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Original Research

Prognostic value of lymph node-to-primary tumor ratio of PET standardized uptake value for nasopharyngeal carcinoma: a recursive partitioning risk stratification analysis

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Abstract

Background: Induction chemotherapy (IC) combined with concurrent chemoradiotherapy has become the standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). Data on the prognostic value of the lymph node-to-primary tumor ratio (NTR) of positron emission tomography (PET) standardized uptake value (SUV) for patients treated with IC were limited.

Objectives: To evaluate the prognostic value of the SUV NTR for patients with LA-NPC treated with IC.

Design: In all, 467 patients with pretreatment ^{18}F-fluorodeoxyglucose PET/computed tomography (CT) scans between September 2017 and November 2020 were retrospectively reviewed.

Methods: The receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off value of SUV NTR. Kaplan–Meier method was used to evaluate survival rates. The recursive partitioning analysis (RPA) was performed to construct a risk stratification model.

Results: The optimal cutoff value of SUV NTR was 0.74. Multivariate analyses showed that SUV NTR and overall stage were independent predictors for distant metastasis-free survival (DMFS) and regional recurrent-free survival (RRFS). Therefore, an RPA model based on the endpoint of DMFS was generated and categorized the patients into three distinct risk groups: RPA I (low risk: SUV NTR <0.74 and stage III), RPA II (medium risk: SUV NTR <0.74 and stage IVa, or SUV NTR $\geqslant 0.74$ and stage III), and RPA III (high risk: SUV NTR $\geqslant 0.74$ and stage IVa), with a 3-year DMFS of 98.9%, 93.4%, and 84.2%, respectively. ROC analysis showed that the RPA model had superior predictive efficacy than the SUV NTR or overall stage alone.

Conclusion: SUV NTR was an independent prognosticator for distant metastasis and regional recurrence in locoregionally advanced NPC. The RPA risk stratification model based on SUV NTR provides improved DMFS and RRFS prediction over the eighth edition of the TNM (Tumor Node Metastasis) staging system.

Keywords: distant metastasis, induction chemotherapy, lymph node to primary tumor ratio, nasopharyngeal carcinoma, positron emission tomography, standardized uptake value

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Introduction

In the era of intensity-modulated radiotherapy (IMRT), locoregional control has been dramatically improved, and distant metastasis has become the primary failure pattern after treatment for nasopharyngeal carcinoma (NPC).[1–3] This highlights the need for effective biomarkers that can accurately predict distant metastasis and guide individualized treatment and disease surveillance.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) combines functional metabolic imaging with anatomical structure imaging, which can reflect intratumoral heterogeneity.[4–6] It has been widely used in the diagnosing and staging of NPC.[5–10] Recently, several studies showed that the lymph node-to-primary tumor ratio (NTR) of PET standardized uptake value (SUV) had potential predictive value in some cancers, such as cervical, esophageal cancer, and breast cancer.[4,11,12] However, in NPC, relevant data were limited and the studies were mainly based on the concurrent chemoradiotherapy (CCRT) mode.[13–16] Nowadays, induction chemotherapy (IC) combined with CCRT has become the standard treatment for locoregionally advanced NPC (LA-NPC) since IC can significantly reduce distant metastasis and improve the overall survival (OS) rate.[17–20] For non-endemic NPC, IC + CCRT can significantly reduce grade 3–4 late radiation toxicities, and the response to IC may provide additional prognostic information.[21] In this context, it was necessary to discuss the prognostic value of SUV NTR for patients treated with IC. However, relevant data on large samples were limited.

This study focused on patients with LA-NPC treated with IC and aimed to (i) evaluate the prognostic value of SUV NTR and (ii) establish a risk stratification model based on SUV NTR to predict distant metastasis.

Patients and methods

Patient selection

From September 2017 to November 2020, 467 patients with pretreatment PET/CT scans were retrospectively reviewed. Inclusion criteria were as follows: (1) pathologically confirmed NPC; (2) underwent ^{18}F-FDG PET/CT scans before treatment; (3) treated with IC and IMRT; (4) no evidence of distant metastasis; and (5) without previous or concomitant malignant diseases. Patients who participated in the randomized, phase III clinical trial to compare the efficacy and safety of sequential chemoradiotherapy [IC + radiotherapy (RT) + adjuvant chemotherapy (AC)] with IC plus CCRT (IC + CCRT) in patients with LA-NPC (NCT03366415) were also included in the present study. The study was carried out following the Good Clinical Practice guidelines and the Declaration of Helsinki.

Except for PET/CT, patients underwent pretreatment evaluations, including a detailed history and physical examination, magnetic resonance imaging (MRI) (preferred) or CT of the head and neck, fiberoptic nasopharyngoscopy or indirect nasopharyngoscopy, electrocardiogram, and complete blood sampling. All patients were staged based on the eighth edition of the International Union Against Cancer/American Joint Committee on Cancer staging system. The study was approved by the Institutional Review Board of our cancer center (No. 2009224-1).

^{18}F-FDG PET/CT imaging

Patients were required to fast for at least 6 h before PET/CT scan. ^{18}F-FDG was given intravenously at a dose of 7.4 MBq/kg. After resting for 1 h, the PET/CT scan was performed using a Siemens Biograph 16HR PET/CT Scanner (Knoxville, TN, USA). The patient kept a supine position with elbows on the forehead in a full carbon flatbed. The scanning range was from the proximal thighs to the head. CT scanning was performed before PET acquisition. The parameters of CT scanning were as follows: 120 kV, 110 mA, slice thickness of 5 mm, rotation time of 0.5 s, and pitch of 1 mm. The PET scan duration was 2–3 min per bed for 6–8 beds. The PET images were reconstructed using the ordered subset maximum expectation iteration method after attenuation correction using CT images. More details have been described previously.[22]

SUV-T was defined as the maximum SUV (SUVmax) of the primary tumor, SUV-N was defined as SUVmax of the lymph nodes, and SUV NTR was defined as the lymph NTR of SUVmax. For multiple lymph nodes, SUVmax is defined as the highest SUVmax of the neck lymph nodes, regardless of the size of the lymph nodes.

Treatment, follow-up, and endpoints

All patients received IC and intensity-modulated radiation therapy. In all, 219 (46.9%) patients received concurrent chemotherapy (CCT), and 175 (37.5%) patients received AC. In total, 92 (19.7%) patients received RT alone after IC mainly due to patient rejection, abnormal liver and kidney function, abnormal myocardial enzymes, intolerance, and the impact of COVID-19. The commonly used induction and AC regimens were TP (docetaxel 60–75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1 or 25 mg/m^2/day on days 1–3) and GP (gemcitabine 1 g/m^2 on day 1 and day 8, cisplatin 75 mg/m^2 on day 1 or 25 mg/m^2/day on days 1–3). CCT consisted of cisplatin 30–40 mg/m^2 weekly or 75–80 mg/m^2 every 3 weeks during IMRT. The radiation (RT) dose was 66–70.4 Gy in 30–32 fractions. The technique of IMRT has been described in a previous study.[3]

Patients were assessed weekly during IMRT. After treatment, the assessment was done every 3 months for the first 2 years, every 6 months for years 3–5, and yearly after that. Each follow-up included a physical examination of the head and neck and complete blood sampling [including Epstein–Barr virus (EBV) DNA levels, and thyroid and pituitary function]. MRI of the nasopharynx, chest CT, and abdominal ultrasound were performed every 6–12 months. Other tests were recommended according to clinical needs.

The primary endpoint of this study was distant metastasis-free survival (DMFS), which was defined as the time from the first treatment to the first occurrence of distant metastasis. The secondary endpoints were local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), progression-free survival (PFS), and OS, which were defined as the time from the first treatment to the first occurrence of local recurrence, regional recurrence, progression, or death from any cause, respectively.

Statistical methods

The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff value of SUV-T, SUV-N, and SUV NTR. Spearman's tests were used to assess the correlations between variables. The Kaplan–Meier method was used to evaluate LRFS, RRFS, DMFS, OS, and PFS rates. The survival rates were calculated from the day of the first treatment to the date each event happened or the last follow-up. Univariate and multivariate analyses were performed to evaluate potential prognostic factors. The recursive partitioning analysis (RPA) was performed to construct a risk stratification model. All the statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 27.0, IBM Corporation, Chicago, IL, USA) and R (version 4.2, the R Foundation for Statistical Computing, Vienna, Austria). A p value of <0.05 (two-tailed) was considered statistically significant.

Results

Patient characteristics

The baseline and treatment characteristics for 467 enrolled patients are shown in Table 1. The median age at diagnosis was 50 years (range of 13–76, with a mean value of 48.6). The male-to-female ratio was 2.7:1. The median value of SUV-T, SUV-N, and SUV NTR was 11.2 (range of 3–37), 9.6 (1.7–43.5), and 0.94 (0.1–6.6). Positive ($\geqslant$500 copies/mL) EBV DNA pre-IC was observed in 352 (75.4%) of the patients.

Survival outcome

With a median follow-up time of 37 months (interquartile range: 30–44 months), the 3-year LRFS, RRFS, DMFS, OS, and PFS rates were 93.6%, 94.3%, 90.9%, 93.7%, and 81.4%. By the time of the last follow-up, a total of 32 patients died. Treatment failure was observed in 78 patients, including 36 patients with locoregional recurrences alone, 30 with distant metastasis alone, and 12 with both locoregional recurrence and distant metastasis.

Determination of optimal cutoff values and correlation analysis

According to the ROC analysis, the optimal cutoff value of SUV NTR was 0.74 for the prediction of distant metastasis. The area under the curve (AUC) was 0.619 [95% confidence interval (CI): 0.541–0.697, $p=0.011$]. The sensitivity, specificity, positive predictive value, and negative predictive value at this value were 90.5%, 35.4%, 58.3%, and 78.8%, respectively. The correlation analysis showed that SUV NTR was weakly correlated with gender, T category, N category, overall stage, and pre-IC EBV DNA. There was a moderate correlation between SUV NTR and SUV-T or SUV-N. Details are shown in Supplemental Table S1.

Table 1. Patient characteristics ($N=467$).

Characteristics	No. (%)
Gender	
Male	341 (73.0)
Female	126 (27.0)
Age (year)	
Median (range)	50 (13–76)
WHO history type	
Non-keratinizing SCC	452 (96.8)
Keratinizing SCC	2 (0.4)
Others	13 (2.8)
T category	
T1–2	132 (28.3)
T3–4	335 (71.7)
N category	
N1–2	292 (62.5)
N3	175 (37.5)
Overall stage	
III	214 (45.8)
IVa	253 (54.2)
Pre-IC EBV DNA	
<500 copies/mL	115 (24.6)
⩾500 copies/mL	352 (75.4)
Therapeutic schedule	
IC + CCRT	200 (42.8)
IC + RT + AC	156 (33.4)
IC + RT	92 (19.7)
IC + CCRT + AC	19 (4.1)
SUV-T, median (range)	11.2 (3–37)
SUV-N, median (range)	9.6 (1.7–43.5)
SUV NTR, median (range)	0.94 (0.1–6.6)

AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; EBV DNA, Epstein–Barr virus DNA; IC, induction chemotherapy; NTR, lymph node-to-primary tumor ratio; RT, radiotherapy; SCC, squamous cell carcinoma; SUV-N, maximal standardized uptake value of lymph nodes; SUV-T, maximal standardized uptake value of the primary tumor; WHO, World Health Organization.

Prognostic value of SUV NTR on survivals

Univariable analysis showed that N category, overall stage, pre-IC EBV DNA, SUV-N, and SUV NTR were prognostic factors for DMFS. N category, overall stage, SUV-N, and SUV NTR were prognostic factors for RRFS. After controlling for potential confounders, SUV NTR, and overall stage remained independent predictors for DMFS [SUV NTR: hazard ratio (HR): 3.75, 95% CI: 1.33–10.61, $p=0.01$; overall stage: HR: 2.11, 95% CI: 1.02–4.35, $p=0.04$] and RRFS (SUV NTR: HR: 5.42, 95% CI: 1.28–23.07, $p=0.02$; overall stage: HR: 2.64, 95% CI: 1.06–6.56, $p=0.04$). Details are shown in Table 2. Patients with high SUV NTR (⩾0.74) had significantly lower DMFS (3-year rates of 87.5% *versus* 97.4%, $p<0.001$) and RRFS (3-year rates of 92% *versus* 98.7%, $p=0.003$) rates compared to those with low SUV NTR. Patients with stage IVa disease had significantly lower DMFS (3-year rates of 87% *versus* 95.3%, $p=0.002$) and RRFS (3-year rates of 91.6% *versus* 97.3%, $p=0.007$) rates compared to those with stage III disease (Supplemental Figure S1).

RPA risk stratification model based on SUV NTR and the overall stage

Given the independent prognostic value of SUV NTR and overall stage, we established an RPA risk stratification model based on the endpoint of DMFS by combining these two indicators: RPA I (low-risk group): SUV NTR < 0.74 and stage III; (2) RPA II (medium-risk group): SUV NTR ⩾ 0.74 and stage III, or SUV NTR < 0.74 and stage IVa; (3) RPA III (high-risk group): SUV NTR ⩾ 0.74 and stage IVa (Figure 1). The 3-year DMFS rates of patients in the low, medium, and high-risk groups were 98.9%, 93.4%, and 84.2%, respectively ($p<0.001$). The corresponding 3-year RRFS rates were 100%, 95.8%, and 89.9%, respectively ($p=0.001$). Survival curves are shown in Figure 2.

The ROC analysis and DCA indicated that the RPA model has the best predictive efficiency for DMFS and RRFS compared to SUV NTR or the overall stage alone. The AUC for predicting DMFS was 0.685 *versus* 0.619–0.621 and 0.692 *versus* 0.626–0.655 for RRFS (Figure 3 and Supplemental Table S2).

Therapeutic schedule within each RPA group

We further analyzed the effect of different treatment schedules (IC + RT, IC + CCRT, IC +

Table 2. Analyses of clinical variables for DMFS by Cox proportional hazard regression.

Variables	Test for DMFS	Univariable analysis	*p* Value	Multivariable analysis	*p* Value
		HR (95% CI)		HR (95% CI)	
Gender	Female *versus* Male	0.42 (0.18–1.01)	0.05	0.46 (0.19–1.09)	0.08
Age	⩾60 *versus* <60	1.07 (0.53–2.18)	0.85	–	
T category	T3–4 *versus* T1–2	0.74 (0.40–1.34)	0.36	–	
N category	N3 *versus* N1–2	2.56 (1.38–4.75)	<0.01	–	
Overall stage	IVa *versus* III	2.89 (1.42–5.89)	<0.01	2.11 (1.02–4.35)	0.04
Pre-IC EBV DNA	⩾500 *versus* <500	4.76 (1.46–15.50)	0.01	3.16 (0.95–10.45)	0.06
SUV-T	⩾7.95 *versus* <7.95	0.98 (0.50–1.92)	0.96	–	
SUV-N	⩾7.25 *versus* <7.25	3.25 (1.37–7.71)	0.01	–	
SUV NTR	⩾0.74 *versus* <0.74	5.11 (1.82–14.31)	<0.01	3.75 (1.33–10.61)	0.01

CI, confidence interval; DMFS, distant metastasis-free survival; EBV DNA, Epstein–Barr virus DNA; HR, hazard ratio; IC, induction chemotherapy; NTR, lymph node-to-primary tumor ratio; SUV-N, maximal standardized uptake value of lymph nodes; SUV-T, maximal standardized uptake value of the primary tumor.

RT + AC) in each RPA group. The results showed no significant difference in DMFS among patients treated with different treatment schedules in the low- and high-risk groups (RPA I and RPA III). In the medium-risk group (RPA II), the DMFS of patients treated with IC + CCRT was higher than those treated with IC + RT (3-year rates of 95.7% *versus* 86.9%, $p = 0.059$). However, the difference did not reach statistical significance. For RRFS, there was no significant difference among patients with different treatment schedules in the low- and medium-risk groups (RPA I and RPA II). However, in the high-risk group (RPA III), patients treated with IC + CCRT had a significantly higher RRFS rate than those treated with IC + RT + AC (3-year rates of 98.4% *versus* 80.5%, $p = 0.02$). Survival curves are shown in Supplemental Figure S2.

Discussion

In this study, we analyzed the prognostic value of pretreatment SUV NTR in 467 patients with LA-NPC. We found that SUV NTR was an independent prognostic factor for DMFS and RRFS. Then we established an RPA model based on SUV NTR and the TNM stage, which could effectively predict distant metastasis and regional recurrence. ROC analysis showed that the RPA model had improved prediction efficiency than SUV NTR or the TNM stage alone. Our data are important since it is the first study with a large cohort to show the prognostic value of SUV NTR combined with the eighth edition of the TNM staging system in patients with LA-NPC treated with IC.

SUVmax may be affected by many factors, including blood glucose, liver and kidney function, injection dose, injection-to-scanning time, scanning speed, and partial volume effect.[23] By contrast, SUV NTR was relatively stable and conducive to comparing different patients. In addition, SUV NTR could reflect the heterogeneity between metastatic lymph nodes and primary tumors.[13] Several retrospective studies[13–16] showed that SUV NTR was an independent predictor of distant metastasis for NPC. However, these studies were mainly based on the CCRT treatment mode. Our study aimed to explore the prognostic value of SUV NTR under the new treatment pattern of IC combined with IMRT. The results showed that SUV NTR remained an effective predictor for distant metastasis and regional recurrence. In addition, the RPA risk stratification model based on SUV NTR displayed improved predictive efficiency in distant metastasis and regional recurrence. The RPA model may help to guide individualized treatment of NPC.

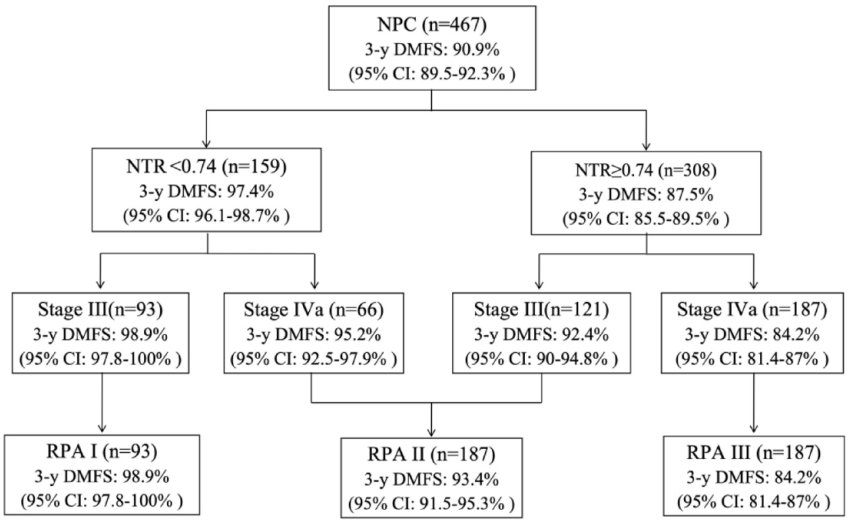

Figure 1. Development of an RPA risk stratification model based on SUV NTR and overall stage for patients with LA-NPC treated with induction chemotherapy.
CI, confidence interval; DMFS, distant metastasis-free survival; LA-NPC, locoregionally advanced nasopharyngeal carcinoma; NTR, lymph node-to-primary tumor ratio; SUV, standardized uptake value.

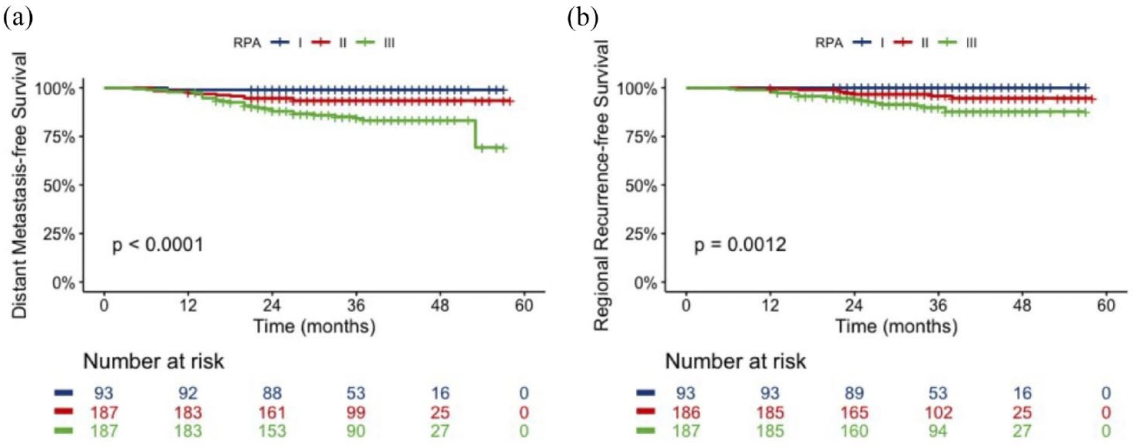

Figure 2. Kaplan–Meier curves for (a) DMFS and (b) RRFS stratified by the RPA risk stratification model.
DMFS, distant metastasis-free survival; RPA, recursive partitioning analysis; RRFS, regional recurrent-free survival.

In the subgroup analysis, we found that the DMFS of patients treated with IC + CCRT was higher than those treated with IC + RT (3-year rates of 95.7% *versus* 86.9%, $p = 0.059$). However, the difference did not reach statistical significance. No significant difference was found in the high-risk group. Possible reasons included the following: (1) The number of cases in each treatment group was relatively small and (2) the current treatment intensity was still insufficient to improve the DMFS for high-risk patients, and more effective systemic treatment was needed. In addition, we found that the RRFS of high-risk patients was significantly higher in the IC + CCRT group than in the IC + RT + AC group. We attributed this to the radiosensitization of CCT. Since the results were subgroup analysis and the number of cases in each subgroup was relatively small, no conclusion could be reached from the present study. Prospective studies were needed.

Many studies have shown that pretreatment of EBV DNA was an effective predictor of DMFS for NPC.[24–26] In our research, the univariable

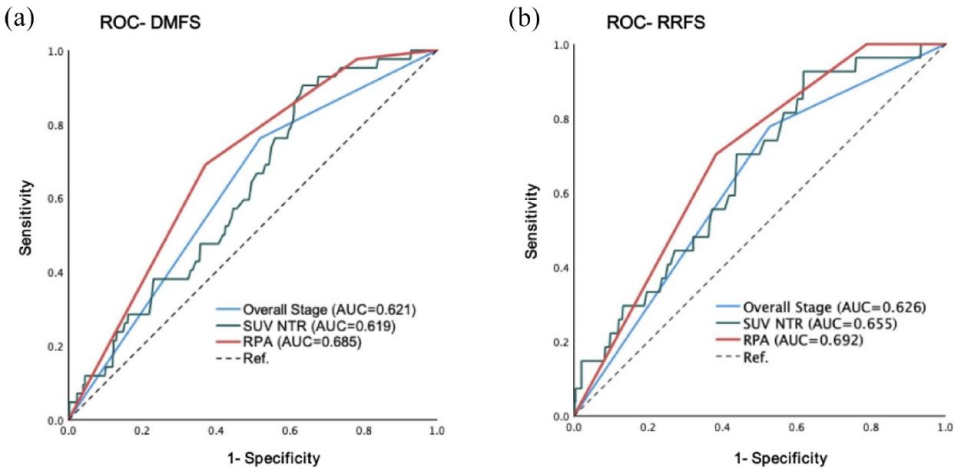

Figure 3. ROC curves comparing the accuracy of the RPA model with SUV NTR and the TNM stage for predicting (a) DMFS and (b) RRFS.
DMFS, distant metastasis-free survival; NTR, lymph node-to-primary tumor ratio; ROC, receiver operating characteristic; RPA, recursive partitioning analysis; RRFS, regional recurrent-free survival; SUV, standardized uptake value.

analysis showed that pre-IC EBV DNA was a potential predictor of DMFS. However, the predictive role disappeared in multivariable analysis. We attributed that to the change of treatment mode since previous studies were mostly based on the CCRT mode, while all patients in our study received IC-based treatment. We speculated that the function of clearing micrometastasis and improving DMFS of IC might reduce the predictive effect of pre-IC EBV DNA. Recently, several studies showed that post-IC EBV DNA was an effective biomarker for LA-NPC.[27–30] There might be an improved performance with the combination of SUV NTR and post-IC EBV DNA for LA-NPC. Further investigations were warranted.

Limitations of our study included its retrospective nature, conducted in a single institution, lack of validation cohort, utilization of multiple strategies, and short follow-up time, which may have the results underpowered. Further research was warranted to validate our results. Despite these limitations, our study is still important since it is the first study with a large cohort to show the prognostic value of SUV NTR combined with TNM stage in patients with LA-NPC treated with IC.

Conclusion

In conclusion, our study demonstrated that SUV NTR was a prognostic biomarker for patients with LA-NPC treated with IC. We developed an RPA risk stratification model based on SUV NTR, which provided improved predictive efficiency for DMFS and RRFS over the eighth edition of the TNM staging system. Studies on optimal individualized treatment and disease surveillance for patients within different risk groups are needed.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of SCC (No. 2009224-1). Informed consent was waived.

Consent for publication

Not applicable.

Author contributions

Fang-Fang Kong: Conceptualization; Formal analysis; Investigation; Writing – original draft.

Guang-Sen Pan: Data curation; Investigation; Methodology; Validation; Writing – original draft.

Meng-Shan Ni: Investigation; Project administration; Software; Writing – original draft.

Cheng-Run Du: Formal analysis; Investigation; Methodology; Software; Visualization; Writing – review & editing.

Chao-Su Hu: Conceptualization; Writing – review & editing.

Hong-Mei Ying: Conceptualization; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supplemental material
Supplemental material for this article is available online.

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