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Original Article

Radiation-induced hypoglossal nerve palsy after definitive radiotherapy for nasopharyngeal carcinoma: Clinical predictors and dose–toxicity relationship

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ABSTRACT

Background and purpose: Radiation-induced hypoglossal nerve palsy is a debilitating and irreversible late complication after definitive radiotherapy for nasopharyngeal carcinoma (NPC) and other skull base tumors. This study sets to evaluate its incidence and clinical predictive factors, and to propose relevant dosimetric constraints for this structure to guide radiotherapy planning.

Materials and methods: We undertook a retrospective review of 797 NPC patients who underwent definitive intensity-modulated radiotherapy (IMRT) between 2003 and 2011. Cumulative incidence and clinical predictors for radiation-induced hypoglossal nerve palsy were evaluated. Archived radiotherapy plans were retrieved and 330 independent hypoglossal nerves were retrospectively contoured following standardized atlas. Optimal threshold analyses of dosimetric parameters (Dmax, D0.5cc, D1cc, D2cc, Dmean) were conducted using receiver operating characteristic curves. Normal tissue complication probability was generated with logistic regression modeling.

Results: With a median follow-up of 8.1 years, sixty-nine (8.7%) patients developed radiation-induced hypoglossal nerve palsy. High radiotherapy dose, premorbid diabetes, advanced T-stage and radiological hypoglossal canal involvement were independent clinical risk factors. Maximum dose received by 1 cc volume (D1cc) was the best predictor for the development of radiation-induced nerve palsy (AUC = 0.826) at 8 years after IMRT. Hypoglossal nerves with D1cc of 74 Gy EQD2 had an estimated palsy risk of 4.7%. Nerves with D1cc <74 Gy EQD2 had significantly lower risk of palsy than those ≥74 Gy EQD2 (2.4% vs 20.8%, p <0.001).

Conclusion: Incidence of radiation-induced hypoglossal nerve palsy was high after definitive IMRT for NPC. D1cc <74 Gy EQD2 can serve as a useful dose constraint to adopt during radiotherapy planning to limit palsy risk to <5% at 8 years after IMRT.

Nasopharyngeal carcinoma (NPC) is a radiosensitive disease. With current widespread use of intensity-modulated radiotherapy (IMRT) and effective systemic chemotherapy, excellent loco-regional control up to the benchmark of 80–90% have been achieved in contemporary series [1,2]. Alongside improved treatment outcomes, treatment-related late complications are of increasing concern among long term survivors.

Radiation-induced cranial nerve palsy is an uncommon but highly debilitating permanent late complication after high dose radiotherapy to the skull base and upper neck [3–6]. In a recent treatment outcome report of a large IMRT-treated NPC cohort, 5.1% of patients developed cranial nerve dysfunction at a median follow-up of 8.8 years [1]. Among all cranial nerves, the hypoglossal nerve consistently ranked one of the highest incidences of radiation injury across various series [4–7]. Anatomically, hypoglossal nerves run a tortuous course from medulla through hypoglossal canal into carotid sheath and then exit to innervate oral tongue [8]. Despite the improved dosimetric conformity with IMRT, the hypoglossal nerves which travel in close proximity to the nasopharynx and upper cervical nodal basins, still often inevitably fall into high-dose treatment volume. Upon radiation injury, the resultant paralyzed hemi-tongues impair speech, articulation,

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chewing and initial phase of swallowing, which in turn greatly impair quality of life of NPC survivors.

Currently, there is limited body of literature that evaluates incidence and risk factors for radiation-induced hypoglossal nerve palsy. Dosimetric study informing potential dose constraints for this structure is also lacking. This study sets to evaluate its risk in a large homogenous cohort of IMRT-treated NPC patients, to identify relevant clinical and dosimetric predictive factors, and to propose practically feasible dose constraints to minimize the risk of this late complication.

Materials and methods

Study population

This retrospective cohort analysis was approved by a regional research ethics committee of Hong Kong Hospital Authority. From June 2003 to December 2011, a total of 836 consecutive patients with non-metastatic nasopharyngeal carcinoma who underwent curative IMRT in Queen Elizabeth Hospital, Hong Kong, were identified from an institutional database. Patients with less than 6 months of follow-up ($n = 27$) and history of tongue resection ($n = 1$) and those who presented with hypoglossal nerve palsy ($n = 11$) were excluded. Demographic, clinical and treatment data of the remaining 797 eligible patients were collected. All patients were staged using American Joint Committee on Cancer Staging Manual (7th Edition) staging criteria with magnetic resonance imaging (MRI).

Treatment

All patients underwent definitive radiotherapy using IMRT technique. Details of radiotherapy technique was previously reported [9]. In essence, radiotherapy treatment was delivered in 33 fractions over 6–7 weeks, with 66–72 Gy given to high-dose clinical target volume at gross nasopharyngeal tumor and neck nodes, and 60–62 Gy to low-dose clinical target volume covering local structure at risks as well as bilateral level Ib-Vb cervical nodal regions. Radiotherapy to node-negative lower necks were delivered with matched anterior cervical fields, the matching junctions were set at cranial border of C4 vertebral body or 3 cm below the most caudal lymph node, whichever is lower. Concurrent cisplatin was used in selected stage II and all stage III-IVB diseases, at a dose of either 100 mg/m^2 every 3 weeks for 2–3 cycles or 30–40 mg/m^2 weekly for 6–7 cycles. Various combinations of induction or adjuvant chemotherapy had been used because of the conduct of a prospective multi-center trial during the study period [10].

Follow-up

Follow-up duration was calculated from the date of completion of IMRT to the date of last clinical visit. Patients were followed up every 3–6 months in first 3 years and then every 6–12 months thereafter. Cranial nerve examination was performed at each follow-up visit. Date of development of hypoglossal nerve palsy, which was defined as any newly identified asymmetry, atrophy, weakness or fasciculation of a hemi-tongue was recorded. Diagnosis of radiation-induced hypoglossal nerve palsy was made only if there was no MRI evidence of loco-regional disease recurrence, or a disease-free period of one year had elapsed after development of new nerve palsy.

Hypoglossal nerve dosimetry

Radiation-induced neuropathy is a late complication that manifests years after radiotherapy, with death as a major competing event. In the current study, nerves that remained intact for at least 8 years from the completion of IMRT were selected as normal controls. After further excluding patients whose treatment plans were not retrievable from archived database, dose–volume data from 165 eligible patients, i.e. 330 individual hypoglossal nerves (46 palsied and 284 normal controls), were analyzed.

We retrospectively contoured bilateral hypoglossal nerves on contrasted simulation computed tomography images following the atlas proposed by Mourad et al. (Fig. 1) [11]. Investigators were blinded of patients' hypoglossal nerve status at the time of contouring. The contouring volume began at the ventral aspect of medulla, extended into hypoglossal canal, and further included

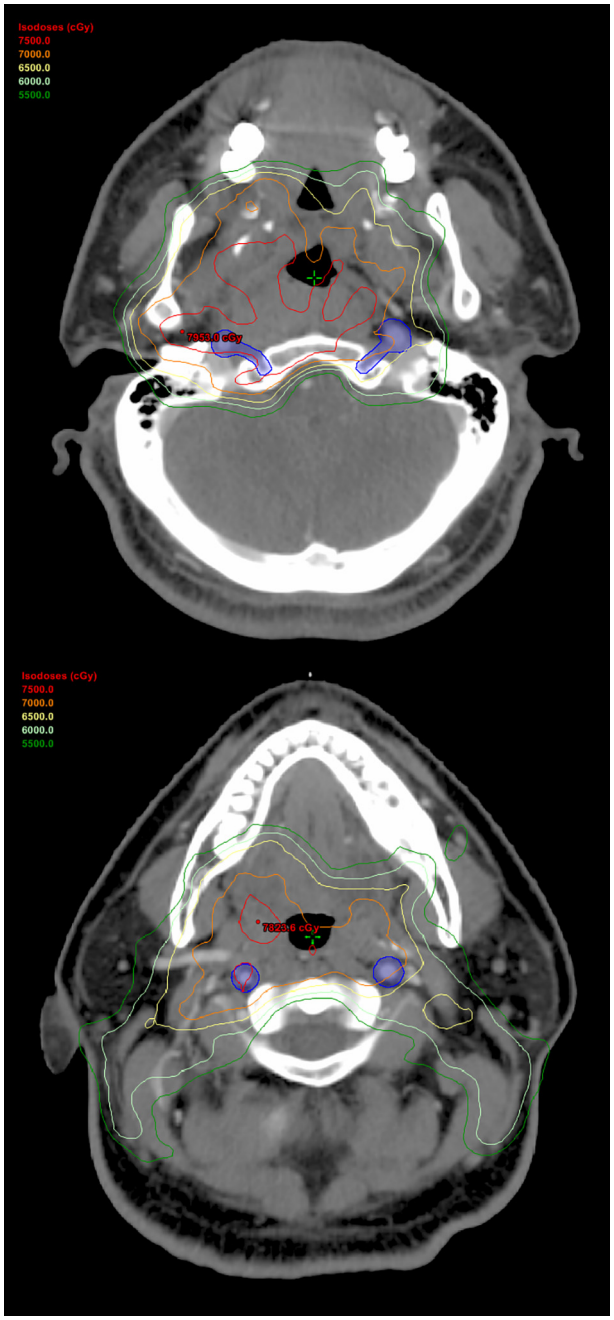

Fig. 1. A representative contour of hypoglossal nerves (bold blue lines) on an archived IMRT plan for a cT4N1M0 NPC. After definitive chemoradiotherapy (72 Gy in 33Fr) with cisplatin, the patient developed radiation-induced right hypoglossal nerve palsy at a latency period of 6.0 years. *Abbreviations: IMRT, intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma.*

3 mm expansion from internal carotid artery, covering the anteromedial portion of internal jugular vein. The caudal borders of contour were unified at lower edge of C3 vertebral body. Dosimetric parameters (Dmean, Dmax, D0.5cc, D1cc, D2cc) were determined from dose–volume histograms, and were converted into equivalent doses in 2 Gy fractions (EQD2) assuming a biological effective dose with alpha/beta ratio of 2 (BED2) for subsequent analyses [12].

Statistical analysis

Descriptive statistics were used for patient demographics and clinical characteristics. Cumulated incidence of radiation-induced hypoglossal nerve palsy was estimated using the Kaplan–Meier method, censoring at death, loss to follow-up, tongue surgery, re-irradiation or the development of nerve palsy due to tumor recurrence. Clinical predictive factors for radiation-induced hypoglossal nerve palsy (age, gender, smoking status, T-stage, N-stage, radiological hypoglossal canal involvement, use of chemotherapy, prescribed radiotherapy dose, pre-existing vascular risk factors including hypertension, diabetes and hyperlipidemia) were evaluated using log-rank test. Multivariable analysis was performed using the Cox proportional hazard model with backward stepwise selection, including all variables with p-value <0.10 on univariable analyses.

Dosimetry of each individual hypoglossal nerve was analyzed independently. Receiver operating characteristic (ROC) curves were used to compare the discriminatory power of dosimetric parameters on subsequent post-IMRT radiation-induced hypoglossal nerve palsies. Probability of palsy and the dose–effect relationship were modeled using logistic regression.

All analyses were performed using SPSS Statistics, version 22.0 (SPSS Inc. Chicago, IL, USA). All tests were two-sided, p-value of <0.05 was considered statistically significant.

Results

At a median follow-up of 8.1 years, 80 out of 797 patients developed hypoglossal nerve palsy after definitive IMRT. Local tumor recurrence accounted for nerve palsy in 11 (14%) patients, while the remaining 69 (86%) were radiation-induced. Crude incidence of radiation-induced hypoglossal nerve palsy was 8.7% (69/797),

Table 1
Patient characteristics.

	All patients (n = 797)				p-Value
	No radiation-induced XII nerve palsy (n = 728)		Presence of radiation-induced XII nerve palsy (n = 69)		
	n	(%)	n	(%)	
Age (years)					
<50	306	(42.0)	36	(52.2)	0.52
≥50	422	(58.0)	33	(47.8)	
Gender					0.59
Male	505	(69.4)	44	(63.8)	
Female	223	(30.6)	25	(36.2)	
Smoking status					
Non-smoker	411	(56.4)	43	(62.3)	0.99
Smoker/Ex-smoker	304	(41.8)	26	(37.7)	
Unknown	13	(1.8)	–	–	
Hypertension					
No	553	(76.0)	42	(60.9)	0.075
Yes	175	(24.0)	27	(39.1)	
Diabetes mellitus					
No	658	(90.4)	57	(82.6)	0.052
Yes	70	(9.6)	12	(17.4)	
Hyperlipidemia					
No	633	(87.0)	54	(78.3)	0.31
Yes	95	(13.0)	15	(21.7)	
Connective tissue disease*					
No	720	(98.9)	67	(97.1)	0.016
Yes	8	(1.1)	2	(2.9)	
T-stage					
T1	184	(25.3)	9	(13.0)	<0.001#
T2	85	(11.7)	1	(1.4)	
T3	347	(47.7)	48	(69.6)	
T4	112	(15.4)	11	(15.9)	
N-stage					
N0	78	(10.7)	5	(7.2)	0.13#
N1	225	(30.9)	22	(31.9)	
N2	379	(52.1)	38	(55.1)	
N3	46	(6.3)	4	(5.8)	
Hypoglossal canal					
Not involved	647	(88.9)	51	(73.9)	<0.001
Involved	81	(11.1)	18	(26.1)	
Chemotherapy					
No	247	(33.9)	11	(15.9)	0.006
Yes	481	(66.1)	58	(84.1)	
Radiotherapy dose (in 33Fr)					
≤70 Gy	412	(56.6)	19	(27.5)	<0.001
>70 Gy	316	(43.4)	50	(72.5)	

Abbreviations: Fr, fraction; XII, hypoglossal.

*Marfan syndrome (n = 1), scleroderma (n = 1), mixed connective tissue disease (n = 1), systemic lupus erythematosus (n = 1), rheumatoid arthritis (n = 1), polymyositis (n = 1), dermatomyositis (n = 4).

#*Comparison made between T1-2 and T3-4; N0 and N1-3.*

in which 74% were unilateral and 26% were bilateral. The estimated 5-year and 8-year cumulative incidences were 2.1% and 12.4% respectively (Supplementary Material Fig. 1). Median time to nerve palsy was 6.4 years (IQR 5.3–7.4). Radiation-induced hypoglossal nerve palsies were isolated in 63 out of 69 (91.3%) patients, while the remaining 6 had concomitant radiation-induced cranial neuropathies, most commonly in abducens and the second/third branch of trigeminal nerves.

Clinical characteristics of patients with or without radiation-induced hypoglossal nerve palsy were summarized (Table 1). On univariable analyses, risk of radiation-induced hypoglossal nerve palsy was higher in patients with connective tissue diseases ($p = 0.016$), T3-4 tumors ($p < 0.001$), tumors that involve hypoglossal canal on staging MRI ($p < 0.001$), use of chemotherapy ($p = 0.006$) and radiotherapy dose >70 Gy ($p < 0.001$). On multivariable cox regression, advanced T-stage [Hazard ratio (HR), 2.31; 95% confidence interval (CI), 1.14–4.67], radiological hypoglossal canal involvement (HR, 2.49; 95% CI, 1.43–4.33), premorbid diabetes (HR, 2.02; 95% CI, 1.08–3.78) and radiotherapy dose >70 Gy (HR, 2.80; 95% CI, 1.62–4.84) were independent clinical predictors (Table 2). Status of pre-existing connective tissue disease was not included in the multivariable model because of small case number. Among the 10 index patients, one with mixed connective tissue disease and another with rheumatoid arthritis developed radiation-induced hypoglossal nerve palsies, at short latency periods of 2.4 and 5.6 years respectively. Among patients who received chemotherapy with IMRT ($n = 539$), after adjustment for all four independent clinical predictors in previous multivariable model, no statistically significant association between cumulative cisplatin dose and the risk of radiation-induced hypoglossal nerve palsy was observed ($p = 0.36$).

Among 330 analyzed hypoglossal nerves, 46 were cases of radiation-induced palsy and 284 were normal controls. Dmax, D0.5cc, D1cc, D2cc and Dmean were all significantly higher in palsied than normal nerves (Table 3). All five parameters had good discriminatory power to predict development of nerve palsy on ROC analyses (Fig. 2A). Among them, D1cc was the best dosimetric predictor with an AUC of 0.826.

Table 2
Multivariable analysis (final model) on clinical predictive factors for radiation-induced hypoglossal nerve palsy.

	Hazard ratio	95% CI	*p*-Value
T-stage (T3-4 vs T1-2)	2.31	1.14–4.67	0.02
Hypoglossal canal involvement (Yes vs No)	2.49	1.43–4.33	0.001
Diabetes mellitus (Yes vs No)	2.02	1.08–3.78	0.028
Radiotherapy dose (>70 Gy vs ≤70 Gy)	2.80	1.62–4.84	<0.001

Abbreviations: CI, confidence interval.

Table 3
Dosimetric parameters in palsied versus normal hypoglossal nerves.

	Dose, median (range) (Gy, EQD2 BED2)		
	Normal nerves	Palsied nerves	*p*-Value
Dmax	80.5 (65.5–93.7)	84.3 (78.4–94.7)	<0.001
D0.5cc	76.4 (63.6–86.5)	80.4 (73.0–87.7)	<0.001
D1cc	74.6 (63.0–84.4)	79.2 (70.1–84.9)	<0.001
D2cc	71.8 (60.5–83.3)	76.8 (63.8–83.4)	<0.001
Dmean	71.0 (62.2–82.1)	74.9 (64.5–81.1)	<0.001

Abbreviations: BED2, biological effective dose using alpha/beta ratio of 2; Dmax, maximal point dose; D0.5cc, maximal dose delivered to 0.5 cc volume; D1cc, maximal dose delivered to 1 cc volume; D2cc, maximal dose delivered to 2 cc volume; Dmean, mean dose; EQD2, equivalent dose in 2 Gy.

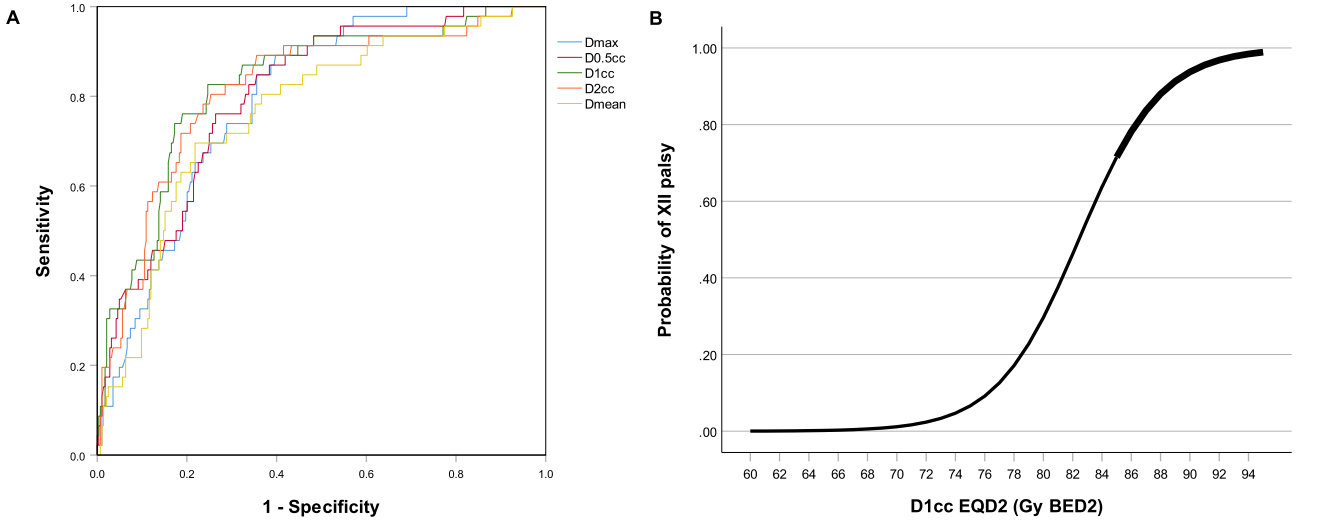

Fig. 2. (A) Receiver operative characteristics curves of dosimetric parameters on the risk of radiation-induced hypoglossal nerve palsy. (B) Normal tissue complication probability model for radiation-induced hypoglossal nerve palsy using D1cc EQD2 (BED2). Bold line indicates the range where estimated dose–response curve exceeded range of observed data. *Abbreviations: BED2, biological effective dose using alpha/beta ratio of 2; Dmax, maximal point dose; D0.5cc, maximal dose delivered to 0.5 cc volume; D1cc, maximal dose delivered to 1 cc volume; D2cc, maximal dose delivered to 2 cc volume; Dmean, mean dose; EQD2, equivalent dose in 2 Gy.*

Table 4
Estimated probability of radiation-induced hypoglossal nerve palsy at different D1cc dose cutoffs.

	Dose (Gy, EQD2 BED2)										
	68	69	70	71	72	73	74	75	76	77	78
Estimated probability of XII nerve palsy	0.6%	0.8%	1.2%	1.7%	2.4%	3.4%	4.7%	6.7%	9.4%	12.8%	17.3%

Abbreviations: BED2, biological effective dose using alpha/beta ratio of 2; D1cc, maximal dose delivered to 1 cc volume; EQD2, equivalent dose in 2 Gy; XII, hypoglossal.

Probability of nerve palsy derived from logistic regression was plotted against D1cc, suggesting a dose-dependent relationship with a steep increase in probability between EQD2 68 and 78 Gy (Fig. 2B). The estimated probability of nerve palsy at different D1cc cutoffs within this range were tabulated (Table 4). If <5% risk of radiation-induced hypoglossal nerve palsy at 8 years after IMRT is considered clinically justifiable, a D1cc cutoff at EQD2 74 Gy would give an estimated palsy rate of 4.7%. The rate of palsy for nerves with D1cc <EQD2 74 Gy and D1cc ≥EQD2 74 Gy in this cohort were 2.4% (3/123) and 20.8% (43/207) respectively ($p < 0.001$).

Discussion

In modern era of IMRT and effective systemic chemotherapy, prognosis of patients with localized nasopharyngeal carcinoma is excellent. With larger number of long term survivors, the prevention of late treatment-related complications has become increasingly important. The reported incidence of radiation-induced cranial neuropathy after IMRT for NPC ranged between 2.9 and 5.1% at follow-up durations between 3.5 and 6.7 years [1,13,14]. Hypoglossal nerve, being the last cranial nerve to exit brainstem, is particularly vulnerable to injury following definitive radiotherapy for NPC. In this study, we reported a rather alarming crude incidence of 8.7% of radiation-induced hypoglossal nerve at a median follow-up of 8.1 years. This estimate was derived from patients who received only first-course radiotherapy, where 22 patients were censored at their time of re-irradiation for local tumor recurrences. The actual incidence of radiation-induced hypoglossal neuropathy is expected to be even higher if the effect of re-irradiation is taken into consideration. The median latency period of 6.4 years was comparable with historical series [4,6], confirming the importance of continual surveillance for this late neurological complication after radical radiotherapy.

In this study, apart from high prescribed radiotherapy dose, we identified advanced T-stage and radiological hypoglossal canal involvement as independent clinical predictive factors for radiation-induced hypoglossal nerve palsy. Both factors were likely a surrogate reflection of large radiotherapy treatment volumes to the base of skull, hence exposing a larger portion of the traversing hypoglossal nerves under high dose radiation. Apart from the differences in radiation doses, patient demographics and comorbidities also affect one's susceptibility to radiation toxicity. Although the exact underlying pathophysiological mechanisms remain elusive, microvascular ischemic injury was proposed to play a core role in radiation neuropathy, putting patients with pre-existing vascular diseases at increased risk [7,15]. In the current cohort, patients with premorbid diabetes were found to be at increased risk of radiation neuropathy, which might be a compound effect with their underlying neural microangiopathic insult. As the interactions between vascular risk factors are complexly multiplicative, further dedicated studies with the control of disease severity and chronicity are required for a definitive conclusion.

Hypoglossal nerve is an interesting organ-at-risk in radiotherapy planning for NPC. Both the canalicular and peri-carotid portions of the nerve are in intimate anatomic relation with primary tumor or regional nodal basins, it therefore almost always falls into zones of high radiation doses, especially in situations where there is posterolateral extension of primary tumor into clivo-petrous region, or in the presence of sizable retropharyngeal and/or level II cervical nodes. More than half of the analyzed hypoglossal nerves in current cohort had mean doses exceeding an EQD2 (BED2) of 70 Gy. As a result, in contrary to most other normal structures, doses delivered to the nerves are at the steep part of sigmoidal dose–effect curve, where the complication probability changes greatly with even a small change in radiation dose. Peripheral nerves are known to be more radioresistant when compared with other neural structures [16]. Normal tissue tolerance data for optic nerve suggested that radiation neuropathy is unusual for Dmax <55 Gy, but the risk increases substantially beyond 60 Gy, with an estimated TD50 at the range of 65–75 Gy [15]. Many therefore employ a stringently constrained Dmax of <54 Gy for optic nerve in head and neck radiotherapy planning. While it is impractical to impose the same constraint for hypoglossal nerve, applying a limit to minimizing hotspots within this structure may help reduce incidence of future neuropathy.

Our study suggested that, among all dosimetric parameters, D1cc was the best discriminator for subsequent radiation-induced hypoglossal nerve palsy. In contrast to optic nerve, which outline could be clearly contoured with the aid of MRI, location of the peri-carotid portion of hypoglossal nerve is not radiographically visible and varies greatly among individuals [17]. Currently available contouring atlas proposed a volumetric expansion from carotid vessel in order to capture its variable path [11]. It is therefore conceivable that a parameter with physical volume such as D1cc performed better than a virtual point estimate of Dmax as a discriminating constraint.

The selection of an optimal D1cc dose limit requires a balance between practical feasibility and toxicity probability. Without imposing a dose constraint on hypoglossal nerves during the planning process, the estimated 8-year incidence of palsy in this cohort was up to 12.4%. A D1cc cutoff of EQD2 <74 Gy could limit this risk to below 5% and serve as a useful dose constraint for early-staged tumor. As for locoregionally advanced tumors with significant postero-lateral skull base infiltration or bulky retropharyngeal nodes, the anatomic course of hypoglossal nerve would likely overlap with high-dose PTV by >1 cc. In these situations, overprotection of the nerves at the expense of target volume coverage may compromise overall tumor control and is not advisable. A pragmatic goal should be to place priority for maintaining PTV dose coverage to ensure tumor control while minimizing hotspots within the traversing nerves. The dose constraints to be adopted in this setting would largely depend on the prescribed dose for high-dose PTV, which varied greatly among different institutions. For instance, similar to a number of published protocols [18,19], our center adopts a slightly hypo-fractionated approach for high-dose target volume. At a prescribed dose of 70 Gy in 33Fr, this translates into an EQD2 (BED2) of 72.1 Gy. If a D1cc of EQD2 <74 Gy is not achievable due to advanced tumor, a less stringent constraint could be set at EQD2 76 Gy, which limits unnecessary hotspots to the nerves but at the same time allow certain degree of dose heterogeneity within PTV during radiotherapy planning.

Radiation neuropathy is an irreversible complication. Treatments including high-dose steroids, hyperbaric oxygen and pentoxifylline–tocopherol–clodronate have been evaluated with inconsistent efficacies [20–23]. In the absence of established rescue treatment, efforts should be made to minimize its risk during the process of radiotherapy planning. Apart from appropriate constraint application and hotspot control, careful target volume delineation is also potentially helpful. Current international consensus guideline on NPC clinical target volume delineation recommended sparing hypoglossal canal from prophylactic irradiation in the absence of extensive postero-lateral infiltration of primary tumor or high jugular lymphadenopathy [24]. This would help limit radiation dose to the traversing hypoglossal nerves in early stage diseases. In situations of loco-regionally advanced disease where induction chemotherapy is contemplated, prospective evidence has suggested that limiting IMRT target volume to post-chemotherapy tumor extent is a feasible approach that reduces radiation doses to normal tissues without compromising tumor control or survival [25]. Whether this would further translate into

less late complications such as radiation-induced cranial neuropathy is currently unknown, long term results are eagerly awaited.

The current study has several limitations. Due to its retrospective nature, data on clinical predictive factors were mostly dichotomized. Smoking pack-years, chronicity and severity of vascular diseases all play a potential role in individual susceptibility of radiation injury. These were not captured and thus not reflected in the multivariable model. Detailed gradings of nerve palsy were also not consistently available in our cohort. This hindered further dosimetric correlation with the severity and functional impact of neuropathy, which could vary greatly from early fasciculations to complete motor paralyses. In addition, not all hypoglossal nerves in the cohort could be analyzed as some of the IMRT plans were not retrievable from archived database. The presence of missing data reduces precision of dosimetric estimation and comparisons. Also, contours of hypoglossal nerves in this study ended caudally at lower border of C3 vertebrae and did not cover the variable distal portions near oral cavities. Therefore, in the rare situation of gross level I cervical lymphadenopathies or extensive anteroinferior tumor extension, the potential resultant radiation injury to this part of nerve would be missed and not reflected in current dosimetric analysis. However, given the very low incidence of level I nodal metastasis in NPC [26], and that radiation damage to hypoglossal nerves occur most commonly at their proximal portions near base of skull, the current contouring method should have captured their dosimetric hotspots in the majority of cases. Finally, our clinico-dosimetric analyses represented the result of a single cohort, further studies are required to validate the proposed risk factors and constraint cutoffs for clinical application.

In conclusion, we report the first study evaluating the risk and clinico-dosimetric predictive factors for radiation-induced hypoglossal nerve palsy after definitive IMRT for NPC. Radiation doses to the nerves play a dictating role on subsequent neuropathy risk. D1cc of EQD2 (BED2) <74 Gy can serve as a practical cutoff that limits risk of palsy to <5% at 8 years after IMRT. Minimizing hotspots along the course of hypoglossal nerve and careful target volume delineation may reduce the rate of this late debilitating complication. Validation study would be helpful to further define the role of dose constraint application for this normal structure in head and neck radiotherapy planning.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.011.

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