Differences in lower cranial nerve complications predicted by the NTCP model between RTOG and reduced-volume IMRT planning in radiotherapy for nasopharyngeal carcinoma

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Background: The aim of this study was to assess the differences in lower cranial nerve (LCN) complications predicted by the normal tissue complication probability (NTCP) model between Radiation Therapy Oncology Group (RTOG) and reduced-volume intensity-modulated radiotherapy (IMRT) planning for nasopharyngeal carcinoma (NPC) radiotherapy.

Methods: A total of fifty patients with NPC were divided into two groups according to T-stages of T1-2 and T3-4, and the LCNs of each patient were contoured on CT simulation images. The targets were contoured based on the RTOG 0225 clinical trial and a working committee for clinical stage NPC in China in 2010. The NTCP differences in LCNs between the two plans were calculated.

Results: The LCN volume of the 50 patients was 10.07 cc. The Dmax and Dmean of LCNs in RTOG plans were significantly larger than those in reduced-volume plans (7,453 *vs.* 7,401 cGy, 6,740 *vs.* 6,436 cGy, P=0.004, 0.000), and these values were lower in the T1-2 group than in the T3-4 group (7,390 *vs.* 7,464 cGy, 6,442 *vs.* 6,733 cGy, P=0.019, 0.000). NTCP in RTOG plans was significantly higher than that in reduced-volume plans (59.98% *vs.* 51.62%, P=0.000), among which NTCP was significantly lower in the T1-2 group than in the T3-4 group (51.72% *vs.* 59.88%, P=0.002). There were strong correlations of NTCP with Dmean and irradiation volume for more than 6,600 cGy (R=0.847, P=0.000; R=0.841, P=0.000).

Conclusions: the clinical T-stage, a high Dmean and a large irradiation volume are important factors in predicting LCN complications. Of the two most common IMRT guidance plans in China, the LCN NTCP based on the reduced-volume plan is significantly lower than that based on the RTOG plan.

Keywords: Nasopharyngeal carcinoma (NPC); intensity-modulated radiotherapy (IMRT); lower cranial nerves (LCNs); normal tissue complication probability (NTCP)

Introduction

Nasopharyngeal carcinoma (NPC) has a high disease incidence in China, and radiotherapy is the primary treatment modality for nonmetastatic NPC patients (1,2). With the application of the intensity-modulated radiotherapy (IMRT) technique, the majority of patients can be cured and have a long-term survival time; thus, reducing the radiation side effects of organs at risk (OARs) to improve the quality of life of patients is particularly important.

Among all known long-term side effects, radiation-induced cranial nerve palsy (RICNP) is not a rare complication; it usually occurs in the lower cranial nerves (LCNs), with an incidence ranging from 0.3% to 20.6% (3-10). RICNP in NPC significantly compromises the patients' quality of life and can even endanger their lives. Damage to the glossopharyngeal nerve (IX) causes loss of sensation in the pharynx and decreases salivation. Palsy of the vagus nerve (X) leads to impaired parasympathetic functions of almost all organs, and palsy of the hypoglossal nerve (XII) causes complete paralysis of the ipsilateral side of the tongue (11). However, LCNs have not served as a conventional OAR when delineating radiotherapy for head and neck cancer, including NPC. One of the reasons may be that the LCNs adjacent to carotid sheath are included in the high-dose irradiation volume. Moreover, the doses of radiation that LCNs are exposed to in the Radiation Therapy Oncology Group (RTOG)-guided IMRT plan (RTOG plan) are difficult to adjust to decrease the possibility of complication development. The reduced-volume IMRT plan (reduced-volume plan) has been used in recent years in the treatment of NPC, and the efficacy of this technique is comparable to that of the RTOG plan (12-14). The application of reduced-volume IMRT may provide the opportunity to decrease the doses received by LCNs. However, few studies have assessed the risk of LCN complications in NPC patients after reduced-volume IMRT. Moreover, the difference in LCN complications between RTOG and reduced-volume IMRT remain unknown. In the present study, therefore, we evaluated the difference in LCN complications predicted by the normal tissue complication probability (NTCP) model between RTOG and reduced-volume IMRT planning in radiotherapy for NPC.

Methods

Patient characteristics

From May 2013 to September 2017, 50 patients with

Table 1 Patient characteristics

Characteristic	n	%
Gender		
Male	31	62.0
Female	19	38.0
Age (y)		
Range	18–85	
Median	58.5	
T-stage		
T1	6	12.0
T2	19	38.0
T3	14	28.0
T4	11	22.0
N-stage		
N0	6	12.0
N1	8	16.0
N2	27	54.0
N3	9	18.0

newly diagnosed NPC receiving curative radiotherapy were retrieved, and the characteristics are summarized in *Table 1*. All patients underwent disease staging according to the American Joint Committee on Cancer staging system [2002] and were divided into two T-stage groups, 25 patients in the T1-2 group and 25 patients in the T3-4 group. All patients had no LCN palsy on physical examination before radiotherapy.

CT-sim scanning and target volume delineation

All patients were positioned and immobilized from the head to the shoulder by a thermoplastic mask. Computed tomography (CT) images with a 3-mm slice thickness of the head and neck region were obtained and imported into the treatment planning system. The target of each patient was contoured according to RTOG 0225 clinical trial (15,16) and reduced-volume IMRT recommendations (12,13,17). For the RTOG-guided definition, the target volume included the gross tumor volume (GTV), the clinical target volume (CTV), and the planning target volume (PTV). The GTVnx and GTVnd covered the visible primary tumor and neck metastatic lymph nodes shown on the CT/

MRI image, respectively. CTV1 encompassed high-risk structures surrounding the primary tumor, CTV2 covered the high-risk neck region, and CTV3 encompassed the low-risk neck region. PTVnx, PTVnd, PTV1, PTV2, and PTV3 consisted of a 3-mm margin in all directions around the corresponding GTV and CTV, respectively. The OARs included the brain stem, spinal cord, parotid glands, lenses, eyes, optic nerves, chiasm, cochlea, mandible, oral cavity and larynx. For reduced-volume IMRT recommendation, the definition of the target volume was the same as that defined in the protocol of RTOG 0225 clinical trial, except for CTV1 contouring. CTV1 was separated into two irradiation dose gradients, including CTV1-h, which encompassed both a 5-mm margin in all directions around the corresponding GTVnx and a 5-mm submucosa of the whole nasopharynx. PTV1-h consisted of a 3-mm margin in all directions around the CTV1-h. The OARs included the brain stem, spinal cord, parotid glands, lenses, eyes, optic nerves, chiasm, cochlea, mandible, oral cavity and larynx.

LCN delineation

The bilateral LCNs were delineated following the guidance provided by Mourad et al. (18). All delineations were based on the CT image of contrast medium enhancement, and scanning was performed with a 3-mm slice thickness. A CT window width of 1,400 and a window level of 400 were selected for delineation of the jugular foramen (JF) and the hypoglossal canal, while a window width of 180 and a window level of 950 were selected for delineation of the internal carotid artery (ICA).

Due to the anatomical nature and proximity of cranial nerves X and XI, they were contoured and grouped as one structure, while cranial nerve XII was contoured individually. Cranial nerves IX and XI emerge from the lateral aspect of the medulla oblongata and pass through the JF. After their exit from the JF, they pass vertically down the neck within the carotid sheath, lying between the internal jugular vein (IJV) and the ICA to the upper border of the thyroid cartilage (i.e., at the level of the lower border of C4). First, bilateral JFs and carotid sheaths, such as the IX, X, and XI cranial nerves, were delineated. The carotid sheath was formed based on delineation of the carotid artery with a 3-mm uniform margin, while the carotid artery was contoured from the inferior JF to the carotid bifurcation. Second, bilateral hypoglossal canals and corresponding carotid sheaths, such as the XII cranial nerve, were contoured. Finally, bilateral merging parts of the IX, X, and XI cranial nerves were delineated. One case of LCN contour is illustrated in Figure 1.

Treatment planning

The Philips Pinnacle Planning System 9.0 was used for IMRT planning. The treatment plan was designed for all patients with a standard coplanar 9-field gantry arrangement and delivered using a Siemens Primus Linac equipped with a 58-leaf MLC. A direct machine parameter optimization (DMPO) module was adopted for treatment planning. The maximum number of segments was set to 80, the minimum segment area was 5 cm^2, and the minimum monitor unit (MU) was 5 MUs. A collapsed-cone convolution algorithm was used to calculate dosage with a dose grid resolution of 3 mm. According to the planning of the RTOG 0225 clinical trial, the prescribed dose was as follows: 6,600–7,040 cGy to the PTVnxd and PTVnd in 32 fractions, 6,000 cGy to the PTV1 and PTV2 in 30–32 fractions, and 5,400 cGy to the PTV3 in 30–32 fractions. For the planning of reduced-volume IMRT recommendations, the prescribed dose was the same as given in the RTOG-0225 guidelines, except for CTV1. The prescribed dose included 6,000 cGy to the PTV1-h in 30–32 fractions and 5,400 cGy to the PTV1 in 30 fractions.

The treatment goals for the IMRT plan were that the prescribed dose would cover 95% of the PTV volume, and the maximum dose would not exceed 107%. Regarding the OARs, the maximum doses to the brain stem and the spinal cord were set to 5,400 and 4,500 cGy, respectively. In addition, the doses to other normal tissues was minimized within a reasonable range without affecting the target coverage.

The incidence of LCN complications predicted by the NTCP model

The maximum dose (Dmax) and the mean dose (Dmean) of bilateral LCNs from RTOG and reduced-volume IMRT planning were investigated in each patient. The Lyman-Kutcher-Burman (LKB) calculation model in Pinnacle[3] was used to predict the incidence of LCN complications (19-21). Because the characteristics of LCNs are similar to those of the optic nerve, the parameters applied in the present study were calculated based on the optic nerve as follows: α/β =3 and the TD50 (the mean dose predicting a 50% risk of complications), n (a parameter that considers the volume effect), and m (the slope of the dose–response curve) were 6,500 cGy, 0.25, and 0.14, respectively (20,22,23).
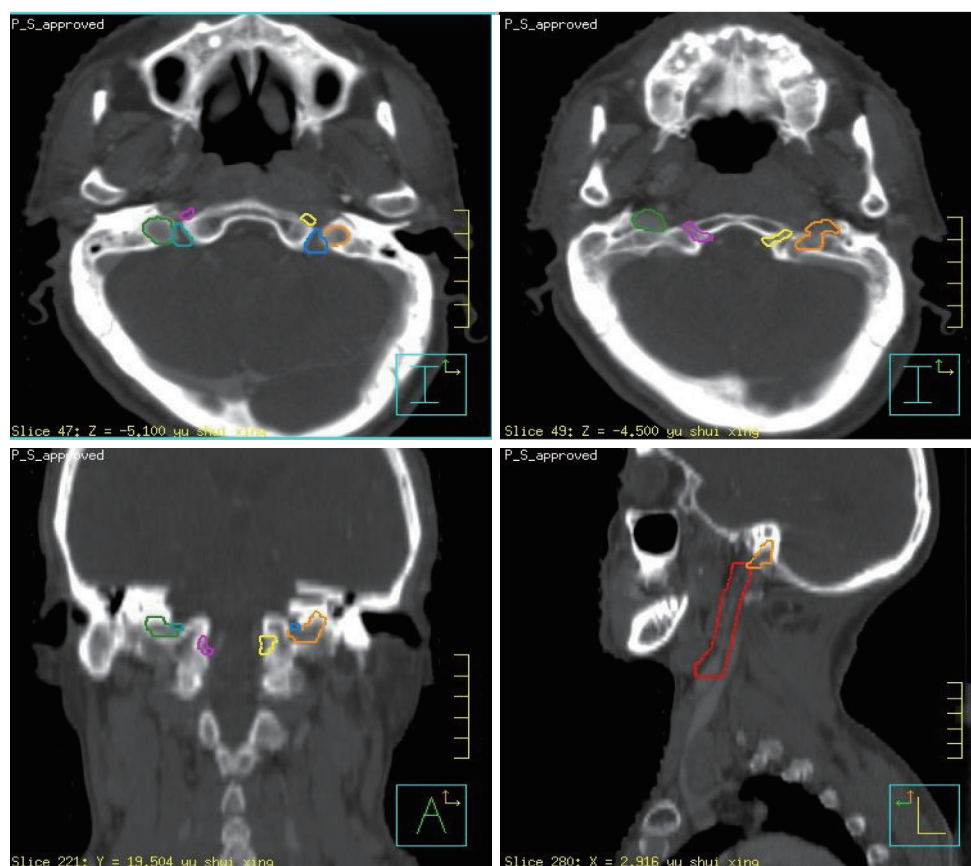
Figure 1 One case of LCN contour: the light blue and teal contours indicate the left and right IX cranial nerves, respectively; the orange and forest green contours indicate the left and right X and XI cranial nerves, respectively; the yellow and purple contours indicate the left and right XII cranial nerves, respectively; and the red contours indicate the bilateral carotid sheaths. LCN, lower cranial nerve.

Statistical analysis

SPSS 19.0 software was used for data analysis, and Sigma Plot 10.0 was used for figure plotting. A paired sample t-test was used to compare the differences in all considered parameters between the RTOG and reduced-volume IMRT planning approaches and between the clinical T1-2 and T3-4 groups. The correlations between LCN NTCP and dose volume were analyzed using Pearson's correlation coefficient. A two-tailed value of P<0.05 was considered statistically significant.

Results

Volume of LCNs and volume ratio included in the target and dose

The LCN volume of 50 patients was (10.07±1.51) cc, 25.73%±15.92% of which was included in PTVnx and

PTVnd and 96.42%±8.57% of which was included in PTV1 and PTV2. The ratios of LCNs included in doses of more than 5,400, 6,000 and 6,600 cGy are shown in *Table 2*. The ratios in the RTOG plans were all significantly higher than those in the reduced-volume plans.

Dosimetry of LCNs in different treatment plans

One case of planning and the dose volume histogram of LCNs is shown in *Figures 2,3*. Dosimetric differences of LCNs in two different treatment plans and different clinical T stages are shown in *Table 3*. The Dmax and Dmean of LCNs in RTOG plans were significantly larger than those in reduced-volume plans [(7,453±170) *vs.* (7,401±148) cGy (t=3.01, P=0.004), (6,740±279) *vs.* (6,436±375) cGy (t=9.86, P=0.000)]. Furthermore, the Dmax and the Dmean of LCNs in patients with clinical T1-2 stages were significantly lower than in patients with clinical T3-4

Table 2 Ratio of LCNs exposed to doses of 5,400–6,600 cGy

Dose (cGy)	Patients	RTOG (%)	Reduced volume (%)	t	P
≥6,600	Total_Pat	61.48±26.03	47.26±23.23	6.16	0.000
	T1-2	53.12±28.85	37.29±21.88	3.76	0.000
	T3-4	69.84±20.15	57.23±20.40	6.38	0.000
≥6,000	Total_Pat	93.13±11.68	64.95±21.78	9.49	0.000
	T1-2	91.86±11.07	57.79±21.42	7.48	0.000
	T3-4	94.40±12.36	72.12±20.05	6.35	0.000
≥5,400	Total_Pat	99.40±0.79	98.58±1.25	7.18	0.000
	T1-2	99.29±0.69	98.17±1.29	5.98	0.000
	T3-4	99.51±0.88	98.98±1.09	4.95	0.000

Total_Pat, total patients; RTOG and reduced volume were the treatment plans based on the IMRT recommendations of RTOG and reduced volume, respectively; *t*, P, difference between the two plans. LCN, lower cranial nerve.
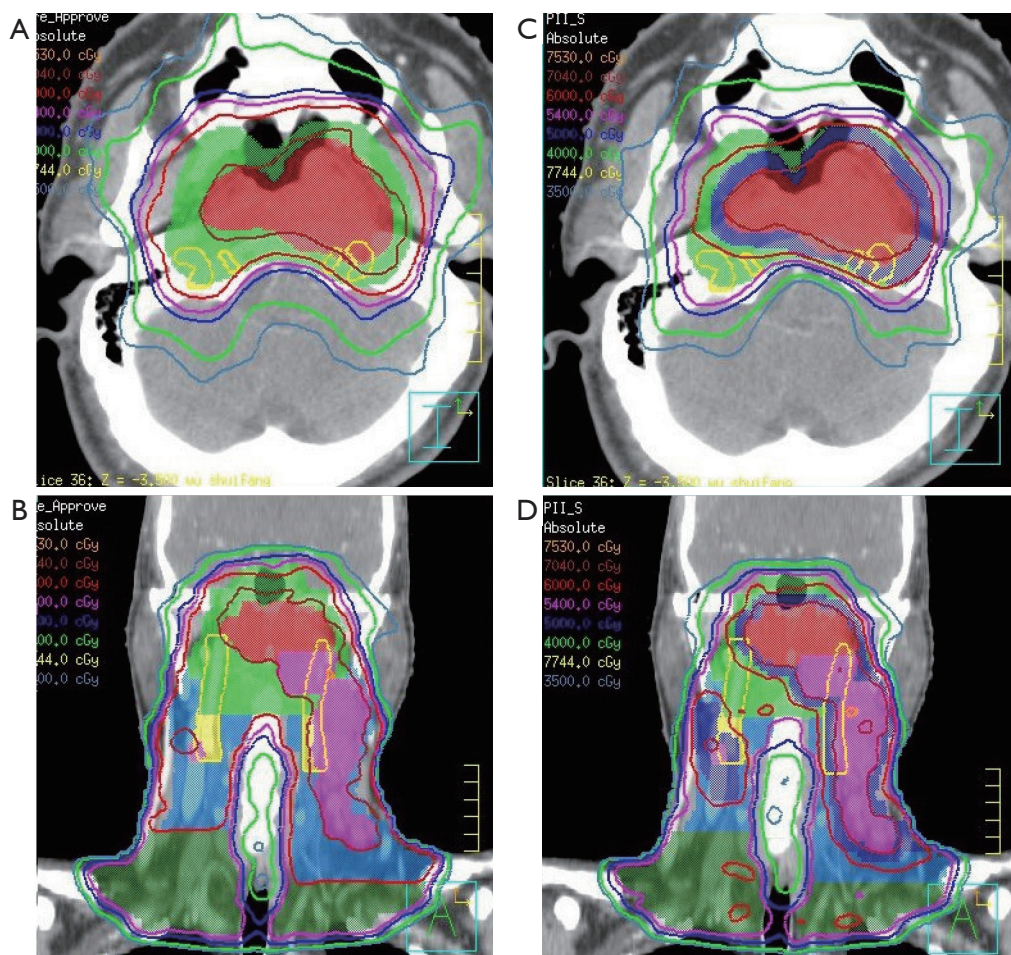

Figure 2 Treatment plan cases: (A,B) correspond to the RTOG plan and (C,D) correspond to the reduced-volume plan. The yellow contours are LCNs; the red and purple targets are PTVnx and PTVnd, respectively. The blue, green, light blue and forest targets are PTV1-h, PTV1, PTV2 and PTV3, respectively. LCN, lower cranial nerve; PTV, planning target volume.

stages [(7,390±187) *vs.* (7,464±119) cGy (*t*=−2.40, P=0.019), (6,442±338) *vs.* (6,733±329) cGy (*t*=−4.78, P=0.000)].

The incidence of LCN complications predicted by the NTCP model in different treatment plans

As shown in *Table 3*, the NTCP in RTOG plans was significantly higher than that in the reduced-volume plans [(59.98±11.87)% *vs.* (51.62±13.86)%, P=0.000], and NTCP was significantly lower in the T1-2 group than in the
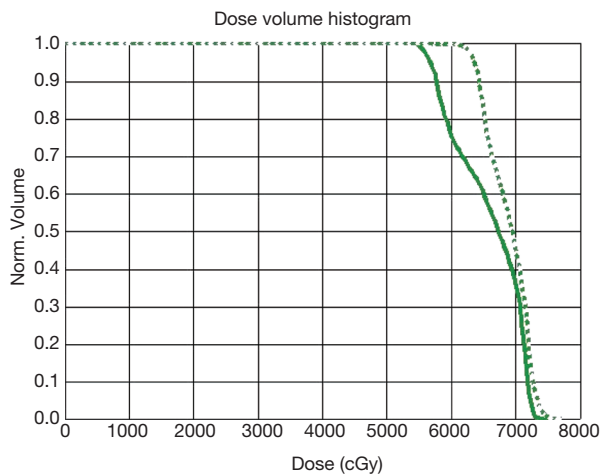

Figure 3 The dose volume histogram of LCNs for one case: The solid and dashed lines indicate the dose volume of LCN-based planning of reduced volume and RTOG. LCN, lower cranial nerve.

T3-4 group [(51.72±11.66)% *vs.* (59.88±14.10)%, *t*=−3.14, P=0.002)].

As shown in *Figure 4*, there was an extremely strong correlation of NTCP with Dmean (R=0.847, P=0.000) and a weak correlation with Dmax (R=0.271, P=0.006). Similarly, there was a strong correlation of NTCP with an irradiation volume of more than 6,600 cGy (R=0.841, P=0.000), a moderate correlation with 6,000 cGy (R=0.709, P=0.000), and a weak correlation with 5,400 cGy (R=0.317, P=0.001).

Discussion

RICNP is not a rare complication and can be a long-term problem after radical radiotherapy for NPC. Prevention of RICNP is paramount because the functional impairment can be profound and refractory to standard therapies.

Several risk factors for RICNP have been described. Kong *et al.* identified initial CNP at diagnosis, chemotherapy, total radiation dose and upper neck fibrosis as independent risk factors for developing RICNP (24). However, the majority of studies on RICNP included patients prior to the availability of IMRT, which improved the therapeutic ratio and/or treatment tolerance in patients with head and neck cancer by facilitating the sparing of normal tissue, and IMRT is already the standard treatment for NPC. The potential overlap among fields irradiated in the neck is often the main cause of RICNP in conventional radiotherapy, while RICNP generally does not appear in IMRT, and neck fibrosis is also expected to significantly

Table 3 Dose and NTCP of the two LCN-based plans

Variable	Patients	RTOG	Reduced volume	*t*	P
Dmax (cGy)	Total_Pat	7,453±170	7,401±148	3.01	0.004
	T1-2	7,425±195	7,355±177	2.53	0.018
	T3-4	7,481±139	7,447±95	1.64	0.113
Dmean (cGy)	Total_Pat	6,740±279	6,436±375	9.86	0.000
	T1-2	6,622±231	6,263±336	6.70	0.000
	T3-4	6,858±277	6,609±334	8.99	0.000
NTCP (%)	Total_Pat	59.98±11.87	51.62±13.86	8.81	0.000
	T1-2	56.56±9.70	46.88±11.61	6.30	0.000
	T3-4	63.40±13.00	56.36±14.52	6.50	0.000

Dmax, maximum point dose; Dmean, mean dose; Total_Pat, total patients; RTOG and reduced volume were the treatment plans based on IMRT recommendations of RTOG and reduced volume, respectively; *t*, P, difference between the two plans. LCN, lower cranial nerve; NTCP, normal tissue complication probability.
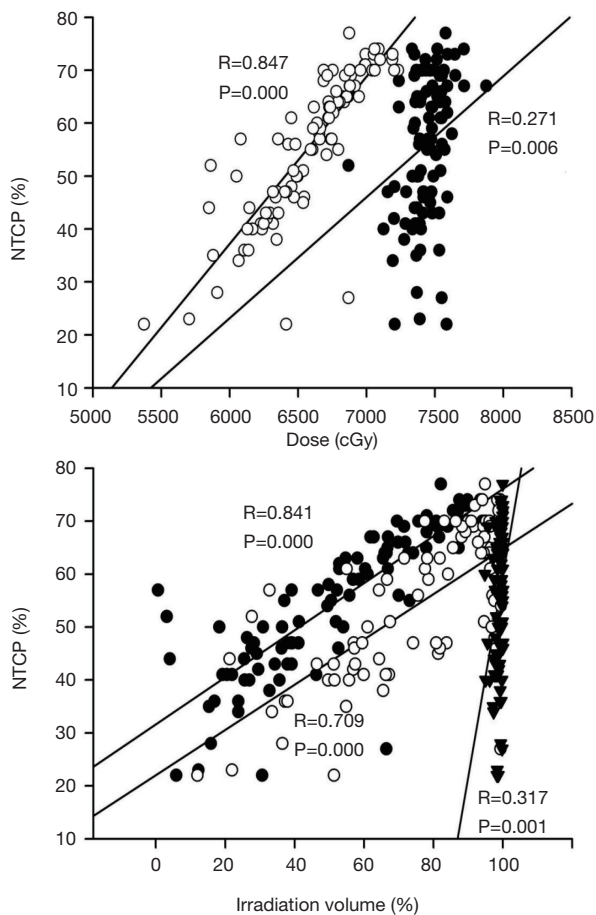
Figure 4 Correlations between NTCP and dose volume: the upper figure illustrates the correlation between NTCP and dose. ○, correlation between NTCP and Dmean; ●, correlation between NTCP and Dmax. The figure below illustrates the correlations between NTCP and irradiation volume. ●, ○ and ▼, correlations between NTCP and irradiation volumes of more than 6,600, 6,000 and 5,400 cGy, respectively. NTCP, normal tissue complication probability.

decrease with the use of IMRT treatment given the dose restraint to posterior neck muscles. However, the effects of dose escalation in IMRT may give rise to the long-term development of CNP (24). Instead of being unable to accurately locate the LCNs in conventional radiotherapy, the precise delineation of LCNs is now possible in IMRT planning with the application of CT and MRI techniques. Dose evaluation and NTCP prediction are also available.

The reduced-volume plan was an expert consensus provided by the Working Committee for the clinical staging of NPC in China in 2010, in which the CTV is reduced

accordingly on the basis of RTOG 0225 clinical trial; its long-term curative effect has also been confirmed to be ideal (12-14). However, theoretically, there could also be reduced toxicity to surrounding OARs. The reduced-volume plan and the RTOG plan are the two most commonly used IMRT plans in China today. The purpose of this study was to evaluate the difference in LCN NTCP between the two IMRT plans.

The results showed that the Dmax and the Dmean of LCNs in the reduced-volume plan were significantly lower than those in the RTOG plan (7,401 *vs.* 7,453 cGy, 6,436 *vs.* 6,740 cGy); NTCP was also significantly lower in the reduced-volume plan (51.62% *vs.* 59.98%). On the other hand, the Dmax, the Dmean and NTCP of LCNs in the T1-2 group were significantly lower than those in the T3-4 group (7,390 *vs.* 7,464 cGy, 6,442 *vs.* 6,733 cGy, 51.72% *vs.* 59.88%). Therefore, our results showed that LCNs can be better spared in T1-2 stage patients with a reduced-volume plan.

RICNP is related to many factors. A total of 512 NPC cases were analyzed retrospectively by Kong *et al.* (25). Cranial nerve injury developed in 81 of 512 cases, and the 5- and 10-year cumulative incidence rates were 10.3% and 25.4%, respectively. Injury to the XII cranial nerves was most common. Multivariate analysis showed that RICNP was mainly associated with tumor invasion, chemotherapy, nasopharyngeal total radiation dose and age, while LCN injury was associated with N staging and radiation field. LCN injury increased for later stages of cervical lymph node. Thirty-one patients with breast cancer were selected by Wu *et al.* (26), and 50 Gy of postoperative adjuvant radiotherapy was delivered to the ipsilateral supraclavicular area and chest wall. Dmax, Dmean, V40, V45, V50, V52.5, and V55 of BP were evaluated. The results showed that there was no relationship between BP neuropathy and Dmax, but the number of lymph node dissections was an independent influencing factor of BP lesions.

In fact, few studies have been reported on LCN injury after radiotherapy in NPC, and even fewer studies on NTCP are available. There is currently a lack of corresponding parameters of NTCP in LCN injury. Because LCNs have characteristics similar to those of the optic nerve, parameters of the optic nerve (TD50, n and m: 6,500 cGy, 0.25, and 0.14) from Burman (20) were used in this study to calculate the NTCP.

In our results, there exists strong correlations of LCN NTCP with Dmean (R=0.847, P=0.000) and an irradiation volume of more than 6,600 cGy (R=0.841, P=0.000), while

there is a weak correlation with Dmax (R=0.271, P=0.006). Though LCNs are serial organs, the irradiation condition of the maximum point dose to the LCN could vary. Sometimes only a tiny volume of the LCN was exposed to the Dmax, while in rest of the LCN volume was exposed to relatively lower doses; thus, the Dmax may not truly reflect the LCN dose. As illustrated in *Figure 4*, NTCP increased with increasing Dmean and for an irradiation volume of more than 6,000 cGy, but NTCP did not increase with Dmax. On the other hand, the higher NTCP in the T3-T4 group may be related to the high irradiation volume of more than 6,600 cGy to the PTVnx and PTVnd (as shown in *Tables 2,3*). In addition, previous studies revealed that LCN injury was related to both a high dose and the irradiated volume, which induced severe fibrosis on the carotid sheath (25,27).

Conclusions

It is feasible to precisely delineate the LCN, which can serve as a routine OAR, and to further predict LCN complications using the NTCP model in IMRT planning for NPC. Both a high Dmean and a large irradiation volume are important factors in predicting complications of LCNs. Of the two most common IMRT guidance plans in China, LCN NTCP was significantly lower for the reduced-volume plan than for the RTOG plan.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.12.75). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Second Affiliated Hospital of Soochow University (No. 2015021). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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