal region developed hypoglossal nerve palsy on the boosted side. In analysis of another model of radiation-induced peripheral neuropathy, several reports showed that the occurrence of brachial plexopathy was

highly dose (3, 11–13) and fractionation (7, 8, 14–16) dependent. Gałecki *et al.* (16) reviewed the published literature and found that the use of doses per fraction in the range from 2.2 Gy to 4.58 Gy, with total doses between 43.5 Gy and 60 Gy, caused a significant risk of brachial plexus injury, which ranged from 1.7% up to 73%. The risk of radiation-induced brachial plexopathy was smaller than 1% using regimens with doses per fraction between 2.2 Gy and 2.5 Gy with total doses between 34 Gy and 40 Gy.

Hyperfractionated or late-course accelerated hyperfractionated radiotherapy was used for 30 cases in our study and was found to be a significant risk factor for only upper CNP (RR = 1.6, $p = 0.008$). A possible hypothesis of CNP after hyperfractionated irradiation is that higher total daily dose is an important factor in damage to cranial nerves. Because multivariate analysis demonstrated that only upper nerve palsy was significantly affected by hyperfractionated irradiation, we postulate that the lower nerves were so significantly affected by muscle fibrosis that fractionation was not found to be significant. In the study by Teo *et al.* (11), a tendency was reported for higher incidence of radiation-induced lower CNP in patients treated with accelerated-hyperfractionated irradiation compared with those treated using conventional fractionation (13.0% vs. 8.7%) during 59.2 months' median follow-up. In that study, neck fibrosis was observed in only 1 and 2 patients in each arm. This finding supports our hypothesis, in that neck fibrosis and hyperfractionation were interlaced factors for CNP in the lower group. Results from our study and the study reported by Teo *et al.* indicate that a twice-daily regimen (such as accelerated-hyperfractionated radiation) is an aggravating factor for radiation-induced CNP.

Our results indicate that radiation technique is a pertinent factor for radiation-induced lower CNP (RR = 3.4, $p = 0.011$). Because of the potential interfraction field overlap of the superior and inferior fields in Technique B, the dose received by the carotid space, where some of the lower cranial nerves pass, could be higher. This finding supports the proposed hypothesis that radiation dose is an important risk factor for the development of CNP. The possible dose increment may also contribute to muscle fibrosis. A retrospective dose calculation using isocentric recalculation revealed that the fractional dose to the carotid space region reached 2.3 Gy when the prescribed dose to the midplane at the level of nasopharynx was 2 Gy. Therefore, patients treated with Technique B received higher total and fractional doses than those treated by Technique A. No difference was expected in the upper group CNP according to radiation technique, because dose fractionation to the cavernous sinus is similar in both techniques. Johansson *et al.* (7, 14) also highlighted hot spots from overlapping fields as a major risk factor for radiation-induced brachial plexopathy in breast cancer.

In addition to radiation dose and fractionation dose, the field of radiation, especially that to the primary regions, is of importance. Sizes of radiation field are associated with both treatment techniques (e.g., Technique A or B) and presenting T category of the disease. Ideally, the T category as well as the field volume of all cases in the series could be retrieved and analyzed as two prognostic factors. However, because the patients included in our cross-sectional study were accrued over a long period (many of the patients were treated in the pre-CT era), redelineation of the tumor volume or restaging using the updated American Joint Committee on Cancer staging system was not feasible. Cranial neuropathy at presentation is an important diagnostic factor for T4 disease, and our results indicate that cranial neuropathy at presentation is significantly associated with the development of upper CNP after definitive radiotherapy for NPC ($p = 0.001$). However, our report is limited because factors such as cavernous sinus or other extent of intracranial invasion, which is a major criterion for defining T4 NPC, could not be included in the analyses.

Although only 45 patients received chemotherapy in our study, our data showed that chemotherapy is significantly associated with CNP (RR = 1.422, $p = 0.021$). Adjuvant chemotherapy resulted in increased risk of peripheral neuropathy in other studies as well (13, 17). Olsen *et al.* (13) compared the complications in breast cancer patients after postmastectomy irradiation, with or without adjuvant cyclophosphamide, methotrexate, and fluorouracil–based chemotherapy. Among the19 patients who developed radiation-induced brachial plexopathy, 17 patients (13% of a total of 128) had chemotherapy, as compared with 2 patients (1.6% of a total of 128) who were not treated with chemotherapy ($p < 0.01$). In our study, various chemotherapy agents and regimens were used. Because concurrent cisplatin-based chemoradiation therapy is the current standard for locoregionally advanced NPC (18–21), and novel regimens are under active investigation (22, 23), the tolerance of cranial nerves to these aggressive treatment strategies requires further study.

Approximately 10% of NPC patients have CNP as one of the presenting symptoms (5, 24). Most CNP on presentation is caused by superior tumor invasion to cavernous sinus, thus the upper-group cranial nerves are more frequently affected (5, 24). Chang *et al.* (5) reported on 330 patients with CNP at the time of NPC diagnosis, with 82%, 4%, and 15% presenting with CNP in the upper, lower, or both groups, respectively. Lin *et al.* (2) and Teo *et al.* (11) separately demonstrated a higher incidence of radiation-induced CNP in cranial nerves IX–XII. King *et al.* (3) analyzed the cause of hypoglossal nerve palsy in patients previously treated with radiation for NPC. They reported that recurrent tumor accounted for only 12% of hypoglossal nerve palsy, whereas radiation-induced neuropathy was the cause in 82% of cases. It seems that upper CNP is more often the result of tumor invasion, whereas lower CNP is the result of radiation-induced CNP. This finding may have important implications in the differential diagnosis of CNP in patients treated for NPC.

The incidence of peripheral neuropathy after high-dose radiation is low (11, 17, 25–27). For radiation-induced CNP in NPC, Huang *et al.* (25) reported a 1% overall incidence in 1032 NPC patients after conventional radiotherapy. Lee *et al.* (26) reported a 5% cumulative incidence of CNP after radiotherapy with 2.5 Gy or 4.2 Gy per fraction in 4527 NPC

patients. Teo *et al*. (11) reported a crude incidence of 8.7% and 13.0% of radiation-induced CNP (IX–XII) after conventional radiotherapy or accelerated-hyperfractionated radiation with a median follow-up of 59.2 months. The incidence of peripheral neuropathy after radiation for breast cancer has been reported as low as 1–2% (17, 27). The crude incidence of CNP was 30.9% in our study; and the cumulative incidences of CNP were 10.4%, 22.4%, 35.5%, and 44.5% at 5, 10, 15, and 20 years, respectively. The nature of this cross-sectional study lent itself to selection bias because the patients accrued were more likely to have complications. A prospective cohort study would be needed to find the true incidence of radiation-induced CNP. However, our purpose was to investigate the characteristics and risk factors of radiation-induced CNP, and it would not be feasible to obtain the critical mass needed to achieve these goals with a prospective cohort study.

Radiation-induced nerve damage is considered a long-term complication. The latent period before occurrences is usually on a scale of years, and very long-term follow-up is required to fully understand the cause–effect relationship between treatment and its complication (2, 7, 14, 28). We found that the median latent period for the occurrence of radiation-induced CNP approached 8 years. A similar latency period was noted in other studies of radiation-induced peripheral neuropathies. Powell *et al*. (15) reported that the incidence of radiation-induced brachial plexus injury rises between 1 and 4 years and then starts to plateau. Johansson *et al*. (7) observed that the incidence of brachial plexus neuropathy increased beyond 10 years and reached its plateau approximately 19 years after treatment. In contrast to these studies, our data do not demonstrate a plateau phase for CNP, which indicated that a life-long risk of radiation-induced CNP might be possible. The annual incidences of onset were stable after 5 years after radiation without substantial differences. This life-long risk of radiation-induced neuropathy hypothesis is supported by the results of Bajrovic *et al*. (28). In that study, the percentage of patients free from plexopathy was 96.1% after 5 years, 75.5% after 10 years, 72.1% after 15 years, and 46.0% after 19 years, respectively. It seems that the late onset after 15 years is not uncommon and that the probability remains constant. This finding is of particular importance as the overall outcome for cancer patients improves, resulting in long-term treatment side effects becoming more frequent.

Treatment strategies and techniques have evolved substantially in the past decade for NPC. In addition to concurrent chemotherapy, the use of neoadjuvant chemotherapy has increased in locally advanced diseases. More importantly, intensity-modulated radiotherapy is commonly used for NPC, and neck fibrosis is expected to decrease significantly with the application of dose restraint to posterior neck muscles. However, the effects of dose escalation in intensity-modulated radiotherapy may give rise to the long-term development of CNP, with similar characteristics as those described in this study. A similar study to ours may provide further understanding in NPC patients treated in the modern era.

In addition to the factors identified in the present series, we speculate that other factors may be associated with radiation-induced neuropathy. Recent studies have supported the hypothesis of genetic components to the observed interpatient variability in normal tissue toxicity after radiotherapy (29). Investigations for the potential genetic association with radiation-induced neuropathy could be considered.

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