The Utility of ^{18}F-FDG-PET–CT Metabolic Parameters in Evaluating the Primary Tumor Aggressiveness and Lymph Node Metastasis of Nasopharyngeal Carcinoma

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ABSTRACT

BACKGROUND: Following changes in primary tumor (T) and lymph node (N) staging for nasopharyngeal carcinoma (NPC) in the *Eighth Edition AJCC Cancer Staging Manual*, simplification of T staging has been proposed. However, a limited range of 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography–computed tomography (^{18}F-FDG PET–CT) metabolic parameters has been investigated. Therefore, we aimed to evaluate the primary tumor invasiveness and the lymph node metastasis (LNM) of NPC from a metabolic perspective.

METHODS: A total of 435 NPC patients underwent ^{18}F-FDG PET/CT before treatment were retrospectively examined. The primary endpoint was differences in standard uptake value (SUV), lean body mass-normalized SUV (SUL), body surface area-normalized SUV (SUS), glucose-normalized SUV (GN), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and glucose-normalized total lesion glycolysis (GNTLG) of primary tumors and LNM between different T and N stages. The metabolic parameters associated with T and N staging were identified.

RESULTS: There were significant differences between all parameters relative to the primary tumor but no significant differences in any parameter relative to the LNM and T stages. Higher mean values of TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ were associated with advanced T stages. Higher mean values of all the LNM parameters were associated with more advanced N stages. Only primary tumor metabolic tumor volume (TMTV), $TSUV_{peak}$, $TSUL_{max}$, and $TSUS_{max}$ showed a significant positive association with T staging, while lymph node metabolic tumor volume (LNMTV) and $TSUS_{max}$ were significantly positive in N staging.

CONCLUSIONS: Our findings suggest that metabolic parameters are useful indicators of tumor invasiveness and LNM based on the Eighth Edition manual. Compared with volume-dependent parameters, TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ may be better indicators of local tumor aggressiveness. SUS_{max} of the primary tumor was associated with LNM. In addition to SUV_{max}, other metabolic parameters (eg, SUL_{max}, SUS_{max}, GN_{max}, and GN_{mean}) could evaluate tumor aggressiveness and LNM better.

KEYWORDS: Nasopharyngeal carcinoma, ^{18}F-FDG PET–CT, metabolic parameters, primary tumor aggressiveness, lymph node metastasis

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Introduction

Nasopharyngeal carcinoma (NPC) exhibits clear geographical distribution patterns, especially in East and Southeast Asia.[1] The geographical global distribution of NPC is extremely unbalanced with over 70% of new cases diagnosed in eastern and southeast Asia corresponding to a 5-year prevalence (all ages) of 12.91 cases per 100 000 in China.[2] With the advancement of radiotherapy technology, induction and concurrent chemotherapy, and the development of an accurate staging system, the treatment of NPC has continuously improved.[1]

In 2017, the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) revised the staging system for NPC[3] in the *Eighth Edition AJCC Cancer Staging Manual*. The *Eighth Edition AJCC Cancer Staging Manual* is currently the most common prognostic tool for NPC and remains the most influential resource for guiding treatment, assessing the treatment response, comparing outcomes between different institutions, and academic research. The main changes to T staging in the Eighth Edition are as follows: medial pterygoid, lateral pterygoid, or prevertebral muscle involvement was included in T2, cervical vertebral invasion was included in T3, and the ambiguous terms infratemporal fossa/masticator space invasion was removed and replaced with extensive soft tissue invasion (soft tissue outside the lateral pterygoid muscle and parotid gland) in T4.[4] Regarding N staging changes, stages N3a and N3b in the Seventh Edition were merged into a single stage, N3, and the N3 criterion was changed to "below the caudal border of cricoid cartilage."[4] However, some studies have expressed support for these changes,[5-9] while others have not.[10-14] Many studies have shown that N staging is reasonable[5-9] while T staging needs further improvement.[10-14] A comparative assessment was conducted by Li et al[11] on the 5-year overall survival (OS) and progression-free survival (PFS) of individuals diagnosed with NPC who presented severe skull base invasion (SBI) versus those with slight SBI. Their results suggested that patients

with slight SBI experienced improved outcomes and that the OS and PFS of patients with slight SBI is not significantly improved by additional induction chemotherapy therapy. They advised to downgrade the stage of NPC patients with mild SBI from T3 to T2 stage. This suggestion could potentially address the issue of conflicting prognoses for T2 and T3 stages and indications for using induction chemotherapy. Pan et al[14] have simplified T stage as the use of 17 anatomical structures in the Eighth Edition is too complicated, its popularization and application are greatly limited. The differences in local control and survival between T stage have narrowed down due to the advances in diagnostics and treatment. Therefore, some studies have proposed the simplification of T staging.[14,15]

Magnetic resonance imaging (MRI) is the preferred imaging technique for assessment, staging, evaluating treatment effectiveness, and monitoring NPC progression due to its advantages of high soft tissue resolution, multiparametric imaging, and non-ionizing radiation.[16] However, 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography–computed tomography (^{18}F-FDG PET–CT) surpasses MRI in accuracy in the identification of cervical nodal metastases, and should therefore be the preferred reference for assessing the metastases of the neck. ^{18}F-FDG PET–CT demonstrates proficient diagnostic accuracy and a low false positive rate in identifying distant metastases, rendering it a viable substitute for conventional approaches. The National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology currently recommend ^{18}F-FDG PET–CT as a proven imaging strategy in NPC management.[16,17]

^{18}F-FDG PET–CT parameters offer metabolic information that can be used to evaluate tumor aggressiveness,[18-20] predict lymph node metastasis (LNM)[21-23] and may be correlated with patient survival.[24] The maximum standard uptake value (SUV_{max}) is the most commonly used metabolic parameter. SUV_{max} is an averaged value of the tracer uptake in sufficient numbers of cancer cells and other cells in the most metabolically aggressive part of the potentially heterogeneous tumor. The limitation of SUV_{max} is that it only represents the maximum uptake within the volume of interest (VOI) and not the entire mass. The use of ^{18}F-FDG-PET–CT parameters reflecting tumor size and metabolic information, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), has been proposed to overcome the limitation. MTV and TLG have been acknowledged as useful indicators for tumor aggressiveness, LNM, and patient survival for various tumors. MTV is defined as the total number of voxels exceeding the predetermined SUV threshold within the VOI, while TLG is calculated by multiplying the MTV by the mean of SUV (SUV_{mean}).[25] Other metabolic parameters, such as the maximum lean body mass (LBM)-normalized SUV (SUL_{max}),[26] maximum body surface area (BSA)-normalized SUV (SUS_{max}),[27] maximum glucose-normalized SUV (GN_{max}), GN_{mean}, and glucose-normalized total lesion glycolysis (GNTLG),[28] have rarely been utilized in previous studies.

Given the changes to T and N staging, and the few[18] F-FDG PET–CT metabolic parameters investigated in previous studies, the main objectives of this study were to evaluate the primary tumor invasiveness and the LNM in the new staging system by comparing metabolic parameters of primary tumors and LNM of different T and N stages. We also aimed to determine the relationship between metabolic parameters and T and N stages to provide reference values for future research.

Patients and Methods

Patients

The clinical records of all patients with NPC with undifferentiated carcinoma diagnosed between June 2016 and January 2020 at Jiangsu Cancer Hospital, Nanjing, China, were investigated. Carcinoma staging was based on the *Eighth Edition AJCC Cancer Staging Manual*, and patients who were not staged according to the latest staging system were re-staged by clinicians according to the Eighth Edition manual. Only patients who had undergone MRI of the neck were eligible. All patients provided written informed consent to participate before the initiation of the study. The Ethics Committee of Jiangsu Cancer Hospital approved this study (protocol code 2022kk026 and date of approval: April 22, 2022).

PET–CT imaging

All patients underwent examination with a PET–CT scanner (Discovery 710; GE Medical Systems, Waukesha, Wisconsin, USA). Intravenous administration of ^{18}F-FDG (0.1–0.2 mCi/kg) was performed in patients who fasted for a minimum period of 6 hours. Before injection, blood glucose concentrations were measured to ensure that they were less than 11 mmol/L. During the radiotracer distribution, patients rested in the waiting room and orally ingested approximately 1 000 mL of water. The patients were instructed to urinate immediately before the examination. PET–CT image acquisition started 50–70 minutes after ^{18}F-FDG injection. CT and PET scan parameters were as follows: vertex to mid-thigh scanning range, 140 kV tube voltage, auto mA (noise index, 28.5) tube current, 0.8 second rotation time, 3.75 mm slice thickness, 2 minutes/bed position emission scan time, and six to seven bed positions scanning range. The acquired PET images were reconstructed with an iterative reconstruction algorithm (VUE point FX + SharpIR: iteration = 2; subset = 24) with CT-based attenuation correction. Images were analyzed on the workstation (Advanced Workstation AW 4.6, GE HealthCare, Chicago, IL, USA).

PET–CT image analysis

An experienced nuclear medicine physician analyzed the images. VOIs were placed around the primary tumor and LNM. Methods for the placement of VOI have been described

Table 1. Clinical characteristics of patients with stages I–IV nasopharyngeal carcinoma.

	I	II	III	IVA	IVB
Number, %	15 (3.45%)	71 (16.32%)	164 (37.70%)	157 (36.09%)	28 (6.44%)
Sex (M/F)	(11/4)	(53/18)	(121/43)	(112/45)	(24/4)
Age (years)	49.07 ± 9.49	50.73 ± 11.50	50.59 ± 11.74	49.48 ± 12.18	52.57 ± 11.86
Height (cm)	169.87 ± 7.33	168.28 ± 7.21	167.81 ± 7.50	166.57 ± 7.11	166.04 ± 9.07
Weight (kg)	72.93 ± 12.12	70.09 ± 11.95	67.45 ± 11.67	63.81 ± 11.07	63.05 ± 11.32
^{18}F-FDG dose (mCi/kg)	0.15 ± 0.03	0.15 ± 0.03	0.15 ± 0.03	0.16 ± 0.04	0.16 ± 0.04
Blood glucose (mmol/L)	5.25 ± 0.60	5.70 ± 0.88	5.86 ± 1.05	5.79 ± 0.88	5.71 ± 0.77

Abbreviation: ^{18}F-FDG, 2-deoxy-2-[fluorine-18] fluoro-D-glucose.
IV includes IVA and IVB.

previously.[29] Within the selected VOI, SUV_{max}, SUL_{max}, SUS_{max}, SUV_{mean}, GN_{max}, GN_{mean}, MTV, TLG, and GNTLG of the primary tumor and LNM with the highest SUV_{max} values were evaluated using the fixed percentage of SUV_{max} threshold algorithm (42% of SUV_{max}).[30] The SUV measures the uptake in a tumor normalized according to the distribution volume. SUV_{max} and SUV_{mean} were defined as the maximum and average values of SUVs, respectively. Glucose-normalized SUV_{max} and SUV_{mean} were defined as GN_{max} and GN_{mean}, respectively.[28] SUV_{peak} is the average SUV computed within a fixed VOI, most often containing (and not necessarily centered on) the hottest pixel value.[31] GNTLG is calculated by multiplying MTV by GN_{mean}.[28] The LBM-normalized SUV was defined as SUL, while the BSA-normalized SUV was defined as SUS.[27]

Statistical analysis

Multigroup comparisons were performed using analysis of variance (ANOVA) to compare the differences in metabolic parameters of the primary tumors and LNM of stages T1–T4 and N0–N3. The Spearman rank correlation coefficient was used to characterize the relationship between the PET parameters and NPC T and N staging. Ordered logistic regression analysis was used to identify the PET parameters that are significantly associated with T and N staging. Two-tailed *P*-values of $<.05$ were considered statistically significant. Statistical Package for Social Sciences software (SPSS, version 22.0, IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

A total of 435 patients with histologically confirmed undifferentiated carcinoma who underwent ^{18}F-FDG-PET–CT imaging before treatment were included in this study.

Clinical characteristics

The clinical characteristics of patients with NPC included in this study are listed in Table 1.

Comparison of PET parameters between stage T1–T4

Significant differences in TMTV, $TSUV_{max}$, $TSUV_{mean}$, TTLG, TGN_{max}, TGN_{mean}, TGNTLG, $TSUV_{peak}$, $TSUL_{max}$, and $TSUS_{max}$ values between stages T1 and T4 tumors were found ($P<.05$).

We did not observe any significant differences in the lymph node metabolic tumor volume (LNMTV), lymph node standard uptake value $(LNSUV)_{max}$, $LNSUV_{mean}$, LNTLG, lymph node glucose-normalized standard uptake value $(LNGN)_{max}$, $LNGN_{mean}$, lymph node glucose-normalized total lesion glycolysis (LNGNTLG), $LNSUV_{peak}$, lymph node lean body mass-normalized SUV $(LNSUL)_{max}$, or lymph node body surface area-normalized SUV $(LNSUS)_{max}$ values between stages T1 and T4 carcinomas ($P>.05$).

The pairwise comparison of the TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ values between stages T1 and T4 showed significant differences ($P<.05$). Further analysis suggested that higher TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ mean values were associated with more advanced T staging.

We observed no significant differences in TMTV, TTLG, and TGNTLG values between stages T1 and T2 ($P>.05$) (Table 2, Figure 1).

Comparison of PET parameters between stages N0 and N3

Significant differences were found between TMTV, $TSUV_{max}$, $TSUV_{mean}$, TTLG, TGN_{max}, TGN_{mean}, TGNTLG, $TSUV_{peak}$, $TSUL_{max}$, $TSUS_{max}$, LNMTV, $LNSUV_{max}$, $LNSUV_{mean}$, LNTLG, $LNGN_{max}$, $LNGN_{mean}$, LNGNTLG, $LNSUV_{peak}$, $LNSUL_{max}$, and $LNSUS_{max}$ values of stages N0–N3 ($P<.05$).

The pairwise comparison of LNMTV, $LNSUV_{max}$, $LNSUV_{mean}$, LNTLG, $LNGN_{max}$, $LNGN_{mean}$, LNGNTLG, $LNSUV_{peak}$, $LNSUL_{max}$, and $LNSUS_{max}$ values between stages N0 and N3 showed significant differences ($P<.05$). Further analysis suggested that higher mean LNMTV, $LNSUV_{max}$, $LNSUV_{mean}$, LNTLG, $LNGN_{max}$, $LNGN_{mean}$, LNGNTLG,

Table 2. Comparison of PET parameters of primary tumors and lymph node metastasis between stages T1 and T4.

	T1 ($N=56$)	T2 ($N=91$)	T3 ($N=147$)	T4 ($N=141$)	F	P
TMTV	4.13 ± 2.39[a]	4.90 ± 3.16[b]	7.96 ± 6.23	20.76 ± 15.75	71.855	.000
$TSUV_{max}$	8.65 ± 3.82	12.01 ± 4.58[c]	13.15 ± 5.19[a]	15.45 ± 6.06	24.441	.000
$TSUV_{mean}$	5.18 ± 2.32	7.38 ± 3.03[c]	8.08 ± 3.36[a]	9.37 ± 3.77	22.557	.000
TTLG	19.77 ± 11.86[a]	34.10 ± 22.31[b]	65.41 ± 72.88	193.88 ± 167.35	65.400	.000
TGN_{max}	8.50 ± 4.34	11.28 ± 5.36	13.38 ± 5.35	15.60 ± 6.47	25.012	.000
TGN_{mean}	5.07 ± 2.65	6.93 ± 3.46	8.22 ± 3.43	9.45 ± 4.01	23.488	.000
TGNTLG	19.55 ± 13.24[a]	31.60 ± 22.93[b]	65.88 ± 69.18	195.93 ± 171.32	66.318	.000
T_{peak}	6.05 ± 2.53	9.02 ± 3.75	10.25 ± 4.21	12.72 ± 5.13	36.207	.000
$TSUL_{max}$	6.60 ± 2.88	9.40 ± 3.65[c]	10.40 ± 4.07[a]	12.37 ± 4.83	28.228	.000
$TSUS_{max}$	2.30 ± 1.19	3.10 ± 1.23	3.48 ± 1.38	4.19 ± 1.59	27.489	.000
LNMTV	4.72 ± 5.19	4.89 ± 5.42	4.41 ± 5.37	3.81 ± 3.29	1.097	.35
$LNSUV_{max}$	9.48 ± 7.47	8.06 ± 6.56	9.49 ± 5.95	9.93 ± 6.00	1.705	.165
$LNSUV_{mean}$	6.03 ± 4.87	5.11 ± 4.26	5.99 ± 3.89	6.17 ± 3.87	1.366	.252
LNTLG	44.33 ± 68.98	39.48 ± 66.48	35.84 ± 57.36	27.83 ± 36.46	1.523	.208
$LNGN_{max}$	8.96 ± 7.27	8.02 ± 6.74	9.56 ± 6.09	10.02 ± 6.29	1.910	.127
$LNGN_{mean}$	5.70 ± 4.72	5.07 ± 4.36	6.04 ± 3.98	6.28 ± 4.05	1.661	.175
LNGNTLG	39.68 ± 59.86	39.41 ± 65.73	35.83 ± 57.25	28.47 ± 37.92	1.028	.380
LN_{peak}	7.39 ± 6.13	6.27 ± 5.39	7.27 ± 4.98	7.23 ± 4.75	0.917	.433
$LNSUL_{max}$	7.33 ± 5.72	6.31 ± 5.01	7.50 ± 4.72	7.92 ± 4.73	2.024	.110
$LNSUS_{max}$	2.41 ± 1.84	2.21 ± 1.93	2.52 ± 1.59	2.69 ± 1.60	1.505	.213

Abbreviations: LN, lymph node; LNGN, lymph node glucose-normalized standard uptake value; LNGNTLG, lymph node glucose-normalized total lesion glycolysis; LNMTV, lymph node metabolic tumor volume; LNSUL, lymph node lean body mass-normalized SUV; LNSUS, lymph node body surface area-normalized SUV; LNSUV, lymph node standard uptake value; LNTLG, lymph node total lesion glycolysis; PET, positron emission tomography; TGN, primary tumor glucose-normalized standard uptake value; TGNTLG, primary tumor glucose-normalized total lesion glycolysis; TMTV, primary tumor metabolic tumor volume; TSUL, primary tumor lean body mass-normalized SUV; TSUS, primary tumor body surface area-normalized SUV; TSUV, primary tumor standard uptake value; TTLG, primary tumor total lesion glycolysis.
[a]Not significantly different from T2.
[b]Not significantly different from T1.
[c]Not significantly different from T3.

$LNSUV_{peak}$, $LNSUL_{max}$, and $LNSUS_{max}$ values were associated with more advanced N stages (Table 3).

Correlation between PET parameters, and T and N staging

The parameters TMTV, $TSUV_{max}$, $TSUV_{mean}$, TTLG, TGN_{max}, TGN_{mean}, TGNTLG, $TSUV_{peak}$, $TSUL_{max}$, and $TSUS_{max}$ were correlated with T staging ($P<.05$), and the correlation coefficients were 0.662, 0.391, 0.384, 0.731, 0.393, 0.384, 0.732, 0.477, 0.415, and 0.421, respectively.

The parameters LNMTV, $LNSUV_{max}$, $LNSUV_{mean}$, LNTLG, $LNGN_{max}$, $LNGN_{mean}$, LNGNTLG, $LNSUV_{peak}$, $LNSUL_{max}$, and $LNSUS_{max}$ were not correlated with T staging ($P>.05$).

All primary tumor and LN parameters, except TMTV ($P=0.120$), were correlated with N staging ($P<0.05$), and the correlation coefficients were 0.165, 0.155, 0.117, 0.202, 0.192, 0.143, 0.150, 0.168, 0.175, 0.506, 0.568, 0.559, 0.560, 0.574, 0.573, 0.574, 0.569, 0.567, and 0.568, respectively.

Relationship between PET parameters, and T and N staging

TMTV, $TSUV_{peak}$, $TSUL_{max}$, and $TSUS_{max}$ had significant positive associations with T staging, and the odds ratio (OR)

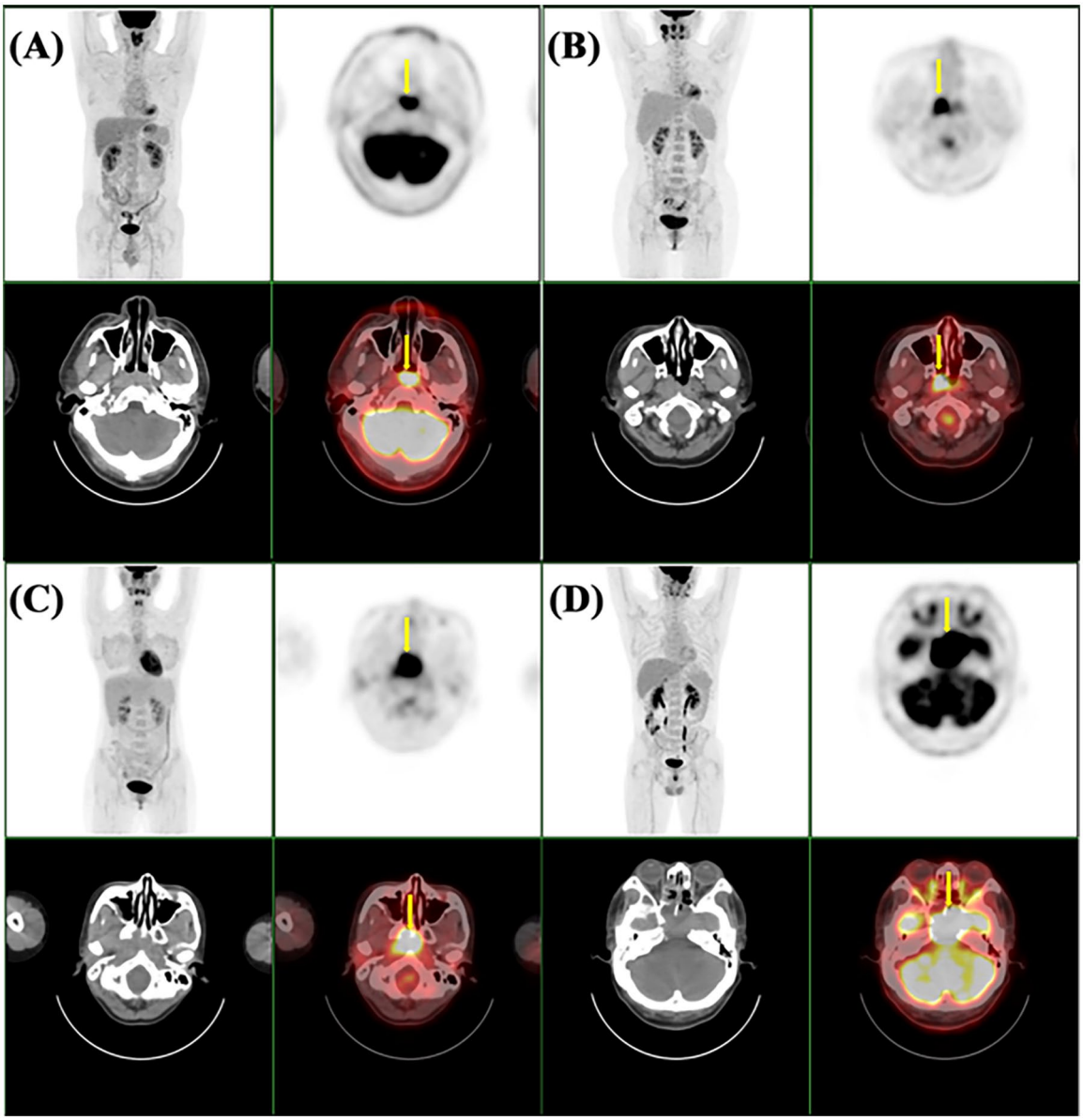

Figure 1. ^{18}F-FDG PET–CT imaging of primary tumors (yellow arrows) in patients with nasopharyngeal carcinoma. A, B, C, and D depict stages T1, T2, T3, and T4 carcinomas, respectively. ^{18}F-FDG PET–CT indicates 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography–computed tomography.

and *P*-values were 1.357 and 0.000, 1.709 and 0.000, 1.436 and 0.020, and 1.643 and 0.033, respectively. LNMTV and $TSUS_{max}$ had significant positive associations with N staging, and the OR and *P*-values were 1.404 and 0.000, and 1.913 and 0.024 (Table 4, Figure 2).

Discussion

The unique ^{18}F-FDG probe is utilized for molecular imaging, exploiting the ability of cancer cells to take up the tracer in proportion to their glucose utilization rate. The Warburg effect refers to the enhanced utilization of glucose through aerobic metabolism in cancer cells, which becomes more pronounced as the cells become less differentiated and more aggressive. Therefore, as a tumor becomes increasingly undifferentiated and aggressive, it results in elevated glucose utilization and increased uptake of the radioactive tracer ^{18}F-FDG.[19,20] Black patients with breast cancer have poorer prognosis and higher mortality. Abubakar et al[19] observed differences in ^{18}F-FDG PET–CT metabolic parameters of locally advanced invasive ductal carcinoma (IDC) among patients of different racial groups and molecular subtypes. A notable increase in the SUV_{max}, MTV, and TLG values of the primary tumor was observed in black patients when compared with patients of other ethnicities. Moreover, the luminal subtype showed a significant increase in SUV_{max}, while both SUV_{max} and TLG values were significantly elevated in the basal subtype of the primary tumor. Overall, Black patients with IDC exhibited markedly elevated PET parameters, implying a more aggressive disease phenotype for this racial group, particularly with luminal and basal carcinoma subtypes.[19]

Table 3. Comparison of PET parameters of primary tumors and lymph node metastasis between stages N0 and N3.

	N0 (*N* = 58)	N1 (*N* = 165)	N2 (*N* = 167)	N3 (*N* = 45)	*F*	*P*
TMTV	7.13 ± 5.36[a]	10.80 ± 13.09[a,b]	13.01 ± 12.49[c]	9.01 ± 10.77[c,d]	4.083	0.007
$TSUV_{max}$	10.96 ± 4.60	12.81 ± 5.64[b]	13.65 ± 5.44[a,c]	14.67 ± 6.72[b]	4.776	0.003
$TSUV_{mean}$	6.73 ± 3.00	7.85 ± 3.58[a,b]	8.29 ± 3.46[a,c]	8.92 ± 4.12[b, c]	4.007	0.008
TTLG	46.43 ± 43.12[a]	89.71 ± 131.73[a]	117.52 ± 135.42[a]	89.83 ± 124.97[b, c,d]	4.887	0.002
TGN_{max}	10.33 ± 5.27	12.62 ± 6.24[b]	13.84 ± 5.55[a,c]	15.03 ± 7.13[b]	6.915	0.000
TGN_{mean}	6.31 ± 3.36	7.73 ± 3.94[b]	8.40 ± 3.52[a,c]	9.12 ± 4.33[b]	6.117	0.000
TGNTLG	45.33 ± 45.73[a]	89.09 ± 134.58[a]	118.93 ± 136.52[a]	90.94 ± 124.50[b, c,d]	5.131	0.002
T_{peak}	8.57 ± 3.83	10.01 ± 4.76[a,b]	10.84 ± 4.77[a,c]	11.16 ± 5.38[b, c]	4.020	0.008
$TSUL_{max}$	8.56 ± 3.70	10.15 ± 4.50[b]	10.80 ± 4.37[a,c]	11.63 ± 5.26[b]	5.072	0.002
$TSUS_{max}$	2.88 ± 1.37	3.39 ± 1.46[b]	3.64 ± 1.49[a,c]	3.97 ± 1.84[b]	5.499	0.001
LNMTV	0	4.13 ± 3.78	5.11 ± 4.02	8.01 ± 8.39	31.945	0.000
$LNSUV_{max}$	0	9.22 ± 5.56	11.26 ± 5.11	14.62 ± 4.78	95.761	0.000
$LNSUV_{mean}$	0	5.80 ± 3.65	7.10 ± 3.34	9.14 ± 3.46	85.870	0.000
LNTLG	0	29.08 ± 47.12	40.25 ± 48.52	83.31 ± 95.17	23.219	0.000
$LNGN_{max}$	0	8.99 ± 5.70	11.40 ± 5.21	14.74 ± 5.36	91.946	0.000
$LNGN_{mean}$	0	5.64 ± 3.73	7.18 ± 3.40	9.38 ± 3.67	85.409	0.000
LNGNTLG	0	27.18 ± 42.26	40.62 ± 48.39	84.92 ± 94.71	26.504	0.000
LN_{peak}	0	6.79 ± 4.46	8.60 ± 4.26	11.48 ± 4.95	81.590	0.000
$LNSUL_{max}$	0	7.23 ± 4.28	8.90 ± 4.06	11.53 ± 3.58	97.197	0.000
$LNSUS_{max}$	0	2.47 ± 1.53	2.99 ± 1.37	3.94 ± 1.29	92.760	0.000

Abbreviations: LN, lymph node; LNGN, lymph node glucose-normalized standard uptake value; LNGNTLG, lymph node glucose-normalized total lesion glycolysis; LNMTV, lymph node metabolic tumor volume; LNSUL, lymph node lean body mass-normalized SUV; LNSUS, lymph node body surface area-normalized SUV; LNSUV, lymph node standard uptake value; LNTLG, lymph node total lesion glycolysis; PET, positron emission tomography; TGN, primary tumor glucose-normalized standard uptake value; TGNTLG, primary tumor glucose-normalized total lesion glycolysis; TMTV, primary tumor metabolic tumor volume; TSUL, primary tumor lean body mass-normalized SUV; TSUS, primary tumor body surface area-normalized SUV; TSUV, primary tumor standard uptake value; TTLG, primary tumor total lesion glycolysis.
[a]Not significantly different from N3.
[b]Not significantly different from N2.
[c]Not significantly different from N1.
[d]Not significantly different from N0.

Some studies have proposed to simplify the T staging.[14,15] Our study aimed to compare metabolic parameters in patients of different T stages and to evaluate the differences in primary tumor aggressiveness by identifying the metabolic parameters associated with T staging. We observed significant differences in the values of primary tumor MTV, SUV_{max}, SUV_{mean}, TLG, GN_{max}, GN_{mean}, GNTLG, SUV_{peak}, SUL_{max}, and SUS_{max} between stages T1–T4. SUV_{max}, SUS_{max}, and GN_{max} only represent the maximum uptake within the VOI, while MTV, TLG, and GNTLG reflect not only the tumor size but also the metabolic information. In our study, we observed no significant differences in TMTV, TTLG, and TGNTLG values between the stages T1 and T2. Conversely, the pairwise comparison of the primary tumor GN_{max}, GN_{mean}, SUV_{peak}, and SUS_{max} between the four groups showed significant differences. Further analysis suggested that higher mean values of TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ were associated with advanced T stages. The T staging of NPC is based entirely on the anatomical tumor extent rather than the size of the malignant tumors.[16] The above results suggest that GN_{max}, GN_{mean}, SUV_{peak}, and SUS_{max} can be used to evaluate the local aggressiveness of the primary tumor and may be more effective indicators compared with volume-dependent parameters, such as MTV and TLG. Our results showed that the primary tumor

Table 4. Summary of logistic regression analysis results of PET parameters, and T and N staging.

VARIABLES	T STAGE		N STAGE	
	OR (95% CI)	*P*	OR (95% CI)	*P*
TMTV	1.357 (1.253–1.470)	0.000	/	/
$TSUV_{max}$	1.200 (0.184–7.813)	0.849	4.286 (0.605–30.382)	.145
$TSUV_{mean}$	0.276 (0.013–5.981)	0.412	0.072 (0.003–1.703)	.103
TTLG	0.975 (0.947–1.004)	0.093	1.010 (0.989–1.032)	.335
TGN_{max}	1.151 (0.174–7.622)	0.884	0.248 (0.035–1.747)	.162
TGN_{mean}	0.827 (0.038–18.226)	0.904	10.501 (0.450–244.928)	.143
TGNTLG	1.012 (0.983–1.041)	0.428	0.991 (0.971–1.012)	.411
T_{peak}	1.709 (1.347–2.166)	0.000	0.989 (0.801–1.221)	.918
$TSUL_{max}$	1.436 (1.090–1.891)	0.010	0.942 (0.654–1.359)	.750
$TSUS_{max}$	1.643 (1.015–2.661)	0.044	1.913 (1.088–3.366)	.024
LNMTV	/	/	1.404 (1.270–1.553)	.000
$LNSUV_{max}$	/	/	2.115 (0.515–8.682)	.298
$LNSUV_{mean}$	/	/	0.268 (0.021–3.382)	.309
LNTLG	/	/	0.987 (0.947–1.029)	.545
$LNGN_{max}$	/	/	0.731 (0.171–3.120)	.672
$LNGN_{mean}$	/	/	2.239 (0.174–28.815)	.536
LNGNTLG	/	/	0.987 (0.946–1.029)	.545
LN_{peak}	/	/	1.103 (0.848–1.433)	.466
$LNSUL_{max}$	/	/	1.048 (0.690–1.592)	.826
$LNSUS_{max}$	/	/	1.173 (0.689–1.996)	.556
McFadden R^2	0.289		0.239	

Abbreviations: CI, confidence interval; LN, lymph node; LNGN, lymph node glucose-normalized standard uptake value; LNGNTLG, lymph node glucose-normalized total lesion glycolysis; LNMTV, lymph node metabolic tumor volume; LNSUL, lymph node lean body mass-normalized SUV; LNSUS, lymph node body surface area-normalized SUV; LNSUV, lymph node standard uptake value; LNTLG, lymph node total lesion glycolysis; OR, odds ratio; PET, positron emission tomography; TGN, primary tumor glucose-normalized standard uptake value; TGNTLG, primary tumor glucose-normalized total lesion glycolysis; TMTV, primary tumor metabolic tumor volume; TSUL, primary tumor lean body mass-normalized SUV; TSUS, primary tumor body surface area-normalized SUV; TSUV, primary tumor standard uptake value; TTLG, primary tumor total lesion glycolysis.

metabolic parameter values were significantly different in patients with tumors of different T stages. In other words, our results suggested that T staging based on the *Eighth Edition AJCC Cancer Staging Manual* is credible from a metabolic perspective.

Our study further aimed to elucidate the relationship between PET-CT parameters and LNM. In our study, all parameters of the primary tumor and LNM, except TMTV, were correlated with N staging. We observed significant differences in all parameters of the primary tumor and LNM between stages N0 and N3. The pairwise comparison of all LNM parameters between the four stages showed significant differences. Furthermore, our analysis showed that higher mean values of LNMTV, $LNSUV_{max}$, $LNSUV_{mean}$, LNTLG, $LNGN_{max}$, $LNGN_{mean}$, LNGNTLG, $LNSUV_{peak}$, $LNSUL_{max}$, and $LNSUS_{max}$ were associated with advanced N staging. Our findings suggest that metabolic information is a useful indicator in N staging of LNM based on the *Eighth Edition AJCC Cancer Staging Manual*. Two metabolic parameters (LNMTV and $TSUS_{max}$) exhibited a significant positive association with N staging. The primary tumor SUS_{max} was associated with LNM. Previous studies have also described the association between PET–CT parameters and LNM. For example, a study by Yilmaz et al[22] showed that higher primary tumor SUV_{max} was associated with a higher probability of LNM in patients with cervical cancer. A study by Crivellaro et al[23] illustrated that primary tumor MTV and TLG were significantly related to the presence of LNM in early-stage cervical cancer. Li et al[32] also proposed that in early-stage cervical cancer, primary tumor TLG may predict LNM. Husby et al[21] demonstrated that

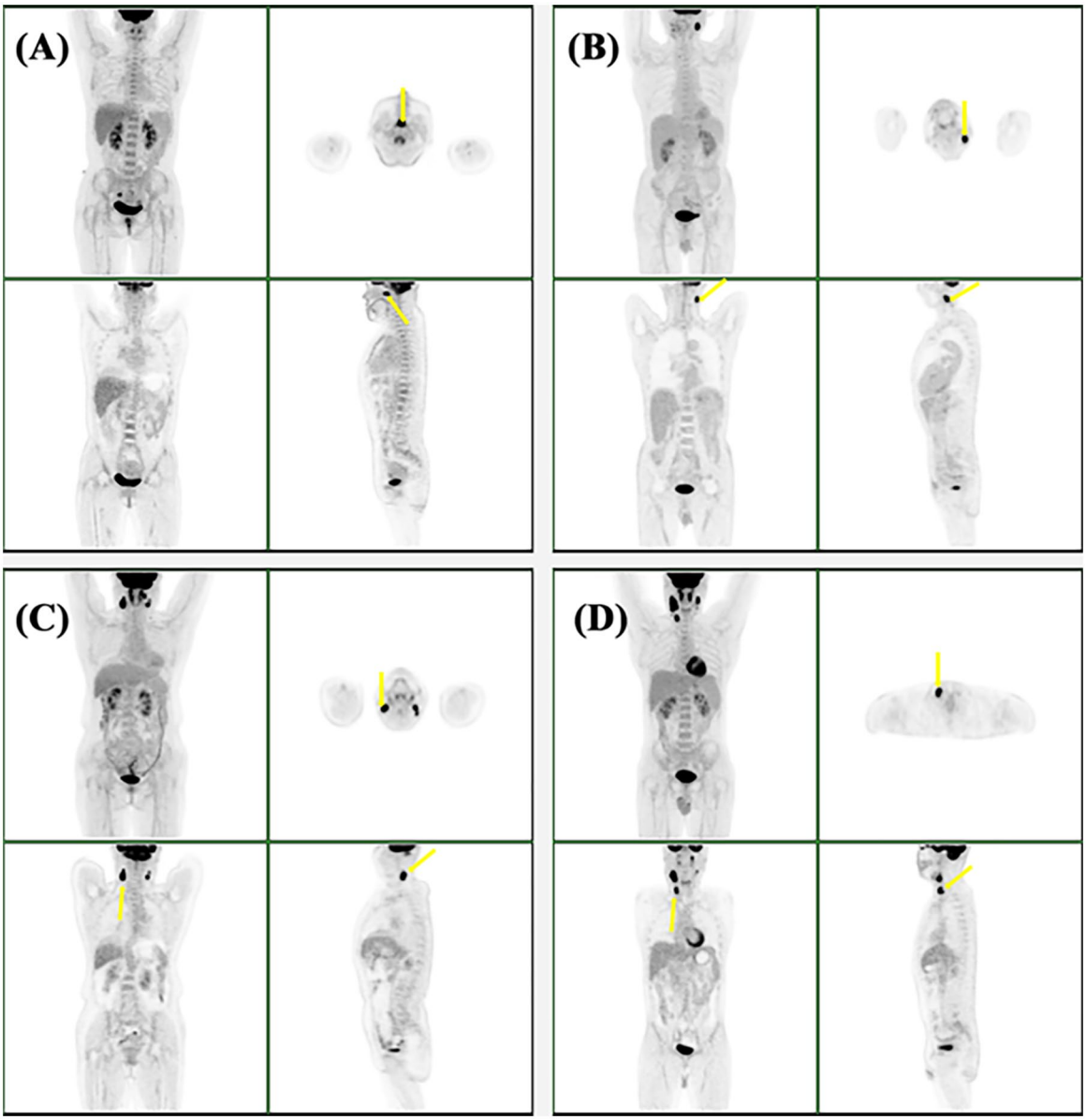

Figure 2. ^{18}F-FDG PET–CT imaging of lymph node metastasis (yellow arrows) in patients with nasopharyngeal carcinoma. A, B, C, and D depict stages N0, N1, N2, and N3 lymph node metastases, respectively. ^{18}F-FDG PET–CT indicates 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography–computed tomography.

SUV_{max}, SUV_{mean}, MTV, and TLG of the primary tumor tend to indicate LNM in endometrial carcinoma. In incidentally detected thyroid cancer, high MTV and TLG are associated with LNM.[33] A study unveiled an association between the retention index (calculated as the difference between SUV_{max} delayed point and SUV_{max} early point, divided by SUV_{max} early point) of the primary tumor and a heightened likelihood of LN metastasis in patients afflicted by non-small cell lung cancer (NSCLC).[34] Another study illustrated that the SUV_{max} of the mediastinal LNM and primary tumor SUV_{max}, SUV_{peak}, SUV_{mean}, MTV, and TLG were significantly associated with the presence of mediastinal LNM in NSCLC. In particular, the study found a strong correlation between the mediastinal LNM SUV_{max}, the primary tumor SUV_{peak}, and the occurrence of mediastinal LNM in patients with NSCLC.[35] PET–CT metabolic parameters have also been used to predict LNM in other tumors, such as vulvar cancer,[36] esophageal squamous cell carcinoma,[37] breast cancers,[38] rectal cancer,[39] and gastric cancer.[40] In addition to some similarities, differences between the findings of our study and those of previous studies were noted. We investigated not only the presence of LNM but also the staging of LNM. In addition, we investigated more metabolic parameters than previous studies. SUL_{max}, SUS_{max}, GN_{max}, and GN_{mean} have rarely been investigated. SUV is typically normalized to total body mass. However, because FDG accumulation in white adipose tissue (WAT) is minimal in the fasting state, SUV in tissues other than WAT tends to be higher in patients with obesity. SUV values of the target tissue in patients with

higher body mass will be higher than those in leaner patients. Therefore, some studies have proposed that SUV should be normalized to LBM instead of total body mass.[26] Normalization to BSA also has been proposed.[27] Our study suggested that $TSUL_{max}$ and $TSUS_{max}$ were positively associated with T staging, while $TSUS_{max}$ instead of SUV_{max} was positively associated with N staging. Few studies have investigated GN. Hence, evidence supporting that GN improves the treatment response monitoring or the prediction of outcomes compared with uncorrected SUVs is lacking.[28] Our study showed that higher mean values of TGN_{max} and TGN_{mean} rather than SUV_{max} and SUV_{mean} were associated with advanced T staging. Our study also suggested that glucose-normalized SUV_{max} and glucose-normalized SUV_{mean} reflect the metabolic parameter differences between T stages. Our study provides reference values for follow-up studies that investigate the utility of other metabolic parameters in addition to SUV_{max} (eg, SUL_{max}, SUS_{max}, GN_{max} and GN_{mean}) to evaluate tumor aggressiveness and LNM.

Currently, the treatment of NPC mainly involves radiotherapy combined with chemotherapy, and most patients do not need surgical resection of the nasopharyngeal primary tumor and LNM. Due to the lack of gross surgical specimens, the depth of tumor invasion and LNM could not be accurately judged from the pathological level. In fact, comprehensive imaging is generally used to stage NPC in clinical practice, but when the disease (primary or metastatic) is in a critical state, clinical staging based on imaging involves certain difficulties. A study by Feng et al[41] showed that a model based on PET and MRI features (1 T2WI feature and 11 PET features) and metabolic parameters (primary tumor SUV_{max} and TLG) exhibited good diagnostic performance for predicting NPC staging in the testing set (AUC, 0.90). Our study retrospectively analyzed the association between various PET–CT metabolic parameters and T and N staging, which may provide novel directions for clinical work and prove helpful for clinicians.

Several limitations of this study should be acknowledged. First, some patients underwent a biopsy of the primary lesion before the PET examination, which may have affected the accuracy of the metabolic parameters measurements. Second, our measurement method for MTV and TLG is only one of the many measurement methods, and we only used a 42% SUV_{max} threshold. The relationship between metabolic parameters determined via more measurement methods and thresholds and the primary tumor and LNM requires further study. Third, outcome analysis was not performed. Follow-up studies with larger, homogeneous patient cohorts are planned to investigate this aspect.

Conclusion

We observed significant differences in certain primary tumor PET–CT metabolic parameters between different T-stage tumors. Further analysis showed that higher mean values of TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ were associated with advanced T staging. Compared with volume-dependent parameters, such as MTV and TLG, TGN_{max}, TGN_{mean}, $TSUV_{peak}$, and $TSUS_{max}$ may be more useful indicators of the local aggressiveness of tumors. Furthermore, our analysis suggests that higher mean values of all the LN metabolic parameters were associated with advanced N staging. Our results indicate that metabolic parameters are useful for T and N staging based on the *Eighth Edition AJCC Cancer Staging Manual*. LNMTV and $TSUS_{max}$ were positively associated with N staging. The SUS_{max} of the primary tumor was associated with LNM. In addition to SUV_{max}, other metabolic parameters (eg, SUL_{max}, SUS_{max}, GN_{max}, and GN_{mean}) were indicated to be useful in the evaluation of tumor aggressiveness and LNM. With further improvement and validation, PET–CT metabolic parameters may become useful predictors of local tumor aggressiveness and LNM of NPC.

Declarations

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Jiangsu Cancer Hospital (protocol code 2022k-k026 and date of approval: April 22, 2022). Written informed consent was obtained from all subjects involved in the study.

Consent for publication

Written informed consent for publication was obtained from all participants.

Author contributions

Conceptualization, Yun Zhang and Yuxiao Hu; Data curation, Yun Zhang, Shuang Zhao and Rong Huang; Formal analysis, Yun Zhang; Funding acquisition, Yun Zhang and Yuxiao Hu; Investigation, Yun Zhang, Shuang Zhao and Rong Huang; Methodology, Yun Zhang and Yuxiao Hu; Project administration, Yuxiao Hu; Resources, Yuxiao Hu; Supervision, Yuxiao Hu; Validation, Yuxiao Hu; Visualization, Yun Zhang; Writing—original draft, Yun Zhang; Writing—review & editing, Yuxiao Hu.

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Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

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