**Original article**

# Prognostic value of node-to-primary tumor maximum standardized uptake value ratio in T1-4N1-3M0 non-small cell lung cancer patients treated with concurrent chemo-radiotherapy

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**Background** This study aimed to identify whether NTR is the independent risk factor for progression-free survival (PFS) and overall survival (OS) in patients treated with concurrent chemo-radiotherapy (cCRT).

**Methods** We retrospectively studied 106 T1-4N1-3M0 non-small cell lung cancer patients treated with cCRT. The maximum standardized uptake value (SUVTumor) of the primary tumor and the metastatic lymph nodes (SUVLN) were measured. The prognostic significance of NTR for predicting PFS and OS was assessed. A multi-adjusted spline regression model was conducted to provide more precise estimates and examine the shape of the associations between NTR and the risk of progression.

**Results** From 2012 to 2017, 106 eligible patients were analyzed. The median follow-up time was 15.3 months (3.5–44.6 months). We determined the maximizing area under the time-dependent receiver operating characteristic curve was at an NTR of 0.73 for predicting PFS. The two-year PFS was significantly lower in the high-NTR group (35.7% vs. 55.4%, $P = 0.02$) and two-year OS (43.4% vs. 61.1%, $P = 0.03$ was also significantly worse. Multivariable analysis revealed that only NTR was an independent prognostic factor for PFS (hazard ratio [HR]: 10.04, $P < 0.001$) and OS (HR: 4.19, $P = 0.03$). The restricted cubic spline regression model showed that NTR had a non-linear relationship with log relative risk for progression.

**Conclusion** NTR was an independent risk factor for predicting PFS and OS in T1-4N1-3M0 non-small cell lung cancer patients treated with cCRT. *Nucl Med Commun* 43: 901–907 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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## Introduction

Lung cancer remains the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 83% of lung cancer [1,2]. The prognosis of locally advanced NSCLC patients who received chemoradiation remains poor, with a median progression-free survival (PFS) of only 8.1–9.1 months, and median overall survival (OS) of 20.6–21.8 months [3]. Due to the poor prognosis of NSCLC, medical research various imagine parameters for prediction of NSCLC clinical results. As a combination of functional imaging and anatomical imaging, 18F-FDG PET/CT has been widely used in the diagnosing, staging, evaluation of treatment efficacy and prognosis of NSCLC [4–6]. Maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) had been proved to be important prognostic factors for predicting clinical outcome [7,8].

In addition to these traditional PET parameters, several recent studies investigated the role of a ratio parameter called the ratio of maximum standardized uptake value (SUV) of metastatic lymph nodes to primary tumor (NTR) [9–12]. Several studies had found that the patients with relatively high NTR are significantly associated with poor outcomes, suggesting that the NTR has different behaviors between tumors with higher and lower metastatic potential [10,12]. However, few studies investigated the prognostic value of NTR in NSCLC patients treated with concurrent chemo-radiotherapy. This study aimed to evaluate the prognostic value of lymph node to primary tumor SUV ratio in T1-4N1-3M0 NSCLC patients treated with concurrent chemo-radiotherapy.

## Materials and methods
### Patient

The institutional review boards of the First Affiliated Hospital of Zhejiang University approved this retrospective

study, and the requirement to obtain informed consent was waived. From January 2012 to December 2017, 106 consecutive patients with T1-4N1-3M0 stage confirmed by bronchoscope histopathology and $^{18}$F-FDG PET/CT were included in this study. The pretreatment workup included chest contrast-enhanced CT, fiberoptic bronchoscopy with transbronchial needle aspiration (TBNA), serum tumor markers and FDG PET/CT. Patients were excluded from the study by the criteria: (1) received neoadjuvant radiotherapy or chemotherapy, (2) received other treatment such as target therapy, immunotherapy and (3) with a history of another malignant tumor.

After pretreatment evaluation, every patient received concurrent chemo-radiotherapy. For radiotherapy, a stereotactic body radiotherapy technique was used in all patients. Gross tumor volume encompassed the primary NSCLC lesion and lymph nodes that were considered to be positive for malignant involvement by FDG PET/CT and TBNA findings. The total cumulative doses for the gross tumor volume were between 45 and 65 Gy. The chemotherapy regimen consisted of cisplatin or carboplatin with paclitaxel or pemetrexed-based doublet therapy, and was performed concurrently with radiotherapy or sequentially after radiotherapy. For the first 3 years after treatment, all patients underwent follow-up examinations that included history taking, contrast-enhanced chest CT, and serum tumor markers at 3-month intervals. Afterward, follow-up studies were performed every 6 months. Once abnormal finding was found, further diagnostic studies were performed, and if feasible, a biopsy was performed to histopathologically confirm the cancer progression. The median follow-up period was 15.3 months (2.4–56.6 months). In all patients diagnosed with disease progression or newly developed metastatic lesions, further palliative treatment was performed according to the clinical condition of the patients and recurrent sites.

### FDG PET/CT protocol
The patients fasted at least 6 hours before examination and the blood glucose concentration was not higher than 110 mg/dl. $^{18}$F-FDG PET/CT images were acquired from a Siemens PET/CT Biograph 16 (Siemens Medical Solutions) and were performed approximately 60 minutes after IV injection of $^{18}$F-FDG with the dosage of 4.44–5.55 MBq/kg. A low-dose unenhanced CT scan was performed from the skull base to the middle of the thigh, with the following parameters: 120 kV, 80 mA, the pitch of 0.829, tube rotation time of 0.5 seconds per rotation, and reconstruction thickness and interval of 5.0 mm, for precise anatomical localization and attenuation correction, and was followed by the PET scan that matched the CT section thickness. The PET images were obtained using the ordered subset expectation maximization method. All collected images were transferred into Syngo workstation (Siemens Medical Solutions) to reconstruct PET, CT and PET/CT fusion images.

### Image analysis
The primary tumor length was measured on the CT images. PET images were interpreted by an experienced radiologist on the MEDEX workstation system and the regions of interest (ROI) were drawn manually on the original site of the tumor and the metastatic lymph nodes. The metastasic lymph nodes are diagnosed by visual assessment in $^{18}$F-FDG PET/CT and contrast-enhanced chest CT and were correlated with, if available, the TBNA finding. The standard uptake maximum value within the ROI (SUVmax) of primary tumor and metastasic lymph nodes was automatically measured. NTR was calculated by dividing the lymph node by primary tumor maximum SUV for each patient.

### Statistical analysis
Cutoff NTR value is determined by the maximizing area under the time-dependent receiver operating characteristic (ROC) curve for predicting PFS. To assess the differences in baseline characteristics according to the NTR stratification, continuous variables were evaluated by Mann–Whitney $U$ tests and categorical variables were evaluated by Pearson's chi-square test or Fisher's exact test as appropriate. To assess the predictive values of variables for PFS and OS, univariate and multivariate analyses were performed using a Cox proportional hazards regression model. Survival time was defined as the time from the day of initiation of chemo-radiotherapy to the day of detection of disease progression (for PFS) or death (OS), or the day of the last follow-up visit to our hospital. The patients were classified as having disease progression when the size of known malignant lesions was increased by 20% or more, or a newly developed metastatic lesion was found on follow-up imaging studies according to the Response Evaluation Criteria In Solid Tumors criteria version 1.1. Of the variables in univariate analysis, those with a $P$-value of <0.05 were included in multivariate analysis. For NTR, survival curves were estimated with the Kaplan–Meier method and compared with the log-rank test. $P < 0.05$ was considered statistically significant. A multi-adjusted spline regression model was conducted to provide more precise estimates and examine the shape of the associations between NTR and the risk of progression. All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, Massachusetts).

## Results
### Determination of cutoff value and patients' characteristics
The cutoff NTR value at 0.73 is determined by the maximizing area under the time-dependent ROC curve for predicting PFS, and the area under the curve was 0.803 [95% confidence interval (CI) 0.719–0.886, Fig. 1]. The sensitivity was 82.2% and the specificity was 62.3%.

The characteristics of the enrolled patients were shown in Table 1. A total of 106 patients with T1-4N1-3M0 NSCLC were included in this study, including 57 males and 49 females, with an average age of 63.2 years. According to the cutoff value of NTR, the patients were divided into two groups. After the grouping, there were 52 patients in the low-NTR group and 54 patients in the high-NTR group, respectively. Patients with low and high NTR seemed to be similar in most characteristics except for SUVtumor and $SUV_{LN}$. Of the 106 enrolled patients, 74 (69.8%) experienced disease progression and 64 (60.4%) died during the clinical follow-up.

### Prognostic value of lymph node to primary tumor maximum standardized uptake value ratio

The age, sex, histological type, histological grade, tumor stage, nodal stage, SUVtumor, $SUV_{LN}$, NTR of all patients were evaluated in the univariate analysis (Table 2). Tumor stage, nodal stage, $SUV_{LN}$ and NTR showed significance in predicting PFS ($P < 0.05$ for all). For OS, tumor stage and NTR were significant prognostic factors ($P < 0.05$ for all). Among the variables, those with a $P$-value of <0.05 in the univariate analysis were selected for multivariate analysis. In multivariate analysis (Table 3), only NTR were determined to be independent prognostic factors for PFS ($P < 0.001$) and for OS ($P = 0.03$). Tumor stage, nodal stage, $SUV_{LN}$ failed to show significance in predicting PFS in multivariate analysis. Tumor stage failed to show significance in predicting OS in multivariate analysis.

### Kaplan−Meier survival analysis

For Kaplan−Meier survival analysis (Fig. 2), NTR was divided into two categories according to the cutoff value of 0.73 which was determined by the time-dependent ROC curve analysis. Kaplan−Meier analysis of patients stratified by NTR cutoff value showed significantly worse 2-year PFS (35.7% vs. 55.4%, $P = 0.02$) and OS 43.4% vs. 61.1%, $P = 0.03$) in patients with high NTR (≥0.73) than in those with low NTR (<0.73).

### Restricted cubic spline analysis

The spline regression (Fig. 3) showed that NTR had a non-linear relationship with log relative risk for progression. The restricted cubic regression spline analysis was in concordance with the multivariable cox proportional hazards models regarding the relationship between NTR and the risk of progression.

## Discussion

The present study demonstrated that NTR is an independent prognostic factor in T1-4N1-3M0 NSCLC patients treated with concurrent chemo-radiotherapy. In multivariate survival model including tumor factor (tumor stage), metastatic lymph node factors (nodal stage and $SUV_{LN}$), NTR was found to be the independent prognostic factor for PFS and OS. We demonstrated that the patients with NTR ≥0.73 had a higher risk of developing disease progression and also a higher risk of mortality.

**Fig. 1**
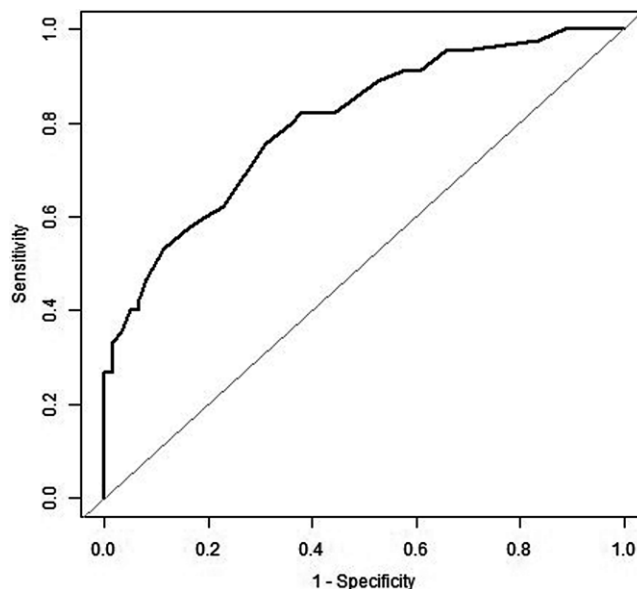


Time-dependent receiver operating characteristic (ROC) curve analysis of progression-free survival prediction according to the node-to-tumor ratio of SUV (NTR). The area under the curve was 0.803 [95% confidence interval (CI) 0.719–0.886]. The best NTR cutoff value was 0.73 for prediction of disease progression. NTR, node-to-tumor SUV ratio.

**Table 1 Patient characteristics before and after grouping by node-to-tumor SUV ratio**

| | | Cohort (n = 106) | Low-NTR (n = 52) | High-NTR (n = 54) | P value |
|---|---|---|---|---|---|
| Sex | Male | 57 (54%) | 32 (62%) | 25 (46%) | 0.731 |
| | Female | 49 (46%) | 20 (38%) | 29 (54%) | 0.965 |
| Age at diagnosis | | 63.2 [43.0–76.8] | 61.5 [43.0–74.6] | 62.7 [45.1–76.8] | |
| Differentiation | Well to Moderate | 73 (69%) | 33 (63%) | 40 (74%) | 0.238 |
| | Poor | 33 (31%) | 19 (37%) | 14 (26%) | |
| Tumor stage (AJCC 7th edition) | T1 | 44 (13%) | 9 (17%) | 5 (9%) | 0.095 |
| | T2 | 62 (30%) | 17 (33%) | 15 (28%) | |
| | T3 | 30 (28%) | 15 (29%) | 15 (28%) | |
| | T4 | 30 (28%) | 11 (21%) | 19 (35%) | |
| Nodal stage (AJCC 7th edition) | N1 | 16 (15%) | 9 (17%) | 7 (13%) | 0.005 |
| | N2 | 50 (47%) | 25 (48%) | 25 (46%) | |
| | N3 | 40 (38%) | 18 (35%) | 22 (41%) | |
| SUVTumor | | 13.6 [2.9–25.7] | 13.3 [6.6–22.5] | 14.1 [2.9–25.7] | 0.106 |
| $SUV_{LN}$ | | 8.9 [2.1–24.3] | 6.5 [2.1–12.8] | 12.4 [7.2–24.3] | <0.001 |
| NTR | | 0.69 [0.14–2.30] | 0.49 [0.14–0.65] | 0.88 [0.66–2.30] | <0.001 |

NTR, node-to-tumor SUV ratio; $SUV_{LN}$, maximal SUV of metastatic node; SUVTumor, maximal SUV of primary tumor.

**Fig. 2**
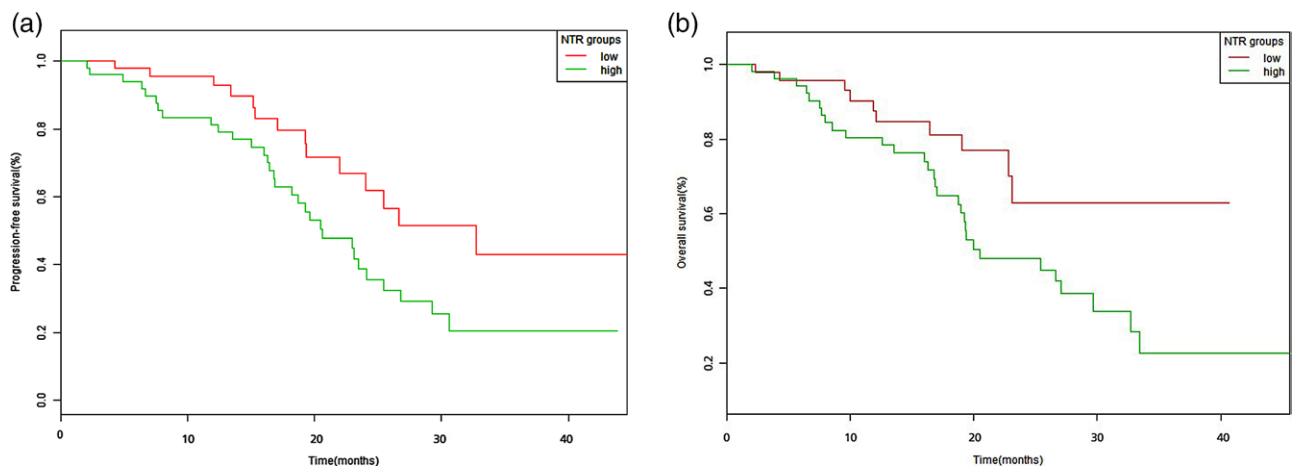


The Kaplan–Meier estimates of (a) progression-free survival (PFS) and (b) overall survival (OS) for patients with NTR ≥ 0.73 (green line) vs. NTR < 0.73 (red line). High NTR (≥0.73) predicted for worse outcomes than low NTR (<0.73) on PFS (2-year: 35.7% vs. 55.4%, $P = 0.02$) and OS (2-year: 43.4% vs. 61.1%, $P = 0.03$). NTR, node-to-tumor SUV ratio.

There are many risk factors for cancer prognosis. Previous studies had indicated that many easy-to-use PET parameters could be a surrogate marker of tumor aggressiveness [13,14]. Many researchers have reported on the role of SUVmax as a prognostic indicator in primary lung cancer [15–18]. However, other studies have failed to find a correlation between pretreatment of SUVmax and subsequent tumor treatment response or survival in patients with NSCLC [18–22]. An important problem with SUVmax is it reflects the highest metabolic pixels within the tumor, which does not necessarily represent the overall metabolic state of the tumor. This problem is particularly important when tumor FDG uptake is highly heterogeneous and most tumors' SUV much lower than SUVmean.

Because of the limitations of SUVmax, volume-based PET parameters such as MTV and TLG are being used. While SUVmax represents the FDG activity of a single pixel, volume-based PET parameters can assess the FDG activity of the whole tumor. MTV and TLG can be used to estimate FDG activity throughout the body to determine the patient's total tumor load as MTV and TLG from multiple lesions can be added together. Several studies have shown that volume-based PET parameters are important predictors of NSCLC survival, even when the SUVmax or SUVmean of the primary tumor has no predictive value [23–26]. Hyun and colleagues [25] evaluated the prognostic impact of volume-based metabolic parameters in 161 NSCLC patients surgically resected after neoadjuvant concurrent radiotherapy and chemotherapy treatment. Multivariate analysis showed the higher pretreatment total MTV was significantly associated with shorter DFS ($P = 0.036$) and OS ($P = 0.012$). In contrast, There was no significant correlation between the SUVmax of primary tumor and DFS and OS.

However, these parameters could be affected by various factors, such as time dependence, dose calibration, and

**Fig. 3**
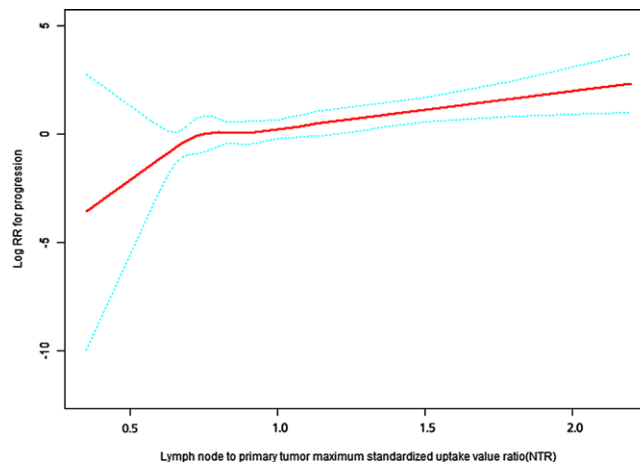


Association of NTR levels with risk of progression. Dashed lines are 95% confidence intervals. Hazards ratios and 95% confidence intervals derived from restricted cubic spline regression. Hazards ratios were estimated using logistic regression modeling, adjusting for the same variables in Table 3. NTR, node-to-tumor SUV ratio.

**Table 2  Univariable analysis of clinical variables with Cox proportional hazard model for progression-free survival and overall survival**

| Variables | PFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Sex (vs. male) | | | | |
| Female | 0.96 (0.39–2.37) | 0.733 | 1.79 (0.66–4.84) | 0.252 |
| Age (year) | 1.10 (0.47–2.58) | 0.833 | 2.07 (0.79–5.44) | 0.142 |
| Histopathology (vs. squamous cell carcinoma) | | | | |
| Adenocarcinoma | 1.04 (1.00–1.08) | 0.032 | 1.05 (0.95–1.16) | 0.385 |
| Differentiation (vs. well to moderate) | | | | |
| Poorly differentiated | 0.61 (0.27–1.40) | 0.245 | 0.73 (0.33–1.61) | 0.436 |
| Tumor stage (vs. T1) | | | | |
| T2 | 1.03 (0.35–3.07) | 0.954 | 1.01 (1.00–1.02) | 0.027[a] |
| T3 | 3.34 (1.23–9.08) | 0.018[a] | 2.96 (1.04–8.41) | 0.042[a] |
| T4 | 5.90 (1.69–20.59) | 0.005[a] | 5.51 (2.08–14.64) | 0.001[a] |
| Nodal stage (vs. N1) | | | | |
| N2 | 1.10 (0.36–3.37) | 0.869 | 1.25 (0.66–2.38) | 0.499 |
| N3 | 5.09 (1.44–17.96) | 0.011[a] | 2.45 (0.73–8.16) | 0.145 |
| SUVTumor | 1.52 (0.70–3.31) | 0.291 | 1.21 (0.48–3.04) | 0.689 |
| SUV$_{LN}$ | 1.06 (1.01–1.11) | 0.009[a] | 1.89 (0.90–4.60) | 0.089 |
| NTR [vs. low NTR (<0.73)] | | | | |
| High NTR (≥0.73) | 7.17 (2.09–24.51) | 0.002[a] | 8.47 (2.93–24.50) | <0.001[a] |

CI, confidence interval; NTR, node-to-tumor SUV ratio; SUV$_{LN}$, maximal SUV of metastatic node; SUVTumor, maximal SUV of primary tumor.
[a]Significance SUVTumor, SUV$_{LN}$ and NTR.

interstudy variability of the arterial input function, which adversely affect the reliability of the SUV as a surrogate of the metabolic rate of glucose consumption [27–29]. It has been recognized that part of the problems can be eliminated if tumor SUV is normalized by using the tumor-to-liver ratio or tumor-to-blood ratio [30,31]. However, these normalized parameters only reflect the metabolic activity of the primary tumor, which has prognostic value for patients without metastasis.

Theoretically, NTR could be the easy-to-use PET parameter for predicting locally advanced cancer patients. Hung *et al.* [32] conducted a study to evaluate the prognostic value of NTR in nasopharyngeal carcinoma. In their report, multivariable analysis showed that NTR was an independent

prognostic factor for distant metastasis-free survival (hazard ratio 2.20, 95% CI 1.20–4.03, *P* = 0.011). Similarly, it has been demonstrated that NTR was an independent factor for predicting prognosis in unresectable esophageal cancer [10], endometrioid endometrial carcinoma [11], and invasive ductal breast cancer [33]. Kaira *et al.* [34] found that higher ratio of SUVmax of the metastatic tumor to the primary tumor (M/P ratio) portended lower response to initial chemotherapy and poorer survival (PFS and OS) in stage IIIB and IV NSCLC patients [22]. However, this study did not explore the prognosis value of M/P ratio of metastatic tumor to the primary tumor (M/P ratio) in stage II or IIIA NSCLC patients with lymph node metastasis. The main advantage of our study was that we used restricted

**Table 3　Multivariable analysis of clinical variables with Cox proportional hazard model for progression-free survival and overall survival**

| Variables | PFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Nodal stage (vs. N1) | 1.82 (0.40–8.22) | 0.44 | | NS |
| Tumor stage (vs. T1) | 1.94 (0.70–5.33) | 0.20 | 1.35 (0.57–3.11) | 0.45 |
| $SUV_{LN}$ | 1.25 (0.66–2.38) | 0.50 | | NS |
| NTR [vs. low NTR (<0.73)] | | | | |
| High NTR (≥0.73) | 10.04 (2.6–37.81) | <0.001 | 4.19 (1.16–15.08) | 0.03 |

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a]Significance PFS, OS and HR.

cubic spline regression to highlight a non-linear relationship between NTR and progression risk after adjusting for various confounding factors. A better understanding of NTR can help clinicians predict the prognosis of locally advanced lung cancer and select more appropriate treatments for patients.

However, this study had several limitations. First, the study was a retrospective single-center study with a relatively small number of patients. Further studies are needed to validate the results of this study. Second, because we only enrolled patients who had locally advanced NSCLC underwent concurrent chemo-radiotherapy, the prognostic value of NTR in other types of treatment (such as target therapy, immunotherapy) is unknown. Finally, we suppose that if the metastatic tumor of lymph nodes has higher metabolic activity than primary tumor, it may indicate higher distant metastatic potential and may eventually lead to a poorer outcome. However, this hypothesis needs further fundamental biological study to prove.

In conclusion, NTR was an independent risk factor for predicting PFS and OS in T1-4N1-3M0 NSCLC patients treated with concurrent chemo-radiotherapy. Patients with low NTR had a better prognosis than those with high NTR. NTR can be used as a biomarker for stratifying the prognosis of cancer patients.

## Acknowledgements

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Due to the retrospective nature of the study, no formal approval from the ethics committee was required according to our national legislation.

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

## Conflicts of interest

There are no conflicts of interest.

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