Prognostic value of nasopharynx tumour volume in local-regional advanced nasopharyngeal carcinoma

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Background: To investigate the prognostic value of pretreatment primary gross tumor with (GTVp) and without retropharyngeal lymph nodes (GTVnx) for predicting survival outcomes in patients with local-regional advanced nasopharyngeal carcinoma (NPC) after intensity-modulated radiation therapy (IMRT).

Methods: From Jan 2012 to Dec 2017, 148 patients with local-regional advanced NPC who had undergone definitive radiotherapy were identified. GTVnx volume and retropharyngeal lymph nodes (GTVrLNs) volume were measured based on registration of MRI with contrast-enhanced CT images. The Kaplan-Meier method was used for survival analysis. Univariate and multivariate prognostic analyses was performed by using the Cox proportional hazard model. Receiver operating characteristic (ROC) curves were used to identify the cut-off point and assess the prognostic value for GTVnx, GTVp and GTVrLNs.

Results: The median follow-up time for the entire group was 27 months (ranging 7 to 80 months). The 3-year overall survival (OS) rate was 85%, and the 3-year local failure-free rate (LFFR), distant failure-free rate (DFFR) and disease-free survival (DFS) rates were 93%, 81%, and 73%, respectively. A positive correlation between GTVnx or GTVp volume and T stage was observed (both P<0.001). The 3-year LFFR, OS, and DFS rate, but not for DMFS, in NPC patients with GTVnx ≤42.7 cm^3 was significantly better than those with >42.7 cm^3 (all P<0.05). Multivariate analysis indicated that GTVnx volume (P=0.041) was the only independent prognostic factor for LFFR, while age and AJCC stage were two independent prognostic factors for OS.

Conclusions: The GTVnx is an independent prognostic factor for local control, while the prognostic value of GTVrLNs is limited. Physicians are recommended to distinguish between GTVnx and retropharyngeal lymph nodes (RLN) involvement when assessing the risk for local recurrence in advanced NPC.

Keywords: Nasopharyngeal carcinoma (NPC); primary tumor volume; prognostic factor; retropharyngeal lymph node (RLN)

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor with remarkable incidence varying among the regions. Based on GLOBOCAN estimates, high incidence of NPC occurs in China and other Southeastern Asia, but a low incidence in most regions of the world. It is estimated that there are more than 50,000 newly diagnosed cases in China and 65,000 worldwide each year. Until now, radiation therapy remains the mainstay therapy for NPC (1). In two-dimensional radiotherapy (2D-RT) era, the pretreatment primary gross tumor (GTVp) volume, including primary nasopharynx tumor and retropharyngeal lymph nodes

(RLNs), of NPC was an important prognostic factor for survival, particularly for local-regional control (2-4). However, an accurate assessment of the tumor volume of NPC in 2D-RT era is difficult and unavailable, which needs a calculation from a three-dimensional perspective. Recently, along with improvement in modern techniques, three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) have been extensively applied for the treatment of NPC, which significantly improves tumor control and long-term survival without excessive toxicity, and GTVp is still considered as a key prognostic factor for NPC in modern era (1,5-7). In addition, several recently published data recommended that pretreatment tumor volume could be incorporated into TNM staging system and directed NPC treatment decision (8-10).

However, the primary nasopharynx tumor and the involved RLNs usually are generally outlined together as gross tumor volume, considering the common phenomena of integration (7,11). As a result, the GTVnx and volume of RLNs (GTVrLNs) are usually considered as primary tumor volume when analysis of the effect of primary tumor volume on prognosis is performed (5,7). Currently, MRI has replaced CT as staging criteria because of its higher sensitivity and superiority in identifying tumor extension. And RLN has been classified as N stage (12-16) and could be delineated at CT and MRI fused imaging accurately (17,18). As a result, it is urgently needed to distinguish GTVnx and RLNs involvement when assessing the prognostic value of these factors in advanced NPC. Indeed, several researches were conducted to investigate the prognostic role of RLN metastasis in NPC patients in the past decades, but the results were controversial. Tham *et al.* demonstrated that RLN metastasis was an independent prognostic factor for distant metastasis in multivariate analysis (P=0.04), while both Chen *et al.* and Ma *et al.* found that RLN metastasis had a tendency to affect the DMFS rates of NPC patients (13,19,20). To our best knowledge, the prognostic value of pretreatment primary gross tumor without retropharyngeal lymph nodes (GTVnx) for predicting survival outcomes in patients with local-regional advanced NPC remains undetermined. Therefore, the aim of current report is mainly to address the prognostic value of pretreatment volume of GTVp, GTVnx, and GTVrLNs for predicting survival outcomes in local-regional NPC patients after IMRT according to an institutional protocol. We also analyze the prognosis of summation of primary GTVnx and GTVrLNs in order to find a cut off value above which the impact on survival parameters was statistically significant.

Methods

Study design and eligibility

The inclusion criteria for this retrospective study were: (I) newly-onset, biopsy-proven and non-metastatic NPC, (II) uniform protocol of definitive radiotherapy and/or combined chemotherapy, (III) available pre-treatment MRI, (IV) and discrimination of RLNs from primary tumor. From Jan. 2012 to Dec. 2017, a total of 148 eligible patients were enrolled in this study. *Table 1* listed the baseline characteristics of included patients. The patients included 116 (78.4%) males and 32 (21.6%) females. The median age was 53 years (13–84 years). This study was approved by the Institutional Review Board of the Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, China. Individual written informed consent was not required because of the retrospective nature of the study.

Treatment planning and delivery

All patients were immobilized in the supine position with a tailored head-shoulder thermoplastic mask, followed by a CT simulation. CT simulation (Brilliance Big Bore, Phillips, Amsterdam, Netherlands) was performed at a slice thickness of 3 mm from the head to 5 cm below the sternoclavicular joint. The target volumes were delineated slice-by-slice using an individualized protocol that complied with the International Commission on Radiation Units and Measurements reports 50 and 62 as previously described (11,21-23).

The primary tumor and the involved RLNs on each axial CT slice were both delineated on the planning system according to the pretreatment contrast axial T1-weighted MRI and CT fused images. In this study, the volume of RLNs was separated from primary nasopharynx tumor (*Figure 1*). For patients given induction chemotherapy, the targets of primary tumor volume were contoured based on the pretreatment MRI images. The inverse IMRT planning system developed by Philips (Madison, WI, USA), the Pinnacle version 8.0 planning system was used to do all treatment plans. The GTVnx, volume of RLNs (in cubic centimeters) was calculated subsequently by the same software. The primary gross tumor volume (GTVp) was obtained by summing the GTVnx and volume of RLNs.

Table 1 Characteristics of 148 patients

Characteristics	Category	Number of patients	%
Age (years)	Range	13–84	
	Median	53	
Gender	Male	116	78.4
	Female	32	21.6
T stage	T1	11	7.4
	T2	34	23.0
	T3	55	37.2
	T4	48	23.4
N stage	N0	4	2.7
	N1	31	20.9
	N2	87	58.8
	N3	26	17.6
TNM stage	III	78	52.7
	Iva	70	47.3
GTVnx (cm^3)	≤42.7	88	59.5
	>42.7	60	40.5
GTVp (cm^3)	≤42.87	84	56.8
	>42.87	64	43.2
Volume of RLN (cm^3)	≤2.08	66	44.6
	>2.08	82	55.4

Radiotherapy

All patients were treated using IMRT. The planning target volume of the primary nasopharynx tumor volume including retropharyngeal lymph nodes (PTV-G) and positive lymph nodes (PTV-LN) received 66–70.4 Gy and 70.4 Gy in 30–32 fractions, whereas 60 and 54 Gy in 30–32 fractions were prescribed to the PTVs of CTV1 and CTV2, or received 70 Gy for PTV-G at 2.12 Gy/fraction, 66 Gy for PTV-LN at 2 Gy/fraction whereas 60 and 54 Gy for PTVs of CTV1 and CTV2 delivered in 33 fractions, or received 70 Gy for PTV-G at 2 Gy/fraction, 66 Gy for PTV-LN and 60 and 54 Gy for PTVs of CTV1 and CTV2 delivered in 35 fractions. RT was delivered over one fraction daily, 5 days per week.

Chemotherapy regimen

Based on the treatment guidelines for NPC at our hospital, concurrent chemotherapy +/– induction chemotherapy or adjuvant chemotherapy was part of the treatment plan for all patients, except those who were unwilling to receive chemotherapy due to poor perform status for local-regional advanced NPC. Induction chemotherapy was consisted of paclitaxel (135 mg/m^2) or docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) every 3 weeks for 2–3 cycles. Concurrent chemotherapy was consisted of cisplatin administered every 3 weeks (100 mg/m^2) or weekly (40 mg/m^2) during RT.

followed-up and statistical analysis

After RT, all patients were assessed every 3 months during the first 2 years, and every 6 months thereafter until death. All events were measured from the date of completion of radiation therapy until documented treatment failure or the last follow-up visit. The primary end-point was: local failure-free rate (LFFR-persistence/recurrence at nasopharynx). The second end-points were overall survival
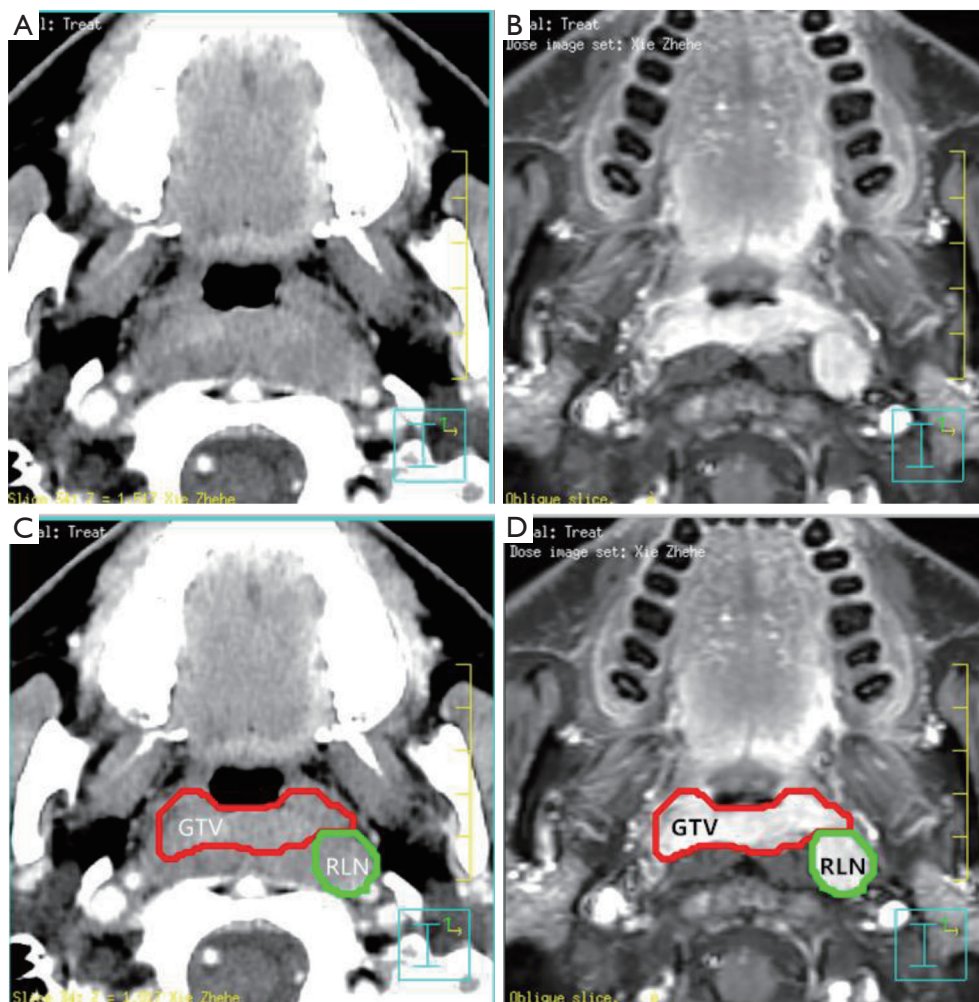
Figure 1 The volume of RLNs (in green), which was separated from primary nasopharynx tumor (in red), was both delineated on the planning system according to the pretreatment contrast axial T1-weighted MRI (B,D) and CT fused images (A,C). RLN, retropharyngeal lymph node.

(OS-death due to any cause), disease-free survival (DFS-staying free of disease after radiotherapy), and distant failure-free rate (DFFR-disease metastasis at distant sites).

The Kruskal-Wallis test was used to examine the differences in GTVp/GTVnx between T stages. Actuarial rates of LFFR, OS, DFS and DFFR rates were calculated with the Kaplan-Meier method, and compared by using log-rank test. Receiver operating characteristic (ROC) curves were used to identify the cut-off values for above endpoints. The areas under the ROC curve (AUC) were used to assess the prognostic value of GTVnx, GTVp. To identify potential factors associated with LFFR, OS, PFS and DFFR. Univariate analyses and multivariate logistic regression model were used to identify independent risk factors. A forward stepwise approach was used to enter new terms into the model, with a limit of $P<0.05$ to enter the terms and the most significant term entered first. All statistical tests were two-sided and P values of 0.05 or less were considered significant. Analyses were performed by use of the NCSS and MedCalc statistical software.

Results

Treatment outcomes

The median follow-up time for the entire group was 27 months (range 7 to 80 months). At the time of this analysis, a total of 4 cases developed regional recurrence, 9

Table 2 T stage and GTVp, volume of RLNs and GTVnx (mean ± SD cm^3)

Variables	T1	T2	T3	T4
GTVnx	15.687±8.281	18.717±14.022	35.147±22.459	85.625±40.484
Volume of RLNs	1.008±1.862	3.886±4.286	3.309±4.715	3.711±5.100
GTVp	16.696±8.212	22.604±15.003	38.456±23.625	89.336±42.187

RLN, retropharyngeal lymph node.

patients experienced local failure. In addition, 24 patients developed distant metastasis. There were a total of 17 deaths: 9 patients died from distant metastasis, 6 patients died from progression of local disease after recurrence, and the causes of death for the additional 2 cases were unknown. The 3-year OS rate of whole cohort was 85%, and the 3-year LFFR, DFFR, and DFS rates were 93%, 81%, and 73%, respectively.

Distribution of tumor volume by T stage

The mean GTVnx of the whole series was 46.30 cm^3 (range, 1.67–245.79 cm^3). *Table 2* showed that the distribution of GTVp volume, GTVrLNs volume and GTVp volume according to T stage. Although the variation within the same T stage was wide, the mean GTVnx and GTVp volume increased in consistent with advanced T stage: T1 (n=11, 15.687 cm^3); T2 (n=34, 18.717 cm^3); T3 (n=55, 35.147 cm^3); and T4 (n=48, 85.625 cm^3). The mean GTVp in different T stage: T1 (16.696 cm^3); T2 (22.604 cm^3); T3 (38.456 cm^3); and T4 (89.336 cm^3). Primary tumor classified as a more advanced T stage had a significantly larger GTVp, GTVnx than those with an early T stage (P <0.001). There was no significant correlation between the volume of RLNs and the T stage.

Identification of GTVp/GTVnx cut-off value

ROC curve was used to search for the best cut-off value of the GTVnx, GTVp on for OS prediction. According to ROC curve results, patients were stratified into two different groups for further analyses. For GTVnx, 3-year LFFR in patients with GTVnx ≤42.7 and >42.7 cm^3 were 97% and 89% (P=0.026), OS, DFFR and DFS were 94% and 69% (P=0.007), 83% and 76% (P=0.59), and 79% and 61%, respectively (P=0.04, *Figure 2*). For GTVp, 3-year LFFR in patients with PTV ≤42.87 and >42.87 cm^3 were 97% and 89% (P=0.034), OS, DFFR and DFS were 94% and 70% (P=0.01), 84% and 75% (P=0.42), and were 80%

and 60%, respectively (P=0.026).

Pairwise comparison of ROC curves among T stage, GTVp, GTVnx for LFFR, OS, DFFR and DFS

Pairwise comparison of ROC curves among T stage, GTVp, GTVnx for LFFR, OS, DFFR, DFS showed GTVnx has a better predictive effect than GTVp in overall survival (P=0.0020). There was no significant difference in the predictive effect of T stage and GTVnx on LFFR, DFFR and DFS. In addition, the predictive effects of T stage, GTVnx, GTVp for LFRR, DFFR, and DFS were all insignificantly different (*Tables 3,4*).

Prognostic factors

The value of various potential prognostic factors, including gender, age, T- and N-classification, TNM stage, GTVnx, GTVp, volume of RLNs (GTVrLNs), on predicting LFFR, DFFR, DFS and OS were evaluated. Univariate analysis demonstrated that age, GTVnx, GTVp were significant prognostic factors for predicting LFFR; age, GTVnx, GTVp, TNM stage for OS; TNM stage for DFFR; and TNM, age, GTVp and GTVnx for DFS (*Table 5*). Multivariate analysis showed GTVnx was the only independent prognostic factor for local control (HR =5.24, 95% CI, 1.074–25.57, P=0.041), age (HR =4.98, 95% CI, 1.81–13.67, P=0.0019) and TNM stage (HR =4.66, 95% CI, 1.06–20.41, P=0.041) were significant prognostic factors for predicting overall survival (*Table 5*).

Discussion

Currently, the treatment decision and prognostic prediction for NPC is mainly dependent on clinical stage. Although tumor volume has not been included in the clinical staging of NPC, multiple researches have demonstrated that volume of GTV-primary is significantly associated with survival and local recurrence in NPC after radiotherapy.
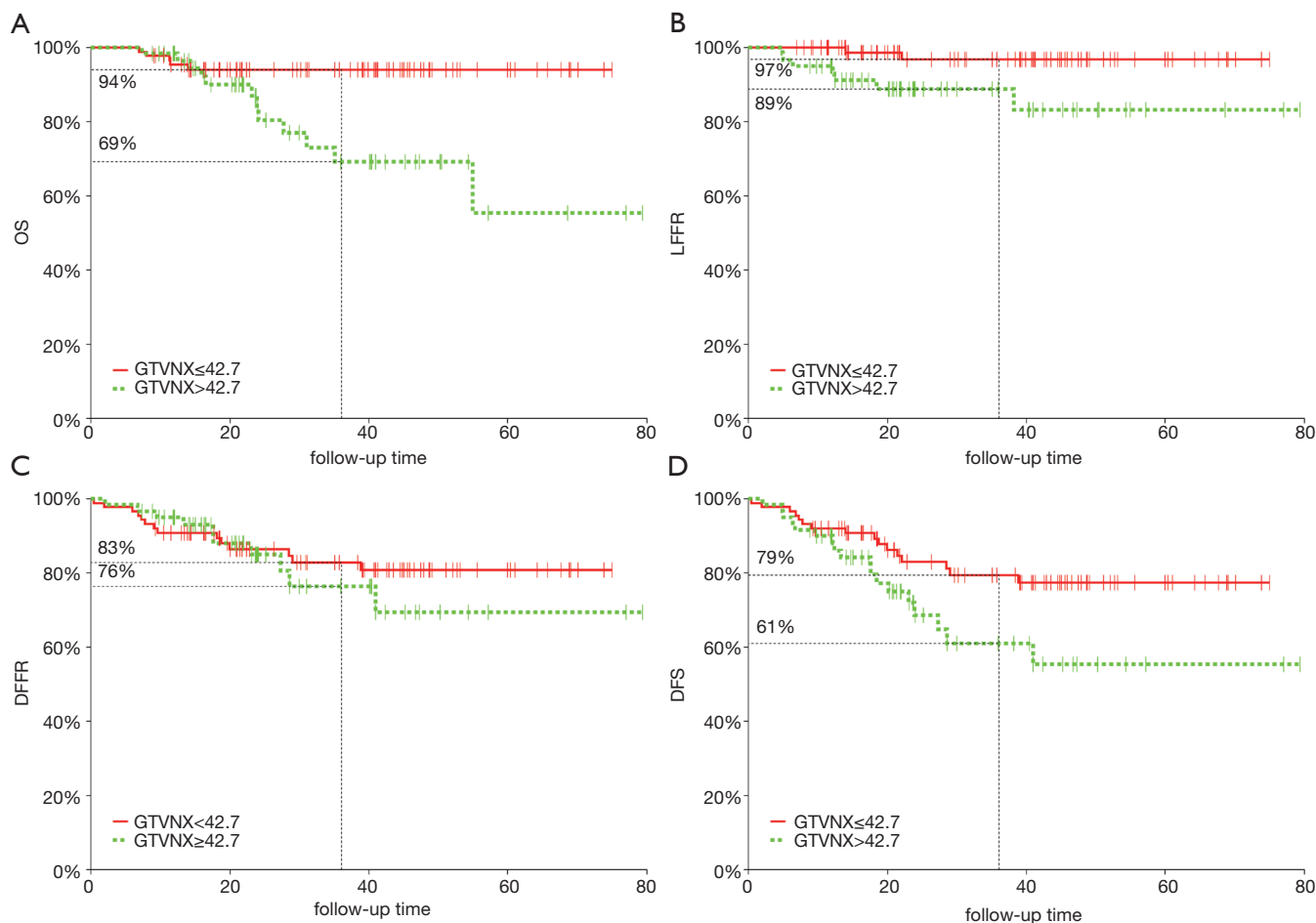
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Figure 2 Three-year of survival curve of (A) overall survival (OS), (B) local failure-free rate (LFFR), (C) distant failure-free rate (DFFR), and (D) disease free survival (DFS) for GTVnx ≤42.7 and >42.7 cm^3.

Table 3 Summary of AUC of T stage, GTVnx, GTVp for LFFR, OS, DFFR and DFS

Characteristics	LFFR			OS			DFFR			DFS		
Variable	AUC	SE	95% CI	AUC	SE	95% CI	AUC	SE	95% CI	AUC	SE	95% CI
T stage	0.701	0.0828	0.620–0.773	0.63	0.0762	0.547–0.708	0.546	0.0605	0.463–0.628	0.613	0.0521	0.530–0.692
GTVp	0.683	0.0932	0.602–0.757	0.632	0.0795	0.549–0.710	0.504	0.0706	0.420–0.587	0.578	0.0579	0.495–0.659
GTVnx	0.698	0.091	0.617–0.771	0.651	0.0778	0.568–0.728	0.506	0.0707	0.423–0.589	0.592	0.0577	0.508–0.672

AUC, areas under the ROC curve; LFFR, local failure-free rate; OS, overall survival; DFFR, distant failure-free rate; DFS, disease-free survival.

Sze *et al.* (5) found that with every 1 cm^3 increase in tumor volume, local failure increased by 1%. In a retrospective study conducted by Wu *et al.* the authors found that GTV-primary volume was an independent prognostic factor for local control, distant metastasis, DFS, and overall survival in NPC (24). Similar results were also observed in a subsequent study performed by Qin *et al.* (25). However, to our best knowledge, most of these included trials define the volume of GTV-primary as the combined volume of GTVnx and RLNs, while several published research show

Table 4 Pairwise comparison of ROC curves among T stage, GTVp, GTVnx for LFFR, OS, DFFR, DFS

Results	LFFR	OS	DFFR	DFS
T-stage *vs.* GTVp				
Difference between areas	0.0172	0.00247	0.0427	0.0348
Standard error	0.0473	0.0481	0.122	0.0402
95% CI	−0.0756 to 0.110	−0.0919 to 0.0968	−0.196 to 0.281	−0.0439 to 0.114
Z statistic	0.363	0.0513	0.351	0.867
Significance level	0.7166	0.9591	0.7259	0.3861
T-stage *vs.* GTVnx				
Difference between areas	0.0028	0.0213	0.0403	0.0212
Standard error	0.047	0.0479	0.05	0.0401
95% CI	−0.0894 to 0.0950	−0.0726 to 0.115	−0.0576 to 0.138	−0.0574 to 0.0997
Z statistic	0.0595	0.445	0.807	0.528
Significance level	0.9526	0.6563	0.4198	0.5975
GTVp *vs.* GTVnx				
Difference between areas	0.0144	0.0189	0.00235	0.0137
Standard Error	0.00847	0.00609	0.141	0.0076
95% CI	−0.00221 to 0.0310	0.00692 to 0.0308	−0.274 to 0.279	−0.00122 to 0.0286
Z statistic	1.699	3.095	0.0167	1.799
Significance level	0.0892	0.0020	0.9867	0.0720

ROC, receiver operating characteristic; LFFR, local failure-free rate; OS, overall survival; DFFR, distant failure-free rate; DFS, disease-free survival.

that RLN metastasis is a risk factor for distant metastasis in NPC, but not for local regional recurrence (12-14). As a result, regarding the volume of RLNs as primary gross tumor when evaluating the prognostic effects of primary gross tumor volume in NPC would be inappropriate. Therefore, we aim to explore the prognostic value of pretreatment nasopharynx tumor volume (GTVnx) with or without RLNs for predicting survival outcomes in patients with local-regional NPC after definitive IMRT.

In consistent with previous results, univariate analysis of the present study shows that both volume of GTVp and GTVnx are significantly prognostic factors for LFFR, OS and PFS, but not for DFFR. However, in multivariate analysis, only GTVnx, but not for GTVp, is a significant prognosticator for local control (HR =5.24, 95% CI, 1.074–25.57, P=0.041). As for the prognostic role of GTVrLNs, no significant association is found between GTVrLNs volume and LFFR, OS, DFS, or DFFR. Therefore, we think that the volume of RLNs should not

be regarded as primary gross tumor when evaluating the prognostic effects of primary gross tumor volume in NPC, although multiple studies also found that volume of GTV-primary (including both GTVnx and RLNs) could also be a risk factor for survival and recurrence. One possible explanation for this finding is that the volume of RLNs is much smaller than the volume of the nasopharynx tumor, and dosimetric advantage of application of IMRT and usage of chemoradiotherapy significantly increases the local-regional control rate for local advanced NPC, which might make no significant differences between GTVnx and GTVp.

Though best cut-off value of the GTVp, GTVp was obtained for survival analysis, they had identical predictive effects on prognosis as comparing to T staging. However, tumor volume overlaps between tumors at different T categories, especially T3/T4 tumors, their volumes vary widely. And tumor volume heterogeneity of the same T classification could potentially cause much difficulty for predicting prognosis. Although the available data showed

Table 5 Univariate analysis and multivariate cox proportional hazards regression analysis of potential risk factors for LFFR, OS, DFFR, DFS

Variables	Category	Univariate												Multivariate											
		LFFR			OS			DFFR			DFS			LFFR			OS			DFFR			DFS		
		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Gender	Male vs. female	1.85	0.46–7.39	0.390	0.25	0.032–1.85	0.170	0.77	0.26–2.26	0.64	0.66	0.26–1.71	0.390	–	–	–	–	–	–	–	–	–	–	–	–
Age	<60 (n=109) vs. ≥60 (n=39)	4.01	1.07–15.00	0.039	6.28	2.31–17.08	0.0003	1.45	0.60–3.52	0.41	2.20	1.10–4.40	0.026	3.42	0.91–12.89	0.070	4.98	1.81–13.67	0.0019	–	–	–	1.69	0.81–3.50	0.16
T stage	T1,2 vs. T3,4	3.95	0.49–31.67	0.200	1.58	0.51–4.85	0.430	1.56	0.62–3.95	0.35	2.07	0.90–4.76	0.088	–	–	–	–	–	–	–	–	–	–	–	–
N stage	N0,1 vs. N2,3	0.39	0.10–1.44	0.160	1.51	0.43–5.25	0.520	3.58	0.84–15.23	0.08	1.22	0.53–2.79	0.065	–	–	–	–	–	–	–	–	–	–	–	–
TNM stage	III vs. IVa	2.78	0.69–11.19	0.150	7.21	2.05–25.29	0.002	3.02	1.28–7.10	0.01	2.80	1.38–5.69	0.0043	4.66	–	–	4.66	1.06–20.41	0.041	2.86	1.22–6.75	0.016	2.2	0.91–5.32	0.08
GTVnx (cm³)	≤42.7 (n=88) vs. >42.7 (n=60)	5.98	1.23–28.90	0.026	4.21	1.48–12.00	0.007	1.25	0.55–2.83	0.59	2.04	1.03–4.01	0.040	5.24	1.074–25.57	0.041	1.52	0.45–5.21	0.500	–	–	–	1.14	0.50–2.59	0.76
GTVrLNs (cm³)	≤0.79 (n=66) vs. >0.79 (n=82)	1.14	0.30–4.24	0.850	0.39	0.14–1.11	0.076	0.62	0.28–1.40	0.25	0.56	0.28–1.12	0.100	–	–	–	–	–	–	–	–	–	–	–	–
GTVp (cm³)	≤42.87 (n=84) vs. >42.87 (n=64)	5.52	1.14–26.70	0.034	3.93	1.38–11.22	0.01	1.39	0.62–3.14	0.42	2.17	1.10–4.30	0.026	–	–	–	–	–	–	–	–	–	–	–	–

LFFR, local failure-free rate; OS, overall survival; DFFR, distant failure-free rate; DFS, disease-free survival.

GTVp and T staging were closely related and GTVp could be incorporated into the TNM system by which the treatment outcomes would be more accurately and predicted (12-16), the cut-off value of tumor volume that predicts a poor prognosis has been reported inconsistently, which might be one main reason for not incorporating tumor volume into the clinical staging of NPC yet. Feng *et al.* (1) reported that primary tumor volume (including both primary nasopharyngeal tumor and retropharyngeal nodes) >40 mL was an adverse prognostic factor for the 5-year local regional control (LRC) rate (RR 2.454, P=0.002). In a retrospective study conducted by Wu *et al.* (24) showed that primary gross tumor volume (including both primary nasopharyngeal tumor and retropharyngeal nodes) >49 mL is an independent prognostic factor for local control based on 321 NPC patients. Our data showed that a volume of 42.7 cm^3 was a useful cut-off point to categorize patients into different prognostic groups. NPC patients with GTVnx ≤42.7 cm^3 had better 3-year LFFR, OS, and DFS (HR =5.98, 95% CI, 1.23–28.90, P=0.026; HR =4.21, 95% CI, 1.48–12.00, P=0.007 and HR =2.04, 95% CI, 1.03–4.01, P=0.04 respectively). The cut-off volume in the present study is smaller than reported by Feng M. et al, the main reason for this difference is that all of the included NPC is locally advanced (Stage III or IV), while nearly 30% of included patients in the Feng' study is early stage I or II. Based on our findings, for patients with GTVnx >42.7 cm^3, altered fractionation or dose escalating or boosting tumors with pretreatment volume could be recommended to further improve outcomes and local-regional control of NPC patients (26-28).

The previous methods of tumor delineation and volume calculation were not very accurate and varied, which lead to inconsistent research results (1-5,7-10). Although TPS could obtain a more accurate tumor treatment volume, induction chemotherapy was often selected as first line treatment scheme (29-31), and CT simulation images usually were collected after chemotherapy, it was more difficult to obtain the accurate pretreatment tumor volume because it was obviously reduced after induction chemotherapy. In our study, for local-regional advanced NPC, the volume exceeds 42.7 cm^3 predicting the unfavorable prognosis, and this part of the patient accounts for about 40%. The staging system should be suitable for all patients. If GTVnx was considered in the staging system, it couldn't direct patient's treatment scheme selection, which was one of key roles of staging system. Pairwise comparison of ROC curves among T stage, GTVp, GTVnx for LFFR, OS, DFFR, PFS,

this research showed GTVnx has a better predictive effect than GTVp in overall survival, P=0.0020, which might be associated with volumes of RLNs, which adversely affects the prognosis effect of the GTVnx. The volume of RLNs should be excluded when the effects of GTVnx on the prognosis were evaluated. There was no significant difference in the predictive effect of T stage and GTVp on LFFR, DFFR and DFS. In addition, the predictive effects of T stage, GTVnx, GTVp for LFRR, DFFR, and DFS were all insignificantly different. All in a word, it was not necessary to incorporated GTV volume into tumor staging under the currently available diagnostic and therapeutic methods.

The major patterns of treatment failure in this group are still the distant metastasis, followed by the local regional failure. Based on the available clinical data, induction chemotherapy followed by concurrent chemoradiotherapy is recommended as the first line treatment option for local-regional advanced NPC patients in order to improve the survival and local control (28-30). However, pretreatment GTVp and GTVnx often shrink significantly after induction chemotherapy and concurrent chemoradiotherapy in NPC patients. Until now, no published data is available regarding the prognostic effect of post-treatment GTVp and GTVnx after chemoradiotherapy in NPC, and further studies are still needed to clearly investigate this issue.

There were several limitations that must be addressed in the current study. First of all, the treatment regimens of included patients are varied, although most local advanced patients received induction chemotherapy and concurrent chemoradiotherapy, which might increase the heterogeneity of the included patients. Another limitation is that this is a retrospective study, thus the inherent bias could not be excluded. In addition, the sample of the present study is relatedly small and follow-up time (median 27 months) is relatively short.

Conclusions

In conclusion, in this retrospective study, we found that GTVnx was a significant prognostic factor for local control while the prognostic value of RLNs volume was limited. Physicians were recommended to distinguish between GTVnx and RLN involvement when assessing the risk for local recurrence in advanced NPC. Further investigations were warranted to confirm our findings.

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Footnote

Conflicts of Interest: 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. This study was approved by the Institutional Review Board of the Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, China. Individual written informed consent was not required because of the retrospective nature of the study.

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