scientific reports

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Neck dose-limiting rings reduce head and neck lymphedema in early nasopharyngeal carcinoma patients undergoing IMRT: a dosimetric-clinical validation

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This study aimed to determine the optimal limiting dose to reduce head and neck lymphedema in patients with early nasopharyngeal carcinoma (NPC) receiving intensity-modulated radiotherapy (IMRT) by setting dose limiting rings at the anterior and posterior regions of the neck. A total of 15 patients with early NPC were included, and 5 sets of IMRT plans were designed for each patient. Plan A was a conventional plan without dose limiting rings, while Plans B-E were set dose limiting rings with gradients of 20 Gy, 18 Gy, 16 Gy, and 14 Gy, respectively, whose remaining parameters were consistent with Plan A. Through Analysis of Variance (ANOVA) for randomized block design data and Bonferroni pairwise multiple comparisons, the impact of dose limiting rings on target coverage and doses to organs at risk was evaluated and the optimal limiting dose was determined. After that, 50 patients with early NPC (25 with rings according to the optimal limiting dose, 25 without rings) were treated with IMRT to determine if there was a difference in the incidence of head and neck lymphedema. Ultimately, 16 Gy was determined as the optimal limiting dose threshold for achieving the balance of target coverage and protection of organs at risk. Compared with the conventional plan, setting cervical anterior and posterior dose limiting rings of 16 Gy did not affect the target dose coverage (all $P > 0.05$), only slightly affected homogeneity index and increased monitor units (MUs) (both $P < 0.05$). The doses of the inner ears, mandible, and brainstem were not affected (all $P > 0.05$), meanwhile, the doses of the oral cavity, larynx, and thyroid were reduced significantly (all $P < 0.05$). The doses of the parotid glands and spinal cord slightly increased (both $P < 0.05$), but still within the tolerance range. Clinical cohort verification showed that setting the dose limiting rings of 16 Gy at the anterior and posterior regions of the neck significantly reduced the occurrence of head and neck lymphedema ($P < 0.05$). Through dosimetric and clinical cohort verification studies, the optimal limiting dose for the cervical anterior and posterior dose limiting rings has been determined, hoping to provide a new design method of IMRT plans to reduce head and neck lymphedema after radiotherapy for early NPC.

Keywords Nasopharyngeal carcinoma, Intensity-modulated radiotherapy, Head and neck lymphedema, Dosimetry, Clinical verification

Nasopharyngeal carcinoma (NPC) is prevalent in southern China, and radiotherapy is the main treatment[1]. Intensity-modulated radiotherapy (IMRT) is the most common radiotherapy method. Compared to conventional 2-dimensional (2D) and 3-dimensional (3D) conformal radiotherapy, IMRT has the advantages of better concentrating the radiation dose on the tumor area and reducing the dose distributions of normal organs, which improves the local control rate and decreases the incidence of side effects[2,3]. For early-stage NPC (stage I and II) with low risk of recurrence and metastasis, the 5-year survival rate of patients undergoing IMRT is over 80%[4]. In addition, the incidence of side effects such as xerostomia, radiation encephalopathy, radiation mandibular necrosis, and radiation nerve injury are markedly decreased[5].

However, IMRT is associated with multiple fields irradiation and normal tissues that are not clearly restricted in the radiation field path may be exposed to additional irradiation[6]. For example, for NPC 7 to 9 radiation fields

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are generally set in the same plane, and the neck skin and subcutaneous soft tissue are not subject to special dose restrictions. This may result in the neck circumference to be irradiated with medium and high doses of more than 25–30 Gy. This can lead to lymphatic duct occlusion and destruction, which may cause lymphatic reflux disorder and lymph remaining in the interstitial space. This results in an increase in the incidence of head and neck lymphedema after IMRT compared to conventional 2D and 3D conformal radiotherapy[7].

Compared to limb edema, head and neck lymphedema after IMRT for NPC has a significant impact on appearance, and can negatively affect patients' psychological well-being. Severe cases may also affect patients' speech, swallowing, breathing, and head and neck mobility, thereby affecting their quality of life[8]. It deserves more attention and active prevention. Especially for early-stage (Stage I and II) NPC patients with very good therapeutic outcomes, further reducing the adverse reaction of head and neck lymphedema and improving the quality of life may have more clinical significance. Previous studies have shown that it is feasible to set up a lymphatic drainage protection zone. This can be done by placing dose limiting rings at < 20 Gy at the anterior and posterior regions of the neck to reduce the irradiation dose and preserve the function of lymphatic ducts by reserving a channel from top to bottom for both the anterior and posterior regions of the neck to facilitate lymphatic reflux[9]. Our prior research suggested that setting limiting ring at < 20 Gy at the anterior and posterior regions of the neck was an independent protective factor for head and neck lymphedema after IMRT for NPC[10]. However, the optimal dose limit is not clear. Animal experiments have shown that when the tails of mice were irradiated with 15 and 30 Gy, the volume increased by 15% and 25% respectively[11], suggesting that radiation has a dose-dependent effect on the occurrence of edema. Theoretically, the lower the dose of the limiting ring, the better protection of the drainage function of lymphatic ducts, and the greater the potential for dosimetric advantages to translate into real clinical benefits. However, at the same time, the difficulty of the radiotherapy plan design increases, which may compromise target coverage and the constraints for organs at risk. Whether further reduction of the limit is possible deserves further research.

In this study, patients with early NPC were selected to determine the optimal limiting dose of rings placed at the anterior and posterior regions of the neck from a dosimetric perspective, so as to obtain the optimal cut-off point of dose limit to provide a balance between the target coverage and protection of organs at risk (head and neck lymphedema can be divided into external (superficial) and internal (deep) lymphedema, and this study focused on the former). Next, we conducted a clinical cohort validation study to compare the incidence of lymphedema between patients who received IMRT with limiting rings designed according to the optimal limiting dose and those who received a conventional IMRT plan to explore whether dosimetric advantages can be translated into clinical benefits.

Materials and methods

General data

Initially, 15 patients with early NPC who underwent radiotherapy computed tomography (CT) localization at Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University, from January 2022 to September 2022 were selected for dosimetric study. The inclusion criteria were patients with appropriate subcutaneous fat thickness, with a body mass index (BMI) greater than 19 and less than 24 kg/m^2; stage I/II disease according to UICC 8th edition staging, including stage T1-2 and N0-1, in which stage N1 only included patients with positive retropharyngeal lymph nodes with a maximum lymph node diameter of < 3 cm, and the level Ib was not irradiated. Patients with positive cervical lymph nodes were excluded. Induction chemotherapy was not performed before CT localization. Among the 15 patients, there were 3 with T1N0 disease, 5 with T1N1 disease, 5 with T2N0 disease, and 2 with T2N1 disease.

Next, 50 patients with early NPC who received IMRT at our hospital from December 2022 to December 2023 were randomly divided into 2 groups using the random number table method ($n = 25$ in each group). In Group 1 patients received conventional IMRT without limiting rings, and in Group 2 patients received IMRT with limiting rings at the anterior and posterior regions of the neck according to the optimal dose limit determined by the dosimetric above. Head and neck lymphedema after radiotherapy was evaluated. The inclusion criteria were: (1) 18 to 65 years old; (2) Good heart, liver, and kidney function such that radiotherapy and chemotherapy can be tolerated; (3) No chronic diseases such as hypertension and diabetes without good control; (4) BMI > 19 and < 24 kg/m^2; (5) No history of major trauma or head and neck surgery; (6) No vein thrombosis of the head and neck or superior vena cava obstruction; (7) No second primary tumor; (8) The T and N staging criteria were the same as those in the aforementioned dosimetric study. Patients with stage I disease were treated with IMRT alone, and patients at stage II disease were treated with concurrent chemoradiotherapy as appropriate (cisplatin or nedaplatin 80–100 mg/m^2, 2 courses 3 weeks apart). This study was approved by the Ethics Committee of our hospital (No. 2021-SW14), and all patients provided written informed consent.

CT simulation localization

Patients were placed in the supine position, with the hands naturally drooping, and their posture was fixed using a head, neck and shoulder thermoplastic mask. Localization CT scanning was performed with a thickness of 3 mm.

Delineation of the targets and organs at risk, and their dose requirements

Targets were named and delineated as follows[12]. The gross tumor volume of nasopharynx (GTVnx) was the nasopharyngeal tumor and positive retropharyngeal lymph nodes as determined by clinical and imaging examinations. The first clinical target volume (CTV1) was extended 0.5 cm from the GTVnx in all directions, including all nasopharyngeal mucosa and 0.5 cm below it. The second clinical target volume (CTV2) was extended 0.5 cm from the CTV1 in all directions (following the principle of distance plus structure, and determining the expanding distance according to the adjacent tissue structure characteristics), as well as the lymph node drainage

area that needed to be irradiated prophylactically. Its inferior boundary was the lower edge of the cricoid cartilage, and it was permissible to spare the lower neck and supraclavicular areas from irradiation[13]. The planning target volume of nasopharynx (PTVnx), the first planning target volume (PTV1), and the second planning target volume (PTV2) were formed by expanding GTVnx, CTV1, and CTV2 by 0.5 cm in all directions. Prescription dosages were: PTVnx 70 Gy/33F; PTV1 60 Gy/33F; and PTV2 54 Gy/33F. Dose evaluation requirements of the target volume were[14]: 100% prescription dose line covered ≥ 95% of the PTV volume; the volume of PTV receiving < 93% of the prescribed dose was < 1%; the volume of PTV receiving > 110% prescription dose was ≤ 20%. The Organ-at-risk dose limits were[13]: the maximum dose (Dmax) of brain stem < 60 Gy; Dmax of optic nerve and optic chiasma < 54 Gy; Dmax of spinal cord < 45 Gy; Dmax of lens < 9 Gy; the mean dose (Dmean) of parotid glands < 26–35 Gy, or the dose received by at least 50% of the volume of one parotid gland should not > 30 Gy; Dmean of inner ear < 45 to 55 Gy (to facilitate calculations the bilateral inner ears were combined into one organ at risk for dose assessment); Dmax of mandible and temporomandibular joint < 70 Gy; Dmean of thyroid < 50 Gy; Dmean of larynx < 45 Gy; Dmean of oral cavity < 40 Gy.

Plan design

The plans of 9-field IMRT with simultaneous integrated boost were designed using Philips Pinnacle^3 9.1 treatment planning system. In the first part of the study, 5 different plans were designed for each of the 15 patients. The conventional radiotherapy plan was designed according to the above target doses and the dose limits to organs at risk, without limiting rings, and was defined as Plan A. Based on Plan A, limiting rings were set at the anterior and posterior regions of the neck, and then limiting rings with a diameter of 1–2 cm were drawn at the center skin and subcutaneous tissue (excluding muscles, bones and other structures) at the anterior and posterior regions of the neck (Fig. 1). The limiting ring at the anterior region started from the lower edge plane of mandible and was extended down to the lowest plane of the target volume (the lower edge of cricoid cartilage). The limiting ring at the posterior region started at the skull base, and extended down to the lowest plane of the target volume. Several dose gradients were set, with a maximum dose of < 20 Gy, 18 Gy, 16 Gy, and 14 Gy, and named Plan B, C, D, and E, respectively, and other plan parameters and conditions were the same as those of Plan A.

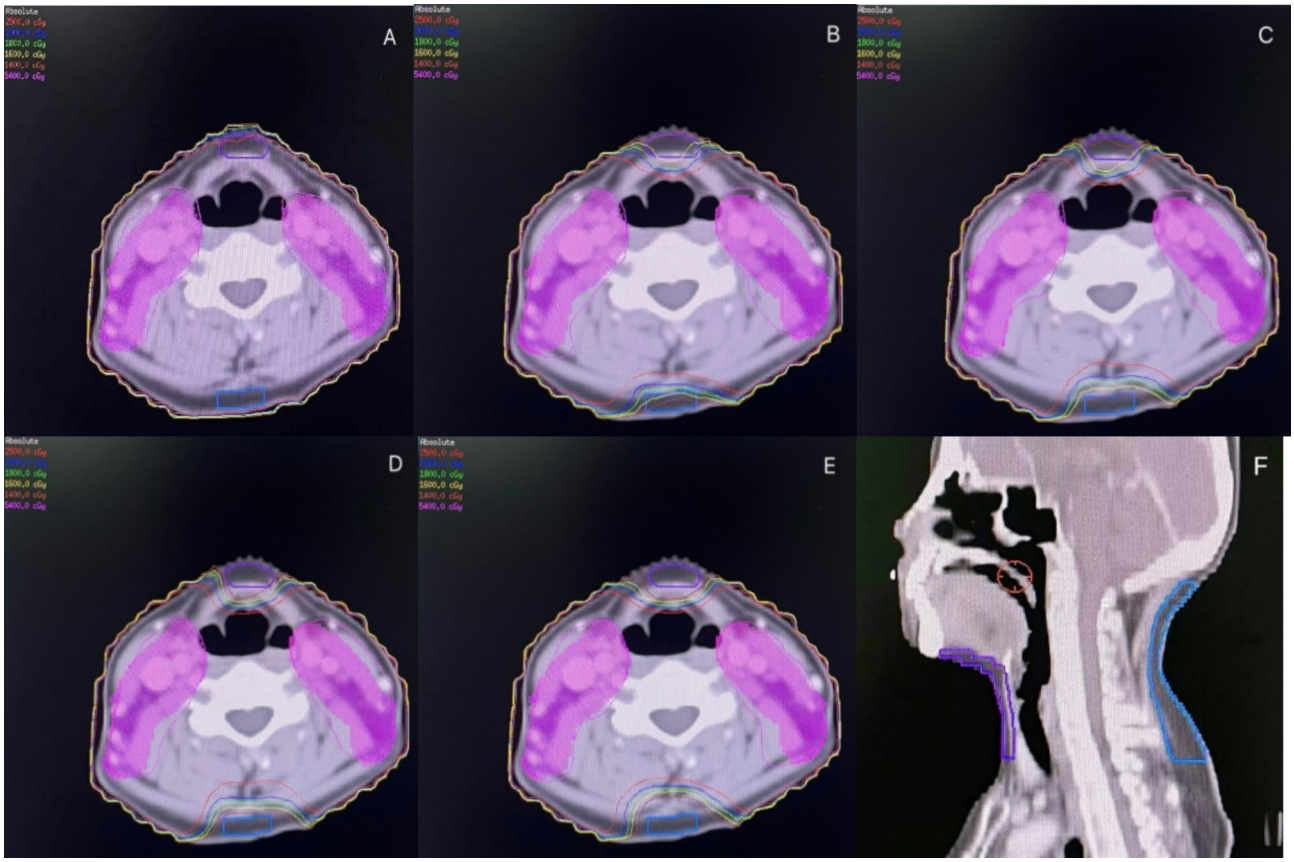

Fig. 1. Schematic diagram of dose limiting rings delineation at the anterior and posterior regions of the neck of a patient with T2N0 disease. (**A**–**E**) Isodose curves of Plans A–E on the same CT cross-section. (**F**) CT sagittal section showing the dose limiting rings delineation at the anterior and posterior regions of the neck of the same patient.

Plan evaluation

The treatment plans were evaluated and compared using dose volume histograms and isodose curves. The dose distribution of the target volume was evaluated by using V100% (%), V93% (%), conformity index (CI), and homogeneity index (HI). The formula for CI is: $CI = (V_{t,\ ref})\ 2/(V_t \times V_{ref})$, where $V_{t,\ ref}$ is the volume of PTV covered by the prescription dose, V_t is the volume of PTV, and V_{ref} is the total volume covered by the prescription dose. The better the conformity, the closer the CI value is to 1[15]. The formula for HI is $= (D_2 - D_{98})/D_{ref}$, where D_2 and D_{98} are the lowest doses accepted by 2% and 98% of the PTV, and D_{ref} is the prescription dose. The better the uniformity, the smaller the HI value[16]. To avoid the influence of PTVnx and PTV1 contained in PTV2 on the high dose value, the volume range of HI evaluation was PTV2-PTVnx-PTV1. Since the target volumes of PTVnx and PTV1 were basically above the upper boundaries of the anterior and posterior limiting rings, the anterior and posterior limiting rings had little effect on them; this study mainly compared the dose coverage of PTV2. In addition, the dose to organs at risk located in the upper and lower boundaries of the anterior and posterior limiting rings was mainly evaluated, including the maximum dose to the spinal cord, brain stem, and mandible, and the mean dose to the bilateral parotid glands, bilateral inner ears, oral cavity, throat, and thyroid gland.

Diagnosis and grade of head and neck lymphedema

All patients were followed up once every 1 to 2 months after radiotherapy. Head and neck lymphedema was recorded, and the highest grade of head and neck lymphedema recorded during follow-up was used in the analysis as the final grading. All patients were evaluated by the same doctor to ensure repeatability and consistency. The diagnosis of head and neck lymphedema was based on disease history, chief complaint, visual examination and palpation, focusing on submandibular, submental, and facial areas. The severity of head and neck lymphedema was graded according to the standard proposed by MD Anderson as follows[17]. Grade 0 = no edema visible to the naked eye, but the patient complained of tight or heavy skin. Grade 1a = soft and visible edema, non-concave, and the edema is fluctuating and reversible. Grade 1b = soft concave edema, edema is fluctuating and reversible. Grade 2 = hard concave edema, irreversible, without fibrosis and other tissue changes. Grade 3 = irreversible edema, with tissue changes. Edema of Grade 0 and above was considered diagnostic of lymphedema.

Statistical methods

Statistical analysis was conducted using SPSS version 22.0 software. Categorical data were described by frequency and percentage, and were compared by χ^2 test or Fisher exact probability method. Continuous data were expressed as mean ± standard deviation, and under the premise of normal distribution and homogeneity of variance, the dose distribution of the target volume and the organs at risk were compared using Analysis of Variance (ANOVA) for randomized block design data. The 15 patients were divided into 15 blocks, and Plans A to E represented 5 different dose gradients, i.e., 5 treatment groups. If the data did not meet the conditions of variance analysis, the Friedman rank sum test was used for analysis. The Kaplan–Meier method was used to estimate survival rates. All analyses were 2-sided, and a value of $P < 0.05$ was considered statistically significant. If there was a difference identified in the variance analysis, the Bonferroni method was used for pairwise multiple comparisons.

Results

Formation of limiting rings at the anterior and posterior regions of the neck

The schematic diagram of the limiting rings outlined at the anterior and posterior regions of the neck, and the dose distribution of 5 radiotherapy plans on CT cross-section of a patient with T2N0 disease are shown in Fig. 1A–E, and a CT sagittal section is shown in Fig. 1F. The images suggested that compared to Plan A, the isodose curves of Plans B to E retracted at the anterior and posterior regions of the neck, forming a low-dose limiting ring area at the anterior and posterior regions of the head and neck. In addition, the degree of isodose curve retraction was more obvious as the dose gradient decreased.

Comparison of target dose

As shown in Table 1, there were no significant differences in V100%, V93%, and CI between Plans A to E (all $P > 0.05$). There were significant differences in HI between Plans A to E ($F = 5.588$, $P = 0.002$). As shown in Table 3, Bonferroni multiple comparisons showed statistically significant differences in HI between Plans A and B, A and C, A and D, and A and E, but there were no statistically significant differences between Plans B, C, D, and E, suggesting that setting limiting rings at the anterior and posterior regions of the neck, compared to the conventional plan, the uniformity of target was slightly worse, but it still met the clinical requirements.

	Plan A	Plan B	Plan C	Plan D	Plan E	F/M	*P*
V100% (%)	95.79 ± 0.63	95.97 ± 0.54	95.89 ± 0.69	95.59 ± 0.71	96.01 ± 0.58	0.339	0.797
V93% (%)	99.55 ± 0.28	99.65 ± 0.31	99.52 ± 0.36	99.62 ± 0.31	99.59 ± 0.29	0.429	0.732
HI	0.121 ± 0.012	0.133 ± 0.014	0.134 ± 0.012	0.140 ± 0.014	0.141 ± 0.013	5.588	0.002
CI	0.840 ± 0.015	0.847 ± 0.016	0.846 ± 0.016	0.852 ± 0.015	0.850 ± 0.013	1.512	0.221
Monitor units (MUs)	586.07 ± 7.77	628.58 ± 7.56	625.22 ± 8.11	632.55 ± 8.05	644.65 ± 8.12	151.572	< 0.001

Table 1. Comparisons of dose distributions of the target and monitor units (MUs) between 5 plans of 15 NPC patients ($\bar{x} \pm s$)

	Plan A	Plan B	Plan C	Plan D	Plan E	F/M	*P*
Bilateral inner ears (Dmean)	41.97 ± 2.34	41.52 ± 2.54	42.30 ± 2.51	41.65 ± 2.63	40.51 ± 2.60	1.456	0.236
Bilateral parotid glands (Dmean)	33.88 ± 1.01	34.94 ± 1.07	34.95 ± 1.00	34.96 ± 1.02	35.99 ± 1.01	10.639	< 0.001
Mandible (Dmax)	57.63 ± 1.96	58.01 ± 1.86	57.44 ± 2.01	57.46 ± 1.81	57.54 ± 1.86	0.286	0.835
Oral cavity (Dmean)	33.01 ± 1.25	32.46 ± 1.21	33.26 ± 1.28	30.58 ± 1.35	29.11 ± 1.28	28.119	< 0.001
Larynx (Dmean)	43.95 ± 1.45	41.20 ± 1.31	39.29 ± 1.42	38.92 ± 1.38	38.67 ± 1.34	41.064	< 0.001
Thyroid (Dmean)	40.03 ± 2.03	36.30 ± 1.98	36.26 ± 1.91	35.67 ± 2.03	35.03 ± 2.15	15.142	< 0.001
Spinal cord (Dmax)	36.73 ± 0.86	37.36 ± 0.80	37.66 ± 0.86	37.76 ± 0.88	38.67 ± 0.91	13.287	< 0.001
Brain stem (Dmax)	56.42 ± 1.89	56.24 ± 1.99	56.87 ± 1.85	56.04 ± 2.02	56.08 ± 1.97	0.501	0.683

Table 2. Comparisons of dose distributions of the organs at risk between 5 plans of 15 NPC patients ($\bar{x} \pm s$, Gy)

	A&B	A&C	A&D	A&E	B&C	B&D	B&E	C&D	C&E	D&E
HI	0.088	0.051	0.001	< 0.001	1.000	0.882	0.551	1.000	0.834	1.000
Bilateral parotid glands (Dmean)	0.038	0.035	0.034	< 0.001	1.000	1.000	< 0.001	1.000	0.044	0.049
Oral cavity (Dmean)	0.583	1.000	< 0.001	< 0.001	0.100	< 0.001	< 0.001	< 0.001	< 0.001	0.016
Larynx (Dmean)	< 0.001	< 0.001	< 0.001	< 0.001	0.002	< 0.001	< 0.001	1.000	0.319	0.539
Thyroid (Dmean)	< 0.001	< 0.001	< 0.001	< 0.001	1.000	1.000	0.543	1.000	0.605	1.000
Spinal cord (Dmax)	0.303	0.026	0.011	< 0.001	1.000	1.000	< 0.001	1.000	0.013	0.033
Monitor units (MUs)	< 0.001	< 0.001	< 0.001	< 0.001	1.000	1.000	< 0.001	0.091	< 0.001	< 0.001

Table 3. Bonferroni multiple comparisons of dose distributions of the target and organs at risk and monitor units (MUs) between 5 plans of 15 NPC patients (the values in the table were P-values for pairwise comparisons).

Comparison of doses to organs at risk

Average dose to the bilateral inner ears

As shown in Table 2, there were no statistical differences in the average doses to the bilateral inner ears between Plans A to E ($F = 1.456$, $P = 0.236$).

Average dose to the bilateral parotid glands

As shown in Table 2, the average doses to the bilateral parotid glands between Plans A to E were significantly different ($F = 10.639$, $P < 0.001$). Bonferroni multiple comparisons showed that the differences in the average doses of bilateral parotid glands between Plans A and B, A and C, A and D, as well as A and E were statistically significant (Table 3), suggesting that setting limiting rings at the anterior and posterior regions of the neck would increase the average dose to the bilateral parotid glands compared to the conventional plan. There were no significant differences in the average doses to the bilateral parotid glands between Plans B and C, B and D, C and D, but there were significant differences between Plans B and E, C and E, D and E, suggesting that when the dose limits were 20, 18, and 16 Gy, the doses to the parotid glands were not significantly different. However, if the dose limit was 14 Gy, the dose to the parotid glands would be significantly increased.

Maximum dose to the mandible

As shown in Table 2, there were no significant differences in the maximum doses to the mandible between Plans A to E ($F = 0.286$, $P = 0.835$).

Average dose to the oral cavity

As shown in Table 2, the differences in the average oral cavity doses between plans A to E were statistically significant ($F = 28.119$, $P < 0.001$). Bonferroni multiple comparisons showed that there were no significant differences between Plan A and B, A and C, and B and C, but there were significant differences between Plan A and D, and C and D (Table 3), suggesting that setting limiting rings at the anterior and posterior regions of the neck could reduce the average oral dose compared with the conventional plan, and the difference was significant when the cut-off point of dose limit was < 16 Gy. However, the difference between Plans D and E was statistically significant, suggesting that the oral dose would be further reduced when the dose limit was 14 Gy.

Average dose to the larynx

As shown in Table 2, there were significant differences in the average larynx doses between Plans A to E ($F = 41.064$, $P < 0.001$). Bonferroni multiple comparisons showed that the differences between Plans A and B, A and C, A and D, and A and E were statistically significant (Table 3), suggesting that setting limiting rings at the anterior and posterior regions of the neck could reduce the average larynx dose compared to the conventional plan. There were differences between Plans B and C, B and D, and B and E, but there were no differences between Plans C and D, C and E, and D and E, suggesting that the cut-off point of dose limit was about 18 Gy, and even if the dose was further reduced, the larynx dose would not be further reduced.

Average dose to the thyroid
As shown in Table 2, the average thyroid doses between Plans A to E were significantly different (F = 15.142, $P < 0.001$). Bonferroni multiple comparisons showed that the differences between Plans A and B, A and C, A and D, and A and E were statistically significant (Table 3), suggesting that setting limiting rings at the anterior and posterior regions of the neck could significantly reduce the average thyroid dose compared with the conventional plan. However, there were no differences between Plans B and C, B and D, B and E, C and D, C and E, and D and E, suggesting that the cut-off point of dose limit was about 20 Gy, and even if the dose was further reduced, the thyroid dose would not be reduced further.

Maximum dose to the spinal cord
As shown in Table 2, there ware significant differences in the maximum doses to the spinal cord between Plans A to E (F = 13.287, $P < 0.001$). Bonferroni multiple comparisons showed that the differences between Plans A and C, A and D, and A and E were statistically significant (Table 3), suggesting that setting limiting rings at the anterior and posterior regions of the neck would increase the spinal cord dose compared with the conventional plan. There were no differences between Plans B and C, B and D, and C and D, suggesting that there were no differences in spinal cord doses when the dose limits were 20, 18, and 16 Gy. The differences between Plans B and E, C and E, and D and E were statistically significant, suggesting that when the dose limit was 14 Gy, the spinal cord dose would be increased compared to dose limits of 20, 18, and 16 Gy. However, it was still far from the maximum tolerated dose of 45 Gy.

Maximum dose to the brain stem
As shown in Table 2, there were no significant differences in the maximum doses to the brain stem between Plans A to E (F = 0.501, $P = 0.683$).

Comparison of MUs
As shown in Table 1, the MUs of Plans A to E were statistically different (F = 151.572, $P < 0.001$). Bonferroni multiple comparisons showed that there were statistical differences between Plans A and B, A and C, A and D, and A and E (Table 3), suggesting that setting limiting rings at the anterior and posterior regions of neck could increase MUs compared to the conventional plan. There were no significant differences between Plans B and C, B and D, and C and D, but there were significant difference between Plans B and E, C and E, and D and E, suggesting that when the dose limits were 20, 18, and 16 Gy, the MUs were not significantly different, but if the limit was 14 Gy, the MUs would be increased.

Determination of the optimal limiting dose
Setting limiting rings at the anterior and posterior regions of the neck did not affect the dose coverage of PTV2, except that the uniformity was slightly affected and the MUs slightly increased. The doses to the inner ear, mandible, and brain stem were not affected, but the doses to the oral cavity, larynx, and thyroid gland were significantly reduced, with the optimal dose thresholds being 14–16 Gy, 18 Gy, and 20 Gy, respectively. When the dose limits were 20, 18, and 16 Gy, there were no differences in the doses to the parotid glands, and the average dose to the parotid glands was increased by about 1 Gy compared with the conventional plan. If the dose limit was 14 Gy, the dose to the parotid glands would be further increased compared to 20, 18 and 16 Gy. Compared to the conventional plan, when the dose limits were 20, 18 and 16 Gy, the max dose to spinal cord was increased by about 1 Gy, but it was still far from the dose limit of 45 Gy. If the dose limit was at 14 Gy, the spinal cord dose was further increased compared to 20, 18 and 16 Gy. Based on above information, 16 Gy was determined as the best dose limit.

Head and neck lymphedema after IMRT
Fifty patients were treated with IMRT, 25 without limiting rings (Group 1) and 25 with limiting rings at 16 Gy (Group 2). The median follow-up time was 18 months (range 11–23 months). The baseline characteristics of the two groups of patients, including age, gender, PS score, BMI, T/N staging, chronic diseases, and the dosage of radiotherapy and chemotherapy, were comparable. The objective response rate and 1-year progression-free survival rate after radiotherapy for both groups were 100%. In the group without limiting rings, there were 20 cases (80.0%) of head and neck lymphedema, among whom 3 were at Grade 0, 14 were at Grade 1 and 3 at Grade 2, and in the group with limiting rings of 16 Gy at the anterior and posterior regions there were 8 cases (32.0%) of head and neck lymphedema, with 3 of them at Grade 0 and 5 at Grade 1. The overall incidence of lymphedema between the two groups showed a significant statistical difference ($\chi^2 = 11.69$, $P < 0.001$).

Discussion
The incidence of head and neck lymphedema after IMRT for NPC is high, significantly affecting the quality of life of patients. However, it is often ignored, and there are few related studies in the literature[18]. There is no effective treatment for head and neck lymphedema, thus, prevention is very important, particularly during the design phase of radiotherapy plans[19]. Our previous study preliminarily suggested that setting limiting rings of < 20 Gy at the anterior and posterior regions of the neck was feasible with respect to dosimetry, and could also reduce lymphedema[10]. However, there is no standard for the optimal dose limit. Theoretically, the lower the dose of the limiting rings, the greater the possibility that the dosimetric advantages can be translated into clinical benefits. Especially for early-stage NPC cases, achieving target dose coverage for the primary tumor and cervical lymph nodes in the design of radiation therapy plans, as well as limiting doses to organs at risk, is relatively easier compared to cases with later T and N staging. The impact of setting dose limiting rings in the anterior and posterior neck may be relatively minor. At the same time, for early-stage patients with such good therapeutic

outcomes, further reducing the side effects of head and neck lymphedema and improving the quality of life is of greater clinical significance. This is also the reason why this study focuses on early-stage cases.

In this study, 15 patients with early-stage NPC were included to examine dosimetry when limiting rings were placed at the anterior and posterior regions of the neck and dose gradients were set at 20, 18, 16, and 14 Gy. Plans were designed to evaluate the impact on the coverage of the target volume and the doses to the organs at risk, so as to determine the optimal limiting dose of the limiting rings. The results suggested that setting limiting rings at the anterior and posterior regions of the neck did not affect the dose coverage of the target volume. According to previous research conducted at Fudan University[9], the V100% of PTV2 decreased compared to the conventional plan, but it still met the clinical requirements when limiting rings were used. However, our results showed that V100% of PTV2 was not affected, which may be related to the different inclusion criteria. This study only includes early-stage patients, and N1 is also limited to cases with only retropharyngeal lymph node enlargement without positive cervical lymph nodes. Relatively speaking, the impact on the radiation therapy plan is smaller. The doses to the inner ear, mandible, and brain stem were not affected. As the limiting doses of rings ranged from 20 to 14 Gy, there were similar linear changes in the doses to the parotid glands, oral cavity, larynx, thyroid, and spinal cord. Since the oral cavity, larynx, and thyroid gland are located near the anterior region of the neck and adjacent to the anterior limiting ring, there is a decrease in dose to these structures as the dose of the limiting ring is decreased. In addition, due to the restriction of the posterior limiting ring, the high values of the dose curve moves towards the central part of the body, just near the spinal cord. Therefore, as the dose of the limiting ring decreases, the spinal cord exhibits a synchronous inverse trend of dose increase. After a final assessment of the pros and cons, 16 Gy was determined as the optimal limiting dose cut-off point to achieve a balance between target coverage and organ protection.

Our results showed that compared to the conventional plan without limiting rings, the use of limiting rings of 16 Gy increased the dose to the parotid glands slightly (about 1 Gy), while the average dose to the oral cavity was decreased by more than 2 Gy. This reduction may lower the dose to the submandibular glands and minor salivary glands within the oral cavity, potentially compensating for some of the decreased saliva production caused by the increased dose to the parotid glands. As a result, it may reduce the subjective sensation of xerostomia to some extent[20]. Additionally, it may be beneficial in reducing the severity of oral mucositis[21]. The average dose to the larynx was decreased by nearly 5 Gy, which is beneficial for reducing the occurrence of laryngeal edema, and it may also be beneficial for reducing the occurrence of internal lymphedema and external lymphedema of the head and neck[22]. In addition, the dose to the thyroid gland was also reduced, which may help to reduce the occurrence of hypothyroidism after radiotherapy[23]. Although the maximum dose to the spinal cord was increased by about 1 Gy, it was still far from the dose limit of 45 Gy. Previous studies showed that by setting the fractionated dose at 2 Gy, when the total dose of spinal cord irradiation was 45 and 50 Gy, the incidence of myelopathy was 0.03% and 0.2%, respectively[24]. Therefore, although the dose to the spinal cord was slightly increased, it was still within a relatively safe range.

The clinical verification study showed that setting limiting rings of 16 Gy at the anterior and posterior regions of neck could reduce the incidence of head and neck lymphedema 60% compared to the conventional radiotherapy plan, and thus its dosimetric advantages may be translated into clinical benefits.

To the best of our knowledge, this study is the first dosimetric and clinical cohort verification study on reducing lymphedema by setting limiting rings at the anterior and posterior regions of the neck in patients with early NPC. It is innovative and practical, but there are also limitations. First of all, this study focused on early NPC, and the conclusion cannot be extrapolated to patients with more advanced NPC. Secondly, there is no objective index for the diagnosis and grading of head and neck lymphedema at present, thus, the judgment of grade is subjective. Thirdly, for certain reasons, this study lacked an assessment of the patients' quality of life, and head and neck lymphedema is also influenced by many factors other than the radiotherapy plan, such as disease stage, concurrent treatment, and comorbidities[25,26]. Therefore, whether the dosimetric advantages can truly translate into clinical benefits merits further research.

In conclusion, through a dosimetry and clinical cohort verification study we determine the optimal cut-off point of the dose of limiting rings at the anterior and posterior regions of neck, hoping to develop a new IMRT plan design method to reduce the head and neck lymphedema after radiotherapy in patients with early NPC.

Data availability

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Received: 31 December 2024; Accepted: 27 March 2025
Published online: 06 April 2025

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Author contributions

KL was major contributor in writing the manuscript. Y.T., H.L. and K.L. analyzed the patient data. K.L. and R.Z. were responsible for the statistical data. K.L. performed the follow-up examination. K.L. and R.Z. were responsible for the study design. All authors read and approved the final manuscript.

Funding

This study was supported by the General Program of Natural Science Foundation of Guangdong Province (No. 2023A1515011670)and the General Guidance Project of Guangzhou Health Science and Technology (No. 20221A011097).

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

This study was performed with the approval of the Ethics Committee of Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University (No. 2021-SW14), and done in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice Guidelines. The participants provided their written informed consent to participate in this study.

Additional information

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