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The impact of different cervical planning target volume designs on efficacy and toxicity in nasopharyngeal carcinoma: a single-center retrospective study

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Abstract

Background In nasopharyngeal carcinoma (NPC) patients, two radiation target delineation patterns are used for the cervical lymph node area.

Purpose This study compares the efficacy and toxicity of two radiation target volume delineation patterns for planning target volumes (PTVs) in NPC patients.

Methods This retrospective analysis included 387 non-metastatic NPC patients treated with concurrent chemoradiotherapy from January 2017 to December 2020. Patients were divided into two groups: the 2-PTV group with two dose gradients (50–54 Gy and 66–70 Gy) and the 3-PTV group with an additional 60–63 Gy dose.

Results After a median follow-up of 51.2 months, the 3-year regional relapse-free survival (RRFS) showed no significant differences between the 3-PTV and 2-PTV groups (96.6% [95% confidence interval (CI): 96.5%–96.8%] and 96.3% [95% CI: 96.2%–96.3%]). In the N3 subgroup, the 3-year RRFS was also comparable between the 3-PTV and 2-PTV groups (96.2% [95% CI: 76%–99%] vs. 95% [95% CI: 69%–99%], $p=0.727$). Importantly, the 2-PTV group demonstrated significantly lower rates of grade 3/4 dermatitis (5.1% vs. 16.5%; HR 0.88, 95% CI: 0.82–0.94, $p=0.002$) and xerostomia (49.6% vs. 67%; HR 0.78, 95% CI: 0.72–0.84, $p=0.002$).

Conclusions The 2-PTV regimen achieved equivalent survival outcomes while significantly reducing treatment-related toxicities compared to the 3-PTV approach. These results suggest that the 2-PTV strategy may offer a more favorable therapeutic profile for NPC patients, particularly in minimizing severe dermatitis and xerostomia.

Keywords Nasopharyngeal carcinoma, Radiotherapy target volume, Treatment toxicity, Radiation dose

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Introduction

Radiotherapy is considered the primary treatment method for nasopharyngeal carcinoma (NPC) according to numerous guidelines [1]. In non-metastatic NPC patients who receive induction chemotherapy and concurrent chemoradiotherapy, the five-year overall survival (OS) rate ranges from 71.4% to 84.8%, while the five-year progression-free survival (PFS) rate ranges from 62.5% to 73.9% [2, 3]. Given the high tendency for nodal metastasis in NPC, all guidelines recommend prophylactic neck irradiation during radiotherapy for NPC patients [1, 4].

For the cervical lymph node area, there are two target delineation patterns. Some centers employ two target volumes [5–7]: (1) Gross tumor volume of cervical node (GTVnd), which includes the positive cervical lymph nodes, (2) Low-risk clinical target volume (CTV2), defined as the GTVnd plus a 6–10 mm margin. This margin includes the retropharyngeal nodal regions, the cervical level where the involved lymph nodes are located, and the elective neck area from level II to level V. Other centers utilize three target volumes [8, 9]. A dose gradient is applied based on GTVnd and CTV2, with High-risk clinical target volume (CTVnd1) defined as GTVnd plus a 3–5 mm margin. Extending GTVnd or CTV by 3 mm creates the planning target volumes (PTVs). The recommended doses are 66–70 Gy for PTVnd, 60–63 Gy for PTVnd1, and 50–54 Gy for PTV2, administered in 30–33 fractions (once daily, five days per week).

The primary reasons for employing CTVnd1 are as follows: Extracapsular extension (ECE) of lymph nodes. Research has demonstrated a correlation between ECE and prognosis in head and neck tumors [10]. A 2006 meta-analysis by A.A. Dunne reported a 5-year survival rate of 58.15% for 632 ECE-negative head and neck squamous cell carcinoma patients, compared to 30.7% for 997 ECE-positive patients [11]. Therefore, it is recommended to expand GTVnd by 3-5mm to encompass an additional target volume known as CTVnd1.

Chin's research on NPC, another virus-associated tumor, found a significantly lower 5-year OS in the ECE-positive group compared to the ECE-negative group (68% vs. 89%, $p < 0.001$) [12], Ma's study reported that 5-year OS rates for N1 and N2 with G3-ECE were 82.0% and 77.1%, respectively, lower than those without G3-ECE (N1: 90.7%, N2: 87.0%) but similar to N3 (78.7%, $p = 0.626$ and 0.976). Therefore, it is recommended that ECE-positive N1–2 patients be classified as N3, Other studies have also confirmed that ECE is an independent prognostic factor [13–16].

The current 9th edition of the AJCC staging system for NPC has incorporated advanced radiologic extracapsular extension (rECE) with involvement of adjacent muscles, skin, and/or neurovascular bundle into the N3 staging criteria. The inclusion of rECE in staging raises critical questions regarding personalized radiotherapy strategies for NPC patients. Specifically, whether escalating the radiation dose to nodal drainage regions in patients with rECE-positive N staging can improve therapeutic outcomes, and whether the potential benefits outweigh the risks associated with high-dose irradiation to additional high-risk nodal areas.

Currently, both approaches are utilized in clinical practice. The aforementioned studies show that both radiotherapy methods can achieve satisfactory therapeutic effects [5–9]. With the introduction of the 9th edition of American Joint Committee on Cancer (AJCC) staging system for NPC, ECE has been incorporated into the criteria for N3 staging [17]. In the current era of advocating for more precise treatment, individualized therapy for high-risk patients has become the mainstream. However, no studies have compared the efficacy and toxicity of these two treatment modalities.

Thus, we conducted a single-center retrospective study to compare the efficacy and radiation-related adverse events in the cervical lymph node area of NPC between these two treatments.

Materials and methods

Study design and participants

This retrospective, single-center study at Nanfang Hospital includes newly diagnosed, untreated NPC patients (M0, nonkeratinizing, non-N0, aged 18–70). All patients were restaged according to the 8th edition of the AJCC staging system. All patients received concurrent cisplatin or carboplatin chemoradiotherapy with intensity-modulated radiation therapy (IMRT). Exclusion criteria included prior chemotherapy, head/neck surgery or radiotherapy, lack of concurrent chemotherapy, non-IMRT radiotherapy, inability to assess efficacy, or loss to follow-up. The protocol was approved by the Ethics Committee of Nanfang Hospital.

Diagnosis and evaluation

In this study, all patients underwent a comprehensive medical evaluation, including a detailed medical history, physical examination, hematological and biochemical profiling, nasopharyngoscopy, histopathological diagnosis, contrast-enhanced MRI of the head and neck, chest CT or radiography, abdominal CT or sonography, and a bone scan.

Clinical outcome and follow-up

The primary endpoint of our study was 3-year regional relapse-free survival (RRFS), which was defined as the time from treatment initiation to documented nodal relapse or non-cancer-specific death. The secondary endpoints of this study were 3-year overall survival (OS), 3-year progression-free survival (PFS), and 3-year distant metastasis-free survival (DMFS), which were defined as the time from treatment initiation to the first occurrence of death, recurrence, or distant metastasis from any cause, respectively. Post-treatment follow-up was conducted every 3 months for the first 2 years, then semi-annually for the next 3 years, and annually thereafter. Assessments included patient history, physical examination, and nasopharyngeal imaging, with the last follow-up recorded on December 31, 2023.

Chemotherapy regimens

All 378 patients received concurrent chemoradiotherapy, with cisplatin administered at a dose of > 200 mg/m^2. For patients with impaired renal function, carboplatin was used as an alternative. Among them, 308/378 (81.5%) patients underwent induction chemotherapy.

Induction Chemotherapy Regimens: TPF Regimen: Docetaxel (60 mg/m^2, Day 1) combined with cisplatin (60 mg/m^2, Day 1) and 5-fluorouracil (600 mg/m^2/day, continuous intravenous infusion on Days 1–5).TP Regimen: Docetaxel (75 mg/m^2, Day 1) combined with cisplatin (75 mg/m^2, Day 1).TC Regimen: Docetaxel (75 mg/m^2, Day 1) combined with carboplatin (AUC 5, Day 1).All induction regimens were administered in 21-day cycles for 1–3 cycles.

Concurrent Chemotherapy Regimens: Cisplatin: 80–100 mg/m^2, intravenous infusion on Day 1.

Carboplatin: AUC 5, intravenous infusion on Day 1. Concurrent chemotherapy was administered in synchrony with radiotherapy, with each cycle lasting 21 days for a total of 1–3 cycles.

Two radiation target volume delineation patterns

Given that both target delineation patterns have demonstrated survival benefits in previous studies, our center primarily adopted the 2-PTV delineation approach from 2017 to 2018. However, with increasing recognition of the clinical significance of nodal microinvasion and ECE, our center gradually transitioned to the 3-PTV delineation strategy between 2018 and 2020 to mitigate the risk of recurrence in high-risk nodal drainage regions.

IMRT was required for all patients. The elective lymph nodes were delineated according to the guidelines [18]. Two different radiation target volume delineation patterns were used: the 2-PTV group and the 3-PTV group. The PTVs were generated from clinical target volumes (CTVs) corresponding to areas at risk. In the 2-PTV group, two dose gradients were applied: PTVnd (lymph nodes planning tumor volume) and PTV2 (low-risk planning tumor volume) received 1.67–1.8 Gy per fraction to a total dose of 50–54 Gy in 28–30 fractions. This was followed by a sequential boost to PTVnd, delivering 1.67–1.8 Gy per fraction to a total dose of 66–70 Gy in 37–39 fractions. In the 3-PTV group, a third dose gradient was added: PTVnd and PTV2 received 1.67–1.8 Gy per fraction to a total dose of 50–54 Gy in 28–30 fractions. PTVnd1 (high-risk planning target volume) received 1.8–1.9 Gy per fraction to a total dose of 60–63 Gy in 30–33 fractions. A sequential boost was then delivered to PTVnd, achieving a total dose of 66–70 Gy in 37–39 fractions at 1.67–1.8 Gy per fraction. All treatments were administered once daily, five days per week. (Fig. 1A–B). Three radiation oncologists, each with over ten years of clinical experience, participated in the delineation of tumor target volumes and OARs.

Dose volume histogram and dose calculation

The dose-volume histograms (DVHs) for OARs were retrospectively analyzed using the treatment planning system. The mean dose (Dmean) was calculated for the parotid and submandibular glands, superior, middle, and inferior pharyngeal constrictors, and thyroid gland, while the maximum dose (Dmax) was calculated for the spinal cord and brachial plexus. The relative volumes and percentages receiving 54/60/63 Gy (V54/V60/V63) were compared between the two groups. For the 2-PTV group, PTVnd1 was simulated by expanding PTVnd by 3mm without altering the original treatment plan, and dose coverage was assessed. The virtual PTVnd1 coverage was then evaluated against clinical dosimetry requirements (Fig. 2A–B).

Radiotherapy toxicity

Radiation toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Patients were monitored weekly during treatment. The treatment planning system was utilized to collect patient radiation dose distribution of the neck and OARs.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25. Patient demographic and clinical characteristics were summarized as frequencies and percentages for categorical variables and means for continuous variables. Actuarial survival between the two treatment groups was estimated using Kaplan–Meier analysis and compared with

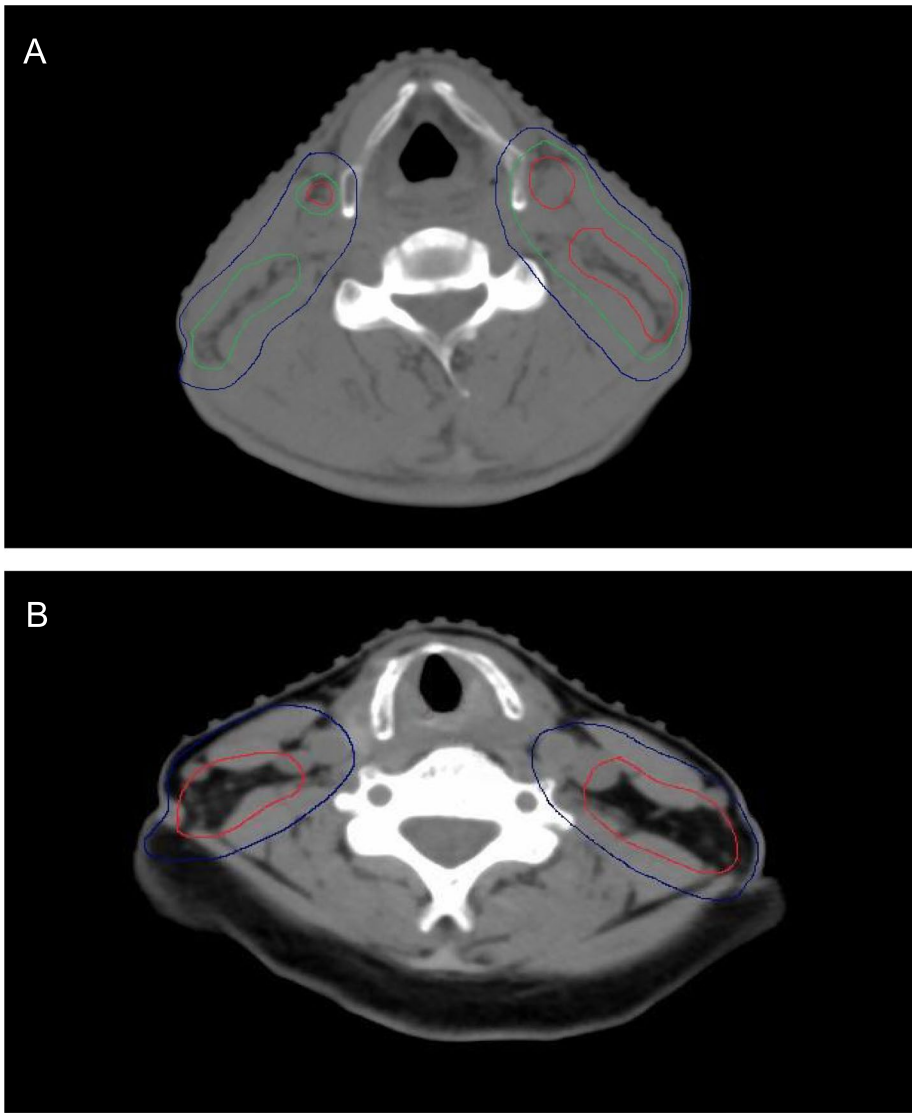

Fig. 1 Examples of target delineation for PTVs before radiation. **A** The 3-PTV group: The recommended doses are 70 Gy for PTVnd (red line), 63 Gy for PTVnd1 (green line), and 54 Gy for PTV2 (blue line). **B** The 2-PTV group: The recommended doses are 70 Gy for PTVnd (red line) and 54 Gy for PTV2 (blue line)

log-rank tests. Adverse reactions were evaluated with the Mann–Whitney U test, and radiation dose distribution was compared using t-tests.

Results

Clinical characteristics of the patients

This study retrospectively included a total of 378 patients from January 2017 to December 2020. Among them, 261 patients were in the 3-PTV group, and 117 patients were in the 2-PTV group. The patient characteristics are detailed in Table 1. Of the total patient population, 75 (19.8%) were classified as N3 patients. The baseline characteristics of the patients were well balanced between the two groups. Additionally, lymph node staging was found to be similar between the two groups ($p = 0.085$).

Local control and survival

At a median follow-up of 51.2 months for surviving patients (interquartile range [IQR]: 36.4–63.5 months), the 3-year RRFS showed no significant differences between the 3-PTV and 2-PTV groups (96.6% [95% CI 96.5%–96.8%] and the 2-PTV group at 96.3% [95% CI 96.2%–96.3%]) and there were no significant differences in the RRFS rate between the two groups (HR 0.95 [95%

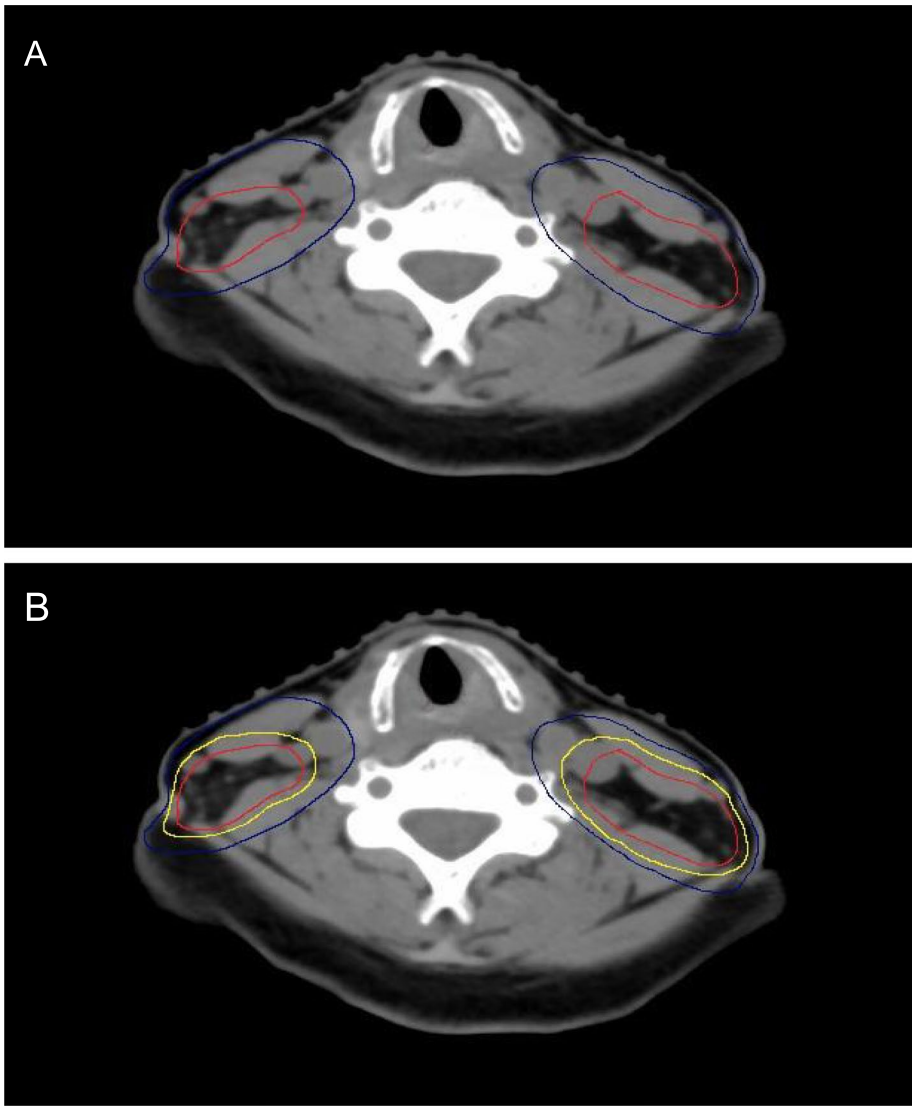

Fig. 2 Examples of target delineation for the virtual PTVnd1. **A** The 2-PTV group: The recommended doses are 70 Gy for PTVnd (red line) and 54 Gy for PTV2 (blue line). **B** The virtual PTVnd1: PTVnd1 was simulated by expanding PTVnd by 3 mm without altering the original treatment plan (yellow line)

CI 0.37–2.46]; $p=0.913$; Fig. 3A). The median durations have not been reached.

The 3-year OS, PFS, and DMFS were similar between the two groups. The overall 3-year OS for all patients was 95% (95% CI 92%–97%), with the 3-PTV group at 96.6% (95% CI 93%–98%) and the 2-PTV group at 91.5% (95% CI 85%–95%). The stratified HR for overall survival was calculated as 2.01 [95% CI 0.92–4.38]; $p=0.074$; Fig. 3B). 3-year PFS was 84.2% (95% CI 80%–88%), and 84.5% (95% CI 77%–90%) in 3-PTV group vs 84.2% (95% CI 79%–88%) in the 2-PTV group (stratified HR 0.95 [95% CI 0·58–1·59]; $p=0.863$; Fig. 3C). The 3-year DMFS was 89.4% (95% CI 85%–93%) in 3-PTV group versus 86.2% (95% CI 78%–91%) in 2-PTV group (stratified HR 1.4 [95% CI 0.78–2.56]; $p=0.27$; Fig. 3D).

In the latest 9th edition of the AJCC, the prognostic significance of ECE has been emphasized for N3 NPC patients. However, due to the time limitations of this study, the 8th edition of the AJCC staging system was used. Therefore, we only analyzed the N3 patient subpopulation to partially represent the ECE-positive subpopulation. The 3-year RRFS for all N3 patients was 96.1% (95% CI 76%–99%). The 3-year RRFS for N3 patients in the 3-PTV group was 96.2% (95% CI 76%—99%), and for N3 patients in the 2-PTV group,

Table 1 Comparison of clinical characteristics between two groups

Characteristics	2-PTV (*N* = 117)	3-PTV (*N* = 261)	*P*
Median follow up time (range), months	71.5 (85- 48.6)	52.4 (84.4–18.9)	< 0.001
Sex			0.473
Male	88 (75.2%)	187 (71.6%)	
Female	29 (24.8%)	74 (28.4%)	
Age, median (IQR), years	48.4 (42–55)	48.1 (39–56)	0.823
Smoking			
Never	7.97 (12.4)	8.41 (13.2)	0.796
Former/current			
Family history of cancer			0.415
No	98 (83.8%)	226 (86.6%)	
yes	19 (16.2%)	35 (13.4%)	
T stage[a]			0.132
0	0 (0.00%)	1 (0.38%)	
1	8 (6.84%)	21 (8.05%)	
2	37 (31.6%)	53 (20.3%)	
3	58 (49.6%)	139 (53.3%)	
4	14 (12.0%)	47 (18.0%)	
N stage[a]			0.077
1	22 (18.8%)	27 (10.3%)	
2	74 (63.2%)	180 (69.0%)	
3	21 (17.9%)	54 (20.7%)	
Clinical stage[a]			0.028
2	11 (9.40%)	9 (3.45%)	
3	72 (61.5%)	156 (59.8%)	
4	34 (29.1%)	96 (36.8%)	

[a] The International Union Against Cancer American Joint Committee on Cancer TNM classification, eighth edition

it was 95% (95% CI 69%–99%). Although the 3-year RRFS of the 3-PTV group had improved compared to the 2-PTV group, there was no significant difference in the 3-year RRFS between the two groups ($p = 0.727$). The 3-year OS, 3-year PFS, and 3-year DMFS were similar between the two groups in the N3 population (Supplementary Fig. 3E–H).

Radiation-related adverse events

In the analyses across all patients, the reported incidence of grade 3 or 4 dermatitis was significantly lower in the 2-PTV group (5.1%) compared to the 3-PTV group (16.5%) (stratified HR 0.88 [95% CI 0.82–0.94]; $p = 0.002$). Additionally, the incidence of xerostomia was significantly lower in the 2-PTV group (49.6%) compared to the 3-PTV group (67%) (stratified HR 0.78 [95% CI 0.72–0.84]; $p = 0.002$). Only one patient in the 3-PTV group experienced grade 3 xerostomia. However, there was no significant difference in the incidence of other toxicities between the 2-PTV and 3-PTV groups for cervical fibrosis (30.3% vs. 25.6%), late dysphagia (26.8% vs. 23.9%), cervical edema (12.6% vs. 9.4%), and hypothyroidism (4.2% vs. 5.1%). As of the last follow-up, 11 (2.9%) patients had grade 3 dysphagia (7 [2.7%] in the 3-PTV group and 4 [3.4%] in the 2-PTV group). No patients experienced grade 3 or 4 fibrosis, cervical edema, or hypothyroidism (Table 2).

Radiation doses distribution and calculation

The GTVnd volume was not significantly different between the 3-PTV and 2-PTV groups (44.31 cm3 vs. 50.34 cm3, $p = 0.184$). However, with the 3-PTV group having an increased dose gradient of 63 Gy, the V63 of the neck field showed a significant difference between the two groups (334.68 cm3 vs. 272.68 cm3, $p = 0.001$; 7.52% vs. 6.22%, $p = 0.001$). The V54 was 19.38% in the 3-PTV group compared to 20.45% in the 2-PTV group ($p = 0.036$). In the 2-PTV group, a new target PTVnd1, simulated with a 3 mm expansion, achieved V63 > 95% in 91% of patients and V60 > 95% in 100% of patients (Table 3). The mean dose to the parotid gland was 44.71 Gy in the 3-PTV group vs 36.99 Gy in the 2-PTV group ($p < 0.001$) and the maximum dose to the brachial plexus was 69.53 Gy versus 67.08 Gy ($p < 0.001$). The mean dose to the total pharyngeal constrictor muscle (PCM) was 56.88 Gy versus 54.84 Gy ($p < 0.001$). We further analyzed the radiation doses to the PCM at different locations. The results showed that the mean dose to the middle PCM was 52.97 Gy in the 3-PTV group versus 58.21 Gy in the 2-PTV group ($p < 0.001$), and the mean dose to the inferior PCM was 43.41 Gy in the 3-PTV group versus 45.22 Gy in the 2-PTV group ($p = 0.02$) (Table 4).

Recurrence pattern

As of the latest follow-up on December 31, 2023, 34 out of 378 patients (9%) experienced regional or local recurrence. Of these, 29 cases (85.2%) had recurrence within the PTVnd (66–70 Gy), 4 cases (11.8%) had partial recurrence within the PTVnd, and 1 case (3.0%) had recurrence in the untreated cervical Ib lymphatic drainage region.

Discussion

This study evaluated the differences in treatment effectiveness and adverse reactions between the 2-PTV and 3-PTV groups in NPC patients. The findings suggest that the 2-PTV group may reduce toxicity, particularly grade 3 or 4 dermatitis and xerostomia, and demonstrate comparable survival outcomes. Despite the sensitivity of NPC to radiotherapy, some patients may still experience

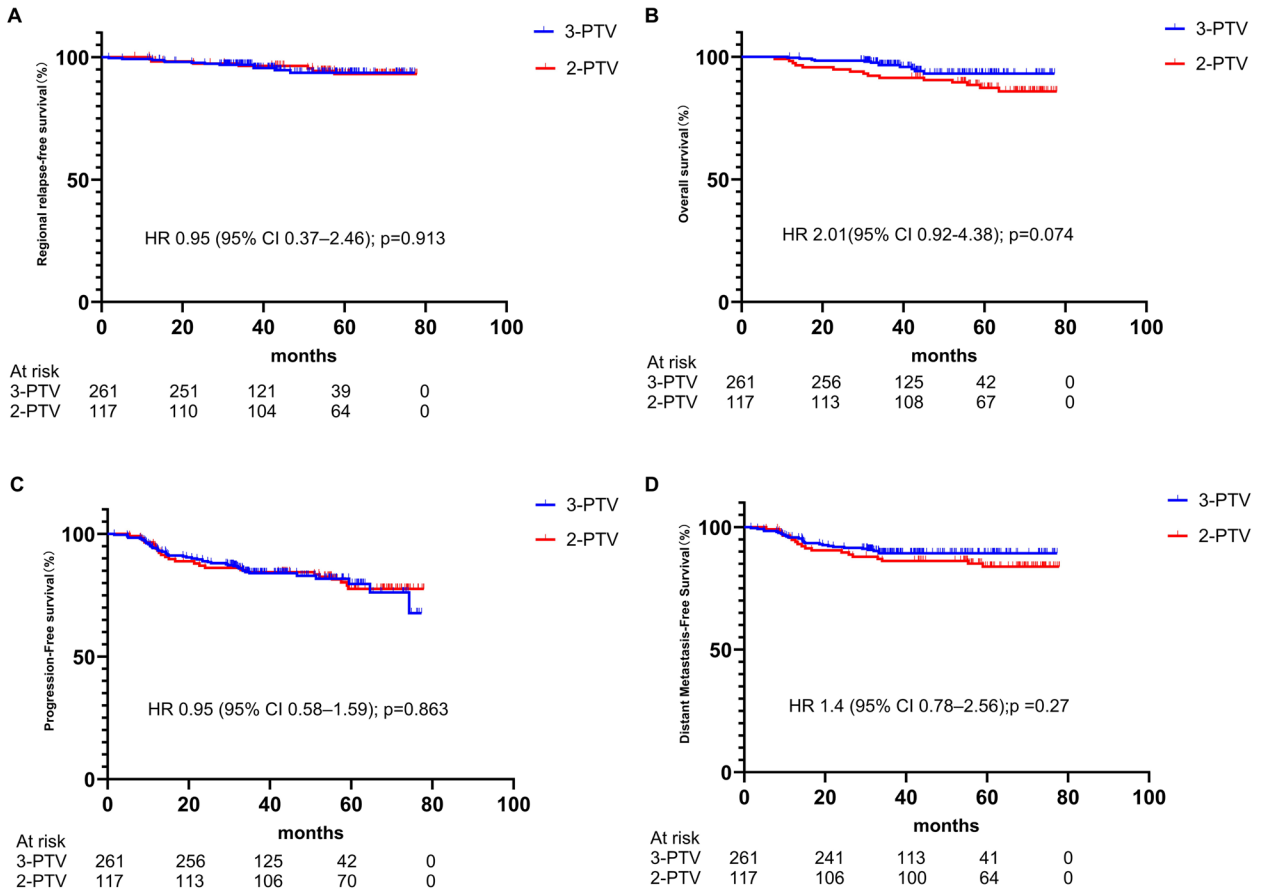

Fig. 3 Survival outcomes between the 3-PTV and 2-PTV groups. **A** Regional relapse-free survival (RRFS); (**B**) Overall survival (OS); (**C**) Progression-free survival (PFS); (**D**) Distant metastasis-free survival (DMFS). Supplementary Fig. 3 Survival outcomes between the 3-PTV and 2-PTV groups in the N3 population. **E** Regional relapse-free survival (RRFS); (**F**) Overall survival (OS); (**G**) Progression-free survival (PFS); (**H**) Distant metastasis-free survival (DMFS)

Table 2 Comparison of toxicities between two groups

	2-PTV			3-PTV			
Toxicity	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 1–2**	**Grade 3**	**Grade 4**	***P***
Dermatitis	83(70.9%)	6(5.13%)	0	186(71.3%)	44(16.9%)	0	< 0.001
Xerostomia	58(49.6%)	0	0	174(66.7%)	1(0.38%)	0	0.003
Cervical fibrosis	28(23.9%)	2(1.71%)	0	73(28%)	6(2.30%)	0	0.214
Brachial plexus injury	11(9.4%)	1 (0.85%)	0	27(10.3%)	0	0	0.689
Late dysphagia	24(20.5%)	4 (3.42%)	0	63(24.1%)	7(2.68%)	0	0.745
Cervical edema	11(9.4%)	0	0	33(12.6%)	0	0	0.627
Hypothyroidism	6(5.1%)	0	0	11(4.21%)	0	0	0.693

recurrence and metastasis after treatment [2, 4]. These findings align with the results of other studies as well. For instance, a study by Tang et al. focusing on patients with stage II–IVA NPC demonstrated a 3-year RRFS of 96.7% in patients who received the 3-PTV design for the cervical lymph node area [19]. Another study by Sun Y et al. showed that patients with NPC who received the 2-PTV design had a 3-year RRFS of 97.7% [20]. In this study, all patients received standard concurrent chemoradiotherapy, with 81.5% of patients undergoing induction chemotherapy. The systemic treatment regimen did not influence the choice of radiotherapy target delineation.

Table 3 Dosimetric comparison between two groups

	2-PTV	3-PTV	P
GTVnd (cm^3)	50.34 (0.11–199.17)	44.31(0.02–298.52)	0.184
V63(cm^3)	272.68 (52.38–724.42)	334.68 (74.61–2345.72)	< 0.001
V54(cm^3)	913.19 (442.59–1625.64)	865.68(373.45–2781.67)	0.071
V63(%)	6.22 (0.8–14.44)	7.52(2.1–43.3)	< 0.001
V54(%)	20.45 (12.1–31.8)	19.38(9.7–51.3)	0.036
V63 of new PTVnd1(%)	97.71 (83.4–100)		
V60 of new PTVnd1(%)	99.30 (94.8–100)		

GTVnd Gross Tumor Volume of the lymph node, *V63* Volume receiving 63 Gy, *V54* Volume receiving 54 Gy, *new PTVnd1* PTVnd1 was simulated by a 3 mm expansion based on PTVnd to evaluate the dose coverage of PTVnd1

Table 4 Dosimetric comparison of organs at risk between two groups

Organ at Risk	2-PTV	3-PTV	P
Spinal cord (Dmax)	37.65 (31.40–56.75)	37.32 (27.40–72.26)	0.525
Brachial plexus (Dmax)	67.08 (50.06–76.19)	69.53 (57.31–144.65)	< 0.001
Parotid gland (Dmean)	36.99 (22.74–55.95)	44.71 (22.73–82.85)	< 0.001
Submandibular gland (Dmean)	66.37 (53.19–33.19)	65.02 (28.43–38.32)	0.587
Pharyngeal constrictor muscle (PCM) (Dmean)	54.84 (42.38–65.47)	56.88 (36.92–108.70)	< 0.001
Superior PCM (Dmean)	67.03 (56.63–73.3)	67.52 (59.13–75.59)	0.37
Middle PCM (Dmean)	52.97 (34.22–67.61)	58.21 (39.34–74.85)	< 0.001
Inferior PCM (Dmean)	43.41 (11.21–58.82)	45.22 (31.5–77.74)	0.02
Thyroid (Dmean)	50.28 (38.47–59.58)	51.29 (40.60–93.53)	0.047

Dmax Maximum dose, *Dmean* Mean dose, *PCM* Pharyngeal constrictor muscle

The AJCC 9th edition underscores the prognostic importance of ECE and nodal size, particularly in N3 patients with high nodal burden [17]. The 2-PTV approach achieved comparable high-risk nodal coverage to the 3-PTV approach, with PTVnd1 (3 mm expansion) resulting in V63 > 95% in 91% of patients and V60 > 95% in 100% of patients. Notably, the 3-year RRFS in N3 patients was similar between the two groups (96.2% vs. 95%, $p = 0.727$). This suggests that even in the subgroup of N3 patients with a high regional nodal tumor burden, the 2-PTV approach yielded efficacy comparable to that of the 3-PTV approach.

The 3-PTV approach, with its toxicity profile, including dermatitis and xerostomia, was significantly higher compared to the 2-PTV group. The incidence of grade 3 or 4 dermatitis in the 2-PTV group was 5.1%, significantly lower than the 16.5% in the 3-PTV group (HR 0.88, 95% CI 0.82–0.94; $p = 0.002$). Additionally, the incidence of xerostomia was significantly reduced in the 2-PTV group (49.6% vs. 67%, HR 0.78, 95% CI 0.72–0.84; $p = 0.002$). These findings suggest that the 2-PTV approach, while maintaining efficacy, significantly improves patients' quality of life by reducing treatment-related toxicities.

For N3 patients, future studies should explore individualized dose escalation strategies based on nodal burden and ECE to optimize local control while minimizing toxicity. Combining radiomic features and biomarkers may help more accurately identify patients who would benefit from higher dose coverage. Given the small sample size and low incidence of positive events in this study, larger prospective studies are needed to validate the potential benefits of the 2-PTV approach for N3 patients.

Additionally, the 2-PTV group showed significantly lower rates of grade 3 or 4 dermatitis and xerostomia compared to the 3-PTV group. The treatment planning system indicated lower V63 and Dmean of the parotid gland in the 2-PTV group, consistent with our findings. Although significant dosimetric differences were observed in the total PCM dose and the doses to the middle and inferior PCMs, we did not detect a notable difference in the incidence of late dysphagia between the two groups. This phenomenon may be explained by the following factors: The occurrence of dysphagia is not only related to the radiation dose to the PCMs but may also be influenced by other factors, such as the patient's baseline functional status, the precision of radiotherapy techniques, and other OARs affecting swallowing function, such as the soft palate. Therefore, simply reducing the dose to the PCMs may not be sufficient to significantly improve swallowing function [21, 22].

In practical clinical practice, it is crucial to ensure that 95% of the prescribed dose line encompasses 95% of the PTV volume [23]. To explore this, we performed a calculation using the treatment planning system. For the 2-PTV group, we expanded the PTVnd by 3mm, creating a new target, PTVnd1, without modifying the original plan. Interestingly, V60 (95% of the 63 Gy dose) exceeded 95% in all patients. This finding may explain the lack of significant survival differences between the groups. However, a 3 mm expansion might be insufficient, highlighting the need for more personalized delineation of high-risk areas. For instance, when lymph nodes invade muscle, even if imaging appears normal post-chemotherapy, the affected muscle should be included in the high-risk area, as recommended by guidelines. Anne W. Lee et al. also suggest expanding PTVnd by 5 + 5 mm for NPC patients with ECE positivity to form a high-risk prevention area for PTV1 [18].

Similarly, if the tumor has infiltrated all muscle spaces in the cervical lymph node region and subsequently regressed after induction chemotherapy, the seemingly "normal" muscle spaces should still be encompassed within the high-risk prevention area [24, 25]. This study analyzed recurrence patterns in 34 patients with neck or local recurrence, finding that 70% occurred within the high-dose region (66–70 Gy). Previous research and studies on head and neck squamous cell carcinoma similarly indicate that treatment failures predominantly occur in this high-dose area, with failure rates higher than those outside it [26, 27]. Kong's study on T4 stage NPC after induction chemotherapy and concurrent chemoradiotherapy found that 90% of recurrences were in-field within the 95% isodose lines, with 10% being marginal failures. No out-of-field failures were reported [28]. These findings suggest that tumor recurrence is mainly attributed to the tumor's resistance to radiation rather than inadequate preventive irradiation coverage.

Consequently, numerous researchers have explored dose de-escalation strategies in radiotherapy. For instance, Tang et al. conducted a study involving patients with NPC T1–4, N0–1, M0 stage and compared irradiation of elective upper-neck versus whole-neck regions. Their results indicated similar rates of 3y-RRFS between these two groups [19]. Additionally, Deschuymer et al.'s investigation on head and neck squamous cell carcinoma demonstrated that reducing the prophylactic dose to either 40 Gy or 50 Gy in low-risk lymph node drainage areas showed no significant difference in the 5-year local recurrence rate [29]. Reducing the high-dose radiation area in nasopharyngeal carcinoma through individualized delineation can lower radiation exposure to normal tissues, thereby reducing the risk of radiation-induced complications such as oral mucositis, dysphagia, and hearing loss.

This study has several limitations that should be acknowledged: Imbalance in Follow-up Duration: There was an imbalance in the follow-up duration between the two groups, with the 2-PTV design group having a significantly longer follow-up period. This discrepancy may introduce bias in the comparison of long-term outcomes. Low Incidence of Key Toxicities: The low incidence of dysphagia, grade 3–4 xerostomia, and hypothyroidism may have contributed to the lack of significant differences between the groups. Increasing the sample size in future studies could improve the statistical power and validity of the findings. Retrospective Single-Center Design: As a retrospective single-center study, potential selection bias and the lack of external validation are inherent limitations. These factors may affect the generalizability of the results to other patient populations or clinical settings. Lack of Acute Toxicity Data: Due to the retrospective nature of this study, data on the incidence of acute radiogenic swallowing difficulties during radiotherapy could not be collected. This limits the ability to fully assess the impact of the treatment modalities on acute toxicity profiles. Interobserver Variability in Contouring: The study did not address interobserver variability in the delineation of CTVs, PTVs, and OARs. Variability in contouring among radiation oncologists may lead to inconsistencies in target coverage and dose distribution, potentially influencing treatment outcomes. This limitation could impact the reproducibility and generalizability of the findings. Future studies should incorporate quality assurance measures, such as standardized contouring guidelines and multi-observer validation, to minimize variability and enhance the reliability of the results. Since our study results demonstrated that the 2-PTV group achieved good dose coverage while reducing late radiotherapy toxicity in patients, and obtained similar survival outcomes compared to the 3-PTV group, our center has been compelled to revisit the 2-PTV contouring method commonly used during the 2017–2018 period. However, as highlighted by the limitations of this study, further multicenter studies with larger sample sizes are still needed to validate the favorable outcomes of the 2-PTV approach.

Overall, the 2-PTV group achieved comparable survival outcomes with less toxicity compared to the 3-PTV group. The findings suggest that clinical radiologists could consider expanding the high-risk prevention area based on individualized tumor target mapping to reduce workload and promote personalized radiotherapy.

Conclusions

The 2-PTV regimen achieved equivalent survival outcomes while significantly reducing treatment-related toxicities compared to the 3-PTV approach. These results suggest that the 2-PTV strategy may offer a more favorable therapeutic profile for NPC patients, particularly in minimizing severe dermatitis and xerostomia.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Conception and design: BC and BFL. Provision of study material or patients: LW, HMW and FT. Collection and assembly of data: YTZ, SCL, LMG, ZTC. Data analysis and interpretation: RRS, SHW. Manuscript writing: LW. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study has been approved by the Institutional Review Board of Nanfang Hospital. Our retrospective study did not affect the treatment strategy, disclose privacy, or harm the interests of patients. Therefore, the Ethical Committee of the Nanfang Hospital provided a waiver of informed consent. All the processes conformed to the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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