

Supplementary value of primary tumor volume for prognostic stratification in patients with T3-4 nasopharyngeal carcinoma: A retrospective cohort study

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Abstract. The present retrospective study evaluated the supplementary value of gross tumor volume of the primary nasopharyngeal tumor (GTVnx) for overall survival (OS) risk stratification in patients with T3-4 nasopharyngeal carcinoma (NPC). A total of 118 patients with T3-4 NPC who received definitive intensity-modulated radiotherapy at Guilin People's Hospital (Guilin, China) between March 2020 and June 2025 were included. GTVnx was obtained from the radiotherapy planning system. A time-dependent receiver operating characteristic (ROC) curve was used to determine the exploratory cut-off for predicting 3-year OS. Survival differences were assessed using the Kaplan-Meier method and log-rank test, and Cox proportional hazards models were used to evaluate the association between GTVnx and OS. Clinical and extended models were compared using the concordance index (C-index), Akaike information criterion (AIC) and time-dependent area under the curve (AUC), and sensitivity analyses were performed to assess robustness. The median

follow-up time was 34.1 months and 18 deaths occurred (15.3%). The 36-month time-dependent ROC analysis identified 78 cm³ as the exploratory cut-off for GTVnx, with an AUC of 0.709. Patients with high GTVnx had poorer OS than those with low GTVnx (log-rank $P < 0.001$). In a multivariable Cox analysis, high GTVnx remained associated with poorer OS after adjustment for T stage and pretreatment Epstein-Barr virus DNA (EBV DNA; hazard ratio, 4.375; 95% confidence interval, 1.474-12.986; $P = 0.008$). Adding GTVnx to the clinical model improved the C-index from 0.759 to 0.817, reduced the AIC from 135.151 to 133.085 and increased the 36-month AUC from 0.748 to 0.787. Sensitivity analyses supported the consistency of the main findings. GTVnx may provide supplementary prognostic information beyond T stage and pretreatment EBV DNA in patients with T3-4 NPC. However, the identified cut-off value and incremental prognostic value require validation in independent cohorts.

Introduction

Nasopharyngeal carcinoma (NPC) has a distinct geographic distribution, with a higher incidence in southern China and Southeast Asia than in most other regions worldwide (1). With the use of intensity-modulated radiotherapy (IMRT), platinum-based concurrent chemotherapy and induction chemotherapy, locoregionally advanced NPC has achieved improved locoregional control and long-term survival (1-3). Nevertheless, patients with T3-4 disease still have risks of recurrence, distant metastasis and death. Further identification of high-risk patients within conventional staging categories may help refine prognostic assessment and support clinical trial stratification (4).

The tumor-node-metastasis (TNM) staging system remains the main framework for treatment decision-making and prognostic evaluation in NPC. It is largely based on the anatomic extent of primary tumor invasion and regional nodal involvement (4,5). However, the T stage is a categorical variable and does not fully reflect continuous differences in tumor burden within the same T-stage category (6,7). Among patients with T3-4 disease, small-volume tumors may be classified as advanced T stage due to the involvement of critical anatomic structures, whereas other tumors may show

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Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; CI, confidence interval; EBV DNA, Epstein-Barr virus DNA; GTVnx, gross tumor volume of the primary nasopharyngeal tumor; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma; OS, overall survival; ROC, receiver operating characteristic; TNM, tumor-node-metastasis

Key words: nasopharyngeal carcinoma, primary tumor volume, gross tumor volume of the primary nasopharyngeal tumor, T3-4 disease, overall survival, time-dependent receiver operating characteristic

extensive infiltration and a much larger primary volume (6). These differences may be associated with variations in tumor cell burden, hypoxia, local treatment complexity and potential treatment resistance (8).

Gross tumor volume of the primary nasopharyngeal tumor (GTVnx) is a routinely available volumetric parameter derived from radiotherapy planning systems and may serve as a quantitative measure of primary tumor burden (9). Previous studies have suggested that a larger primary tumor volume is associated with poorer local control, increased risk of distant metastasis and unfavorable overall survival (OS) (7,8). GTVnx has also been incorporated with Epstein-Barr virus (EBV) DNA, clinical stage or imaging features for risk stratification, while radiomic and molecular biomarkers have been increasingly investigated for prognostic assessment in NPC (10-13). However, most previous studies evaluated patients across all T stages or the broader locoregionally advanced population (8,10). Whether GTVnx can further identify patients with poor OS within the anatomically high-risk T3-4 subgroup has remained elusive.

Beyond statistical significance, the clinical value of a prognostic marker also depends on its incremental value beyond established clinical factors (14,15). Time-dependent receiver operating characteristic (ROC) analysis (14), the concordance index (C-index) (16) and Akaike information criterion (AIC) (17) can assess model performance from complementary perspectives, including discrimination at a specific time point, overall discriminative ability and model fit, while accounting for complexity. Therefore, the present retrospective study evaluated the association between GTVnx and OS in patients with T3-4 NPC and explored whether GTVnx provides incremental prognostic information beyond conventional clinical factors.

Patients and methods

Patients. The present single-center retrospective cohort study included 118 patients with T3-4 NPC who received definitive IMRT at Guilin People's Hospital (Guilin, China) between March 2020 and June 2025. All patients had pathologically confirmed NPC and underwent pretreatment staging examinations, including contrast-enhanced magnetic resonance imaging (MRI) of the nasopharynx and neck, chest imaging, abdominal imaging and bone assessment using bone scintigraphy, skeletal MRI or positron emission tomography/computed tomography (CT), as clinically indicated. As the present study period spanned different TNM classification periods, all patients were retrospectively restaged according to the 9th edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM classification system before statistical analysis using available pretreatment clinical, imaging and pathological information.

The inclusion criteria were as follows: i) Pathologically confirmed NPC; ii) T3-4 disease; iii) receipt of definitive IMRT; iv) availability of complete pretreatment imaging and radiotherapy planning data for GTVnx assessment; and v) available follow-up data for OS. The exclusion criteria were as follows: i) Distant metastasis at initial diagnosis; ii) previous head and neck radiotherapy or treatment for another malignancy; iii) concurrent active malignancy; and iv) missing key clinical, radiotherapy planning or follow-up data. The study

protocol was approved by the Ethics Committee of Guilin People's Hospital (Guilin, China; approval no. 2025-316KY) and written informed consent for the use of medical data for research purposes was obtained from all patients at admission.

Treatment and target delineation. All patients received definitive IMRT. GTVnx was manually delineated by radiation oncologists based on pretreatment contrast-enhanced MRI, simulation CT images and clinical examination findings. The delineation included all radiologically and clinically visible primary nasopharyngeal lesions and was performed according to institutional target delineation protocols for NPC. All GTVnx contours were independently reviewed and confirmed by two senior radiation oncologists before radiotherapy planning to minimize inter-observer variability. The GTVnx volume was automatically calculated by the radiotherapy planning system and recorded in cm³. Cervical nodal target volumes, clinical target volumes and organs at risk were delineated according to the institutional head and neck radiotherapy protocol. All patients received platinum-based combined treatment, including induction chemotherapy, concurrent chemoradiotherapy, concurrent targeted therapy, adjuvant chemotherapy and maintenance chemotherapy when indicated. The specific treatment regimen was determined by the attending physician according to disease stage, performance status and organ function. None of the patients received immunotherapy during the study period.

Variables and outcomes. Data on age, sex, histological subtype, T stage, N stage, clinical stage, pretreatment EBV DNA level, radiotherapy dose, GTVnx and follow-up outcomes were collected. The pretreatment plasma EBV DNA level was dichotomized using a cut-off value of 400 copies/ml, consistent with previous studies and commonly used clinical thresholds for risk stratification in NPC (18). OS was defined as the time from the start of radiotherapy to death from any cause. Patients who were alive at the last follow-up were censored.

Statistical analysis. All statistical analyses were performed using R software (version 4.5.0; R Foundation for Statistical Computing) and SPSS (version 25.0; IBM Corp.). Continuous variables were first assessed for normality. Normally distributed variables were presented as the mean $\pm$ standard deviation and were compared using the independent-samples t-test. Non-normally distributed variables were presented as the median (first quartile, third quartile) and were compared using the Mann-Whitney U-test. Categorical variables were summarized as counts and percentages and were compared using the χ^2 test or Fisher's exact test.

A 36-month time-dependent ROC curve was used to evaluate the ability of GTVnx to discriminate patients according to their OS outcomes. The 36-month time-point was selected based on the maturity of follow-up data as it approximated the median follow-up duration of the cohort (34.1 months) and represented an intermediate-term survival endpoint. The variability of the cut-off value was further assessed using bootstrap resampling with 1,000 repetitions, and the median bootstrap-derived cut-off value and 95% percentile interval were calculated. Patients were then divided into low- and high-GTVnx groups

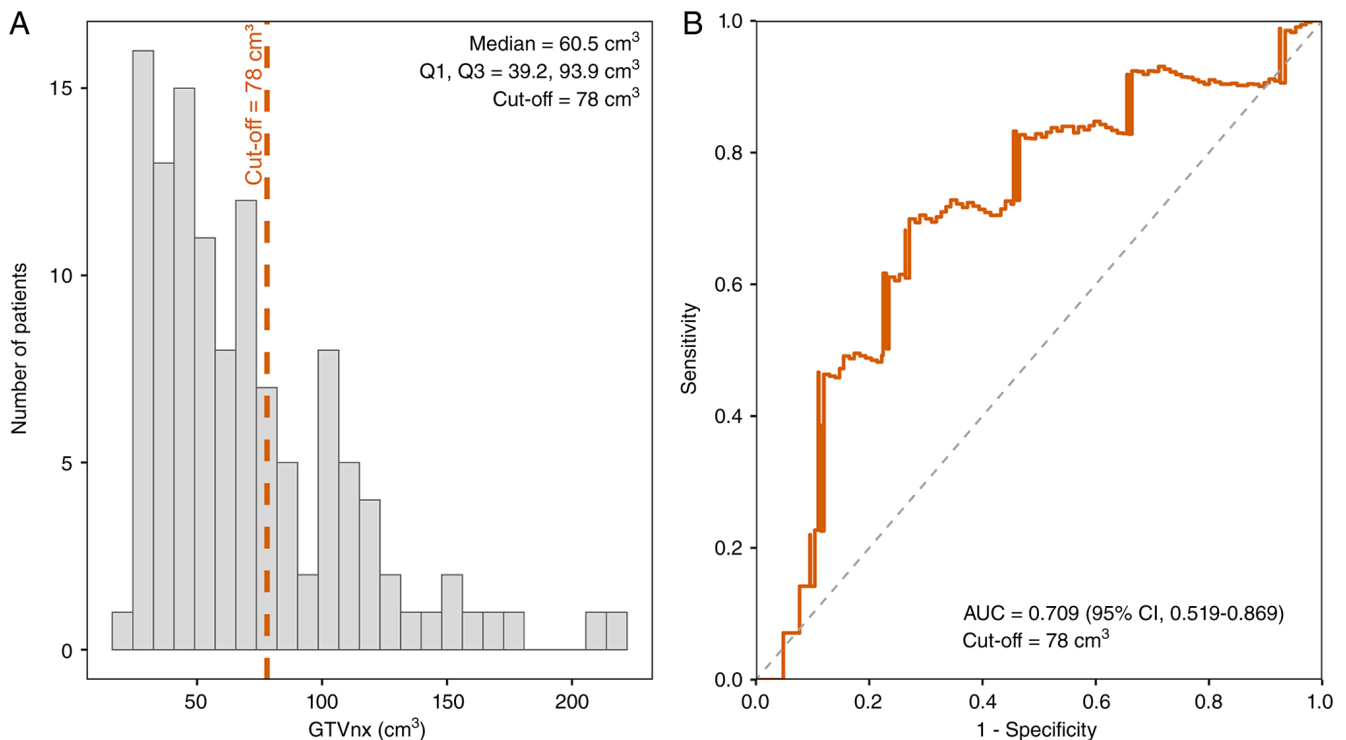


Figure 1. Distribution of GTVnx and determination of the prognostic cut-off. (A) Distribution of GTVnx in the overall cohort. The dashed line indicates the cut-off value of 78 cm³. (B) Time-dependent ROC curve based on 3-year OS. AUC, area under the curve; OS, overall survival; ROC, receiver operating characteristic; GTVnx, gross tumor volume of the primary nasopharyngeal tumor; CI, confidence interval; Q1, first quartile; Q3, third quartile.

based on this cut-off. OS curves were generated using the Kaplan-Meier method and differences between groups were compared using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Given the limited number of OS events (n=18), the events-per-variable ratio was below the commonly recommended threshold of 10 events per variable. Therefore, multivariable Cox regression models and incremental model performance analyses were considered exploratory and hypothesis-generating. Variables included in the multivariable models were selected a priori based on established clinical relevance and prognostic significance rather than solely on univariable statistical significance. The clinical model included T stage and pretreatment EBV DNA, and the incremental prognostic value of GTVnx was subsequently evaluated by adding GTVnx to this model. Considering the risk of model overfitting caused by limited outcome events, the N stage was not incorporated into the primary model and was examined separately in sensitivity analyses. Model performance was compared using the C-index, AIC and the 36-month time-dependent area under the curve (AUC). In addition, bootstrap resampling was used to estimate the CI of the difference in C-index between the clinical and extended models.

To assess the robustness of the findings, several sensitivity analyses were performed as follows: i) Further adjustment for N stage based on the main model; ii) replacement of T stage with overall clinical stage; iii) inclusion of GTVnx as a continuous variable in the model, with the HR calculated per 10 cm³ increase; and iv) use of a conventional ROC-derived alternative cut-off to repeat the Kaplan-Meier survival

analysis. A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient baseline characteristics. A total of 118 patients with T3-4 NPC were included in the present study. The median age was 53 years (range, 23-75 years), and the cohort included 84 male and 34 female patients (Table I). Based on the 78 cm³ cut-off determined by the 36-month time-dependent ROC analysis (Fig. 1), patients were divided into the low-GTVnx group (GTVnx ≤ 78 cm³; n=80) and the high-GTVnx group (GTVnx > 78 cm³; n=38). Compared with the low-GTVnx group, patients in the high-GTVnx group had significantly higher proportions of male patients, T4 disease, stage III disease and pretreatment EBV DNA ≥ 400 copies/ml. There were no statistically significant differences between the two groups in terms of age, age category, N stage, histological subtype, follow-up duration, loss to follow-up rate, concurrent targeted therapy, adjuvant chemotherapy or capecitabine/S-1 maintenance chemotherapy (all $P > 0.05$). The baseline characteristics are shown in Table I.

Follow-up and survival outcomes. The median (25th, 75th percentile) follow-up time for the overall cohort was 34.1 (20.4, 49.3) months. There was no statistically significant difference in median follow-up time between the low- and high-GTVnx groups. During follow-up, 18 deaths occurred (15.3%). The proportion of OS events was significantly higher in the high-GTVnx group than in the low-GTVnx group (31.6 vs. 7.5%; $P = 0.002$). The 3-year OS rate was lower in the high-GTVnx group than in the low-GTVnx group (74.1 vs. 95.1%; $P < 0.001$).

Table I. Baseline characteristics of patients with T3-4 nasopharyngeal carcinoma according to GTVnx group.

Characteristic	Total (n=118)	GTVnx $\leq 78 \text{ cm}^3$ (n=80)	GTVnx $> 78 \text{ cm}^3$ (n=38)	P-value
Age, years	52.4 $\pm$ 11.9	51.6 $\pm$ 11.3	54.2 $\pm$ 10.0	0.234
Age group, years				0.103
≤ 40	18 (15.3)	16 (20.0)	2 (5.3)	
$> 40, \leq 60$	78 (66.1)	49 (61.3)	29 (76.3)	
> 60	22 (18.6)	15 (18.8)	7 (18.4)	
Sex				0.031
Male	84 (71.2)	52 (65.0)	32 (84.2)	
Female	34 (28.8)	28 (35.0)	6 (15.8)	
T stage				< 0.001
T3	57 (48.3)	50 (62.5)	7 (18.4)	
T4	61 (51.7)	30 (37.5)	31 (81.6)	
N stage				0.360
N1	9 (7.6)	8 (10.0)	1 (2.6)	
N2	75 (63.6)	49 (61.3)	26 (68.4)	
N3	34 (28.8)	23 (28.7)	11 (28.9)	
Clinical stage				0.001
Stage II	45 (38.1)	39 (48.8)	6 (15.8)	
Stage III	73 (61.9)	41 (51.2)	32 (84.2)	
Histological subtype				0.663
Non-keratinizing undifferentiated carcinoma	112 (94.9)	75 (93.8)	37 (97.4)	
Non-keratinizing differentiated carcinoma	6 (5.1)	5 (6.3)	1 (2.6)	
EBV DNA, copies/ml				0.033
< 400	54 (45.8)	42 (52.5)	12 (31.6)	
≥ 400	64 (54.2)	38 (47.5)	26 (68.4)	
GTVnx, cm^3	60.5 (39.2, 93.9)	46.6 (33.9, 61.0)	109.0 (95.9, 131.0)	< 0.001
Induction chemotherapy	118 (100)	80 (100)	38 (100)	-
Concurrent chemoradiotherapy	118 (100)	80 (100)	38 (100)	-
Concurrent targeted therapy	63 (53.4)	41 (51.2)	22 (57.9)	0.499
Adjuvant chemotherapy	31 (26.3)	22 (27.5)	9 (23.7)	0.660
Capecitabine/S-1 maintenance chemotherapy	63 (53.4)	42 (52.5)	21 (55.3)	0.779

All patients received platinum-based induction chemotherapy followed by platinum-based concurrent chemoradiotherapy. Various induction chemotherapy regimens were used according to clinical practice, including cisplatin- or nedaplatin-based combinations. No patients received immunotherapy during the study period. Data are presented as mean $\pm$ standard deviation, median (interquartile range) or n (%), as appropriate. EBV DNA, Epstein-Barr virus DNA; GTVnx, gross tumor volume of the primary nasopharyngeal tumor; S-1, tegafur/gimeracil/oteracil potassium.

GTVnx distribution and cut-off determination. GTVnx showed a right-skewed distribution in the overall cohort, with a median value of 60.5 cm^3 and first and third quartiles of 39.2 and 93.9 cm^3 , respectively. Time-dependent ROC analysis for 3-year OS showed that GTVnx had discriminatory ability for predicting 3-year OS, with an AUC of 0.709. Based on the Youden index, the optimal cut-off value for GTVnx was 78 cm^3 , with a sensitivity of 69.9% and a specificity of 72.9%. The distribution of GTVnx and the time-dependent ROC curve are shown in Fig. 1. The

bootstrap assessment of cut-off variability is presented in Table SI.

Prognostic value of GTVnx

Kaplan-Meier survival analysis. Kaplan-Meier survival analysis showed that, when patients were stratified according to the 78 cm^3 cut-off, the high-GTVnx group had significantly poorer OS than the low-GTVnx group (log-rank $P < 0.001$; Fig. 2). Cox regression analysis showed that, compared with patients with GTVnx $\leq 78 \text{ cm}^3$, those with GTVnx $> 78 \text{ cm}^3$

Table II. Univariable and multivariable Cox regression analyses for overall survival in patients with T3-4 nasopharyngeal carcinoma.

Variable	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Age, years	1.042 (0.993-1.094)	0.091	-	-
Sex, female vs. male	1.354 (0.502-3.650)	0.549	-	-
T stage, T4 vs. T3	2.330 (0.828-6.556)	0.109	1.089 (0.359-3.303)	0.881
N stage, N3 vs. N0-2	2.115 (0.810-5.518)	0.126	-	-
Clinical stage, III vs. II	4.042 (1.153-14.171)	0.029	-	-
EBV DNA, ≥ 400 vs. < 400 copies/ml	6.223 (1.972-19.636)	0.002	5.041 (1.516-16.763)	0.008
GTVnx, > 78 vs. ≤ 78 cm ³	5.623 (2.088-15.143)	0.001	4.375 (1.474-12.986)	0.008

The multivariable Cox model included T stage, EBV DNA and GTVnx. The likelihood ratio test was statistically significant ($\chi^2=21.195$, $P<0.001$). ‘-’ indicates that the variable was not included in the multivariable model. CI, confidence interval; EBV DNA, Epstein-Barr virus DNA; GTVnx, gross tumor volume of the primary nasopharyngeal tumor; HR, hazard ratio.

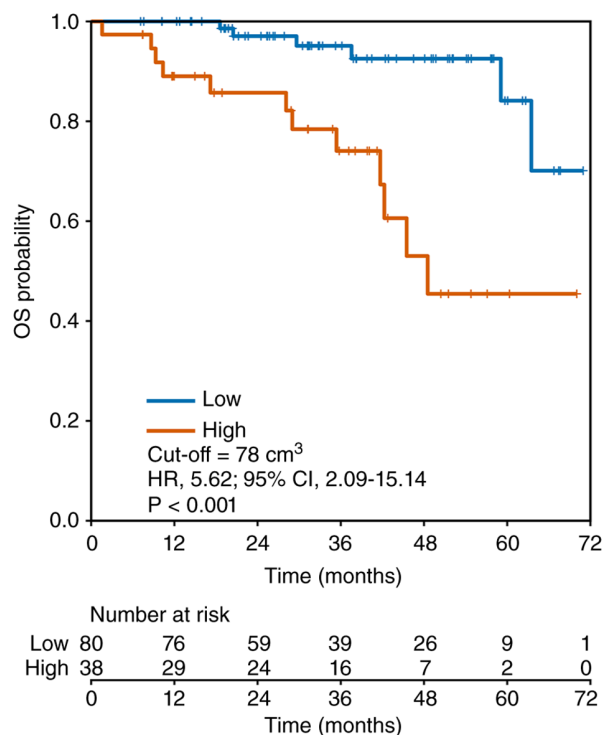


Figure 2. Kaplan-Meier OS curves according to the GTVnx group. Kaplan-Meier curves for OS in patients stratified by the 78 cm³ GTVnx cut-off. Numbers at risk are shown below the plot. GTVnx, gross tumor volume of the primary nasopharyngeal tumor; OS, overall survival; CI, confidence interval; HR, hazard ratio.

had a significantly increased risk of death (HR, 5.62; 95% CI, 2.09-15.14; $P<0.001$).

Cox survival analysis. Univariable Cox regression analysis showed that stage III disease, EBV DNA ≥ 400 copies/ml and high GTVnx were significantly associated with poorer OS. Multivariable Cox regression analysis further showed that, after adjustment for T stage and EBV DNA, high GTVnx remained independently associated with unfavorable OS (HR, 4.375; 95% CI, 1.474-12.986; $P=0.008$). The results of the univariable and multivariable Cox analyses are shown in Table II.

Incremental prognostic value of GTVnx beyond the clinical model. In the same 118 patients with 18 deaths, the extended model incorporating GTVnx showed improved predictive performance compared with the clinical model including only T stage and EBV DNA. The C-index increased from 0.759 to 0.817, with a bootstrap-estimated difference in C-index of 0.052 (95% CI, -0.009-0.127). The 36-month AUC increased from 0.748 to 0.787, and the AIC decreased from 135.151 to 133.085 after adding GTVnx, with a Δ AIC of -2.066 (Table III).

Sensitivity analysis. After further adjustment for N stage based on the main model, the association between GTVnx and poorer OS remained consistent. Replacing T stage with overall clinical stage did not materially change the results. When GTVnx was included as a continuous variable, each 10 cm³ increase in GTVnx remained associated with an increased risk of death. In addition, after using a conventional ROC-derived cut-off of 106 cm³ as an alternative threshold for regrouping, the high-GTVnx group still showed a trend toward poorer OS. Detailed results are provided in Table SII and Fig. S1. Overall, the sensitivity analyses supported the robustness of the main findings.

Discussion The present study examined whether GTVnx could provide additional prognostic information in patients with T3-4 NPC. The main finding was that patients with a larger GTVnx had poorer OS, and this association persisted after adjustment for T stage and pretreatment EBV DNA. When GTVnx was added to a clinical model based on these conventional factors, the C-index, AIC and time-dependent AUC all changed in a favorable direction, although the absolute improvement was modest. Similar results were obtained across sensitivity analyses using alternative model specifications and variable definitions. These findings suggest that GTVnx may help refine prognostic assessment within the T3-4 subgroup, although further validation is required before clinical application.

TNM staging remains the foundation for prognostic assessment and treatment decision-making in NPC (4). However, T stage is primarily based on the anatomic extent of tumor invasion and does not directly quantify tumor

Table III. Comparison of predictive performance between the clinical and extended models.

Metric	Clinical model	Extended model
Variables included	T stage + EBV DNA	T stage + EBV DNA + GTVnx
C-index	0.759	0.817
Bootstrap difference in C-index	-	0.052 (95% CI, -0.009-0.127)
36-month AUC	0.748	0.787
AIC	135.151	133.085
Δ AIC	-	-2.066

The clinical model included T stage and EBV DNA, whereas the extended model additionally included GTVnx. Higher C-index and AUC values and lower AIC values indicate improved model performance. '-' indicates that the variable was not included in the multivariable model. Δ AIC was calculated relative to the clinical model. AIC, Akaike information criterion; AUC, area under the curve; C-index, concordance index; EBV DNA, Epstein-Barr virus DNA; GTVnx, gross tumor volume of the primary nasopharyngeal tumor.

burden (19). In clinical practice, patients classified as T3-4 may have substantially different primary tumor volumes. Certain tumors are assigned to an advanced T category due to the involvement of critical anatomic structures, even when the measurable primary volume is relatively limited. By contrast, other tumors within the same T category may show more extensive infiltration and a much larger volume (19,20). As a continuous volumetric parameter routinely derived from radiotherapy planning systems, GTVnx may capture part of this heterogeneity (19). The association between larger GTVnx and poorer OS suggests that tumor volume provides additional information regarding disease burden.

Previous studies have linked primary tumor volume with locoregional control, distant metastasis and survival outcomes in NPC (9,21-23). Most of these studies evaluated mixed-stage cohorts or the broader locoregionally advanced population (9,23). The present study stands out by focusing specifically on patients with T3-4 disease, a subgroup already considered anatomically high-risk. The present findings indicate that tumor volume may still distinguish prognostic differences within this advanced T-stage category (24,25). It may serve as a simple quantitative adjunct to conventional staging, particularly when patients with the same T stage show markedly different primary tumor burdens.

The incremental predictive value of GTVnx should also be interpreted with caution (26-28). Although adding GTVnx to the clinical model resulted in an improvement in model performance, the magnitude of incremental improvement was modest. The bootstrap CI for the difference in C-index included zero, suggesting uncertainty regarding the magnitude of improvement. This may be partly because the clinical model already included established prognostic factors, such as T stage and pretreatment EBV DNA (18). Although N stage showed a clinically meaningful HR, it was not included in the primary model due to the limited number of OS events and the potential risk of overfitting. However, sensitivity analysis incorporating N stage demonstrated consistent results, suggesting that the prognostic association of GTVnx remained consistent. In addition, GTVnx and T stage are not completely independent, as larger tumors are more likely to involve adjacent anatomic structures. These

overlapping features may limit the additional contribution of GTVnx when it is combined with established clinical variables. Therefore, GTVnx should be viewed as supplementary risk information rather than as a stand-alone basis for treatment selection. For patients with a larger GTVnx, clinical interpretation should still integrate T stage, N stage, EBV DNA, treatment response and the general condition of the patient (29,30).

Several limitations should be acknowledged. First, this was a single-center retrospective study, and selection bias and unmeasured confounding cannot be excluded. Second, the relatively small number of OS events may have limited the statistical power and stability of multivariable modeling. Therefore, the prognostic value of GTVnx requires further evaluation. Third, the 78 cm³ cut-off identified by time-dependent ROC analysis was derived from the present cohort and should be considered an exploratory threshold rather than a generally applicable clinical threshold. Although bootstrap analysis showed good agreement between the original cut-off and the median bootstrap-derived cut-off, the relatively wide percentile interval indicated uncertainty regarding the precision of the cut-off estimate. Therefore, this cut-off requires validation in larger independent cohorts before clinical application. Fourth, the present study focused on OS and did not systematically assess progression-free survival, locoregional recurrence-free survival or distant metastasis-free survival. Finally, dynamic EBV DNA, response to induction chemotherapy, radiomic features and molecular biomarkers were not included. Larger multicenter studies with external validation are needed to confirm the stability of GTVnx and to determine how it can be integrated with other prognostic factors.

In summary, in patients with T3-4 NPC, GTVnx was associated with poorer OS and may provide supplementary prognostic information beyond T stage and pretreatment EBV DNA. The 78 cm³ cut-off derived from time-dependent ROC analysis helped identify patients at higher risk, and adding GTVnx to the clinical model modestly improved model performance. GTVnx should be regarded as an auxiliary quantitative parameter rather than an alternative to TNM staging. Further multicenter studies with larger sample sizes and external validation are needed to confirm these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HH and QQC conceived and designed the study; HH, YSL, YJO, MP, XYT, TFZ and QG collected the data; HH and HRH performed the statistical analyses; HH, YSL, CQC and QQC analyzed and interpreted the data; HH and YSL drafted the manuscript; CQC and QQC supervised the study and critically revised the manuscript; HH and QQC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guilin People's Hospital (Guilin, China; approval no. 2025-316KY) and was conducted in accordance with the Declaration of Helsinki. Written informed consent for the use of medical data for research purposes was obtained from all patients at admission.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

- Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y and Ma J: Nasopharyngeal carcinoma. *Lancet* 394: 64-80, 2019.
- Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, Halámková J, Mattheis S, Baujat B, Hardillo J, *et al*: Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 32: 452-465, 2021.
- Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, Sun Y, Chen XZ, Li JG, Zhu XD, *et al*: Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase 3, multicentre, randomised controlled trial. *Lancet Oncol* 17: 1509-1520, 2016.
- Pan JJ, Mai HQ, Ng WT, Hu CS, Li JG, Chen XZ, Chow JCH, Wong E, Lee V, Ma LY, *et al*: Ninth version of the AJCC and UICC nasopharyngeal cancer TNM staging classification. *JAMA Oncol* 10: 1627-1635, 2024.
- Du XJ, Wang GY, Zhu XD, Han YQ, Lei F, Shen LF, Yang KY, Chen L, Mao YP, Tang LL, *et al*: Refining the 8th edition TNM classification for EBV related nasopharyngeal carcinoma. *Cancer Cell* 42: 464-473.e3, 2024.
- King AD and Bhatia KS: Magnetic resonance imaging staging of nasopharyngeal carcinoma in the head and neck. *World J Radiol* 2: 159-165, 2010.
- Chen C, Fei Z, Pan J, Bai P and Chen L: Significance of primary tumor volume and T-stage on prognosis in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy. *Jpn J Clin Oncol* 41: 537-542, 2011.
- Wu Z, Su Y, Zeng RF, Gu MF and Huang SM: Prognostic value of tumor volume for patients with nasopharyngeal carcinoma treated with concurrent chemotherapy and intensity-modulated radiotherapy. *J Cancer Res Clin Oncol* 140: 69-76, 2014.
- Yang LN, Song YR, Zhang H, Tu HL, Lu MY, Liu DQ, Sui JD, Li D, Xie Y and Wang Y: Monocyte count combined with GTVnx is an independent prognostic factor in non-metastatic nasopharyngeal carcinoma receiving radiotherapy. *Front Oncol* 15: 1541212, 2025.
- Chen QY, Guo SY, Tang LQ, Lu TY, Chen BL, Zhong QY, Zou MS, Tang QN, Chen WH, Guo SS, *et al*: Combination of tumor volume and Epstein-Barr virus DNA improved prognostic stratification of stage II nasopharyngeal carcinoma in the intensity modulated radiotherapy era: A Large-scale cohort study. *Cancer Res Treat* 50: 861-871, 2018.
- Liu L, Pei W, Liao H, Wang Q, Gu D, Liu L, Su D and Jin G: A Clinical-radiomics nomogram based on magnetic resonance imaging for predicting Progression-free survival after induction chemotherapy in nasopharyngeal carcinoma. *Front Oncol* 12: 792535, 2022.
- Khongwirothphan S, Oonsiri S, Kitpanit S, Prayongrat A, Kannarunimit D, Chakkabat C, Lertbutsayanukul C, Sriswasdi S and Rakvongthai Y: Multimodality radiomics for tumor prognosis in nasopharyngeal carcinoma. *PLoS One* 19: e0298111, 2024.
- Liu HT, Li M, Qu SH, Cheng JJ, Liang P, Lu JL, Deng S, Gu JZ, Luo YQ, Gui Z, *et al*: Overexpression of STOML1 is associated with good prognosis in nasopharyngeal carcinoma. *Oncol Lett* 30: 461, 2025.
- Park SY, Park JE, Kim H and Park SH: Review of statistical methods for evaluating the performance of survival or other Time-to-Event prediction models (from Conventional to Deep Learning Approaches). *Korean J Radiol* 22: 1697-1707, 2021.
- Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, Ghassemi M, Liu X, Reitsma JB, van Smeden M, *et al*: TRIPOD+AI statement: Updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ* 385: e078378, 2024.
- Hartman N, Kim S, He K and Kalbfleisch JD: Pitfalls of the concordance index for survival outcomes. *Stat Med* 42: 2179-2190, 2023.
- Akaike H: A new look at the statistical model identification. *IEEE Trans Autom Control* 19: 716-723, 1974.
- Zhang L, Tang LQ, Chen QY, Liu H, Guo SS, Liu LT, Guo L, Mo HY, Zhao C, Guo X, *et al*: Plasma Epstein-Barr viral DNA complements TNM classification of nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy. *Oncotarget* 7: 6221-6230, 2016.
- Lin SJ, Guo QJ, Liu Q, Ng WT, Ahn YC, AlHussain H, Chan AW, Chow J, Chua MLK, Corry J, *et al*: International consensus guideline on delineation of the clinical target volumes at different dose levels for nasopharyngeal carcinoma (2024 version). *Int J Radiat Oncol Biol Phys* 123: 415-431, 2025.
- Luo X, Fu J, Zhong Y, Liu S, Han B, Astaraki M, Bendazzoli S, Toma- Dasu I, Ye Y, Chen Z, *et al*: SegRap2023: A benchmark of organs-at-risk and gross tumor volume segmentation for radiotherapy planning of nasopharyngeal carcinoma. *Med Image Anal* 101: 103447, 2025.
- Chiang CL, Guo Q, Ng WT, Lin S, Ma TSW, Xu Z, Xiao Y, Li J, Lu T, Choi HCW, *et al*: Prognostic factors for overall survival in nasopharyngeal cancer and implication for TNM staging by UICC: A systematic review of the literature. *Front Oncol* 11: 703995, 2021.
- Ni W, Qi W, Xu F, Cao W, Xu C, Chen J and Gao Y: Prognostic value of nasopharynx tumour volume in local-regional advanced nasopharyngeal carcinoma. *Ann Transl Med* 8: 223, 2020.

23. He YX, Wang Y, Cao PF, Shen L, Zhao YJ, Zhang ZJ, Chen DM, Yang TB, Huang XQ, Qin Z, *et al*: Prognostic value and predictive threshold of tumor volume for patients with locally advanced nasopharyngeal carcinoma receiving intensity-modulated radiotherapy. *Chin J Cancer* 35: 96, 2016.
24. Yan G, Feng Y, Wu M, Li C, Wei Y, Hua L, Zhao G, Hu Z, Yao S, Hou L, *et al*: Prognostic significance of MRI-based late-course tumor volume in locoregionally advanced nasopharyngeal carcinoma. *Radiat Oncol* 17: 111, 2022.
25. Shen C, Lu JJ, Gu Y, Zhu G, Hu C and He S: Prognostic impact of primary tumor volume in patients with nasopharyngeal carcinoma treated by definitive radiation therapy. *Laryngoscope* 118: 1206-1210, 2008.
26. Jiang S, Rosner BA and Colditz GA: Statistically significant association does not imply improvement in prediction of clinical outcomes. *Cancer Prev Res (Phila)* 18: 727-733, 2025.
27. Steyerberg EW, Pencina MJ, Lingsma HF, Kattan MW, Vickers AJ and Van Calster B: Assessing the incremental value of diagnostic and prognostic markers: A review and illustration. *Eur J Clin Invest* 42: 216-228, 2012.
28. Cook NR: Quantifying the added value of new biomarkers: How and how not. *Diagn Progn Res* 2: 14, 2018.
29. Peng H, Chen BB, Wang XH, Mo YX and Han F: Prognostic value of regression rate of plasma EBV DNA after induction chemotherapy for stage II-IVA nasopharyngeal carcinoma. *Front Oncol* 11: 689593, 2021.
30. Zheng H, Zhou P, Wang J, Yu YF, Zhou R, Lin Q and Wu SG: Prognostic effect of residual plasma Epstein-Barr viral DNA after induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma. *Cancer Med* 12: 14979-14987, 2023.



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