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Original Article

Prognostic significance of normalized distance from maximum standardized uptake value to tumor centroid on [^{18}F]FDG PET/CT in head and neck squamous cell carcinoma

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ABSTRACT

Objective: The maximum [^{18}F]FDG uptake of a cancer lesion has been found to relocate from the center to the periphery during progression. This behavior suggests that the normalized distances from the hotspot of radiotracer uptake to the tumor centroid (NHOC) and to the tumor perimeter (NHOP) could serve as novel geometric PET parameters indicative of tumor aggressiveness. This study aimed to explore the prognostic relevance of NHOC and NHOP in [^{18}F]FDG PET/CT for predicting the response to concurrent chemoradiotherapy (CCRT) and progression-free survival (PFS) in patients with head and neck squamous cell carcinoma (HNSCC).
Materials and Methods: We retrospectively reviewed 116 HNSCC patients who received CCRT and were assessed with pre-treatment (PET1) and three months post-treatment PET/CT (PET2). Along with conventional PET parameters, NHOC and NHOP for primary tumors on PET1 and the percent changes in NHOC and NHOP between PET1 and PET2 were measured.
Results: Of all the PET1 parameters assessed, NHOC was the most effective in predicting the CCRT response, achieving an area under the receiver operating characteristic curve of 0.645. In multivariate logistic regression and survival analysis, NHOC identified as an independent predictor for both complete metabolic response ($P = .028$) and PFS ($P = .006$). In a subgroup of 46 patients exhibiting residual primary tumors on PET2, both the percent changes in NHOC ($P = .048$) and NHOP ($P = .041$) were significantly associated with PFS.
Conclusions: NHOC and the percent changes in NHOC and NHOP following CCRT may serve as effective [^{18}F]FDG PET/CT parameters for predicting clinical outcomes in HNSCC patients.

Importancia pronóstica de las distancias normalizadas desde el punto de captación máxima del radiotrazador hasta el centro del tumor en la PET/CT con [^{18}F]FDG en el carcinoma de células escamosas de cabeza y cuello

Palabras clave:
Quimiorradioterapia
F-18 fluorodesoxiglucosa
Carcinoma de células escamosas de cabeza y cuello
Tomografía por emisión de positrones
Radiómica

RESUMEN

Objetivo: Se ha observado que la captación máxima de [^{18}F]FDG de una lesión cancerosa se desplaza desde el centro hacia la periferia durante la progresión. Este comportamiento sugiere que las distancias normalizadas desde el punto de captación máxima del radiotrazador hasta el centro del tumor (NHOC) y el perímetro del tumor (NHOP) podrían servir como nuevos parámetros geométricos de PET indicativos de la agresividad del tumor. Este estudio tuvo como objetivo explorar la relevancia pronóstica de NHOC y NHOP en la PET/TC con [^{18}F]FDG para predecir la respuesta a la quimiorradioterapia concurrente (CCRT) y la supervivencia libre de progresión (PFS) en pacientes con carcinoma de células escamosas de cabeza y cuello (HNSCC).

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Materiales y métodos: Revisamos retrospectivamente a 116 pacientes con HNSCC que recibieron CCRT y fueron evaluados con PET/TC antes del tratamiento (PET1) y tres meses después del tratamiento (PET2). Junto con los parámetros PET convencionales, se midieron NHOC y NHOP para tumores primarios en PET1 y los cambios porcentuales en NHOC y NHOP entre PET1 y PET2.
Resultados: De todos los parámetros PET1 evaluados, NHOC fue el más eficaz para predecir la respuesta CCRT, logrando un área bajo la curva de características operativas del receptor de 0,645. En la regresión logística multivariante y el análisis de supervivencia, NHOC se identificó como un predictor independiente tanto de la respuesta metabólica completa (P = ,028) como de la PFS (P = ,006). En un subgrupo de 46 pacientes que presentaban tumores primarios residuales en PET2, tanto los cambios porcentuales en NHOC (P = ,048) como en NHOP (P = ,041) se asociaron significativamente con la PFS.
Conclusiones: NHOC y los cambios porcentuales en NHOC y NHOP después de CCRT pueden servir como parámetros [^{18}F]FDG PET/CT eficaces para predecir los resultados clínicos en pacientes con carcinoma espinocelular de cabeza y cuello.

Introduction

Head and neck squamous cell carcinoma (HNSCC) encompasses heterogeneous groups of malignant tumors originating from epithelial cells of the nasopharynx, oropharynx, hypopharynx, and larynx.[1] With the decline in tobacco use, the incidence of HNSCC has gradually decreased.[2] Conversely, the prevalence of human papillomavirus (HPV)-related oropharyngeal cancer on the rise, and HNSCC remains the seventh most common cancer globally.[2,3] Owing to non-specific symptoms, more than 60% of patients with HNSCC present with locally advanced cancer.[2] In patients with locally advanced HNSCC without distant metastasis, concurrent chemoradiotherapy (CCRT) is considered the standard of care, offering improved clinical outcomes and a higher likelihood of preserving organ function compared to surgery.[4,5] However, over 50% of patients with locally advanced HNSCC eventually experienced cancer progression or metastasis, predominantly within the first two years following treatment.[4] Consequently, prognostic biomarkers that can predict treatment response and survival outcomes need to be explored in HNSCC patients who have undergone CCRT.[4,6]

In patients with HNSCC, 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography/computed tomography (PET/CT) demonstrated a high diagnostic accuracy for detecting metastasis.[5] Furthermore, in locally advanced HNSCC patients treated with CCRT, [^{18}F]FDG PET/CT revealed a high diagnostic sensitivity and specificity for identifying residual or recurrent cancer lesions, and [^{18}F]FDG PET/CT-guided surveillance after CCRT demonstrated survival results comparable to those with planned neck dissection after CCRT.[7,8] Therefore, [^{18}F]FDG PET/CT has been recommended for utilization in both the pre-treatment assessment and 3–4 months post-treatment for response evaluation in patients with locally advanced HNSCC.[5] Typically, conventional metabolic parameters of [^{18}F]FDG PET/CT, such as the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), are employed to estimate the metabolic tumor burden.[6,9] In addition to conventional parameters, a variety of radiomic features capable of quantifying metabolic heterogeneity and the shape features of a malignant lesion have shown potential in predicting treatment response and prognosis.[10,11] Recent research utilizing mathematical modeling of tumor growth discovered that the maximum metabolic activity of a cancer lesion tends to shift toward the lesion edge as the cancer grows.[12] Based on this result, the normalized distances from the hot spot of radiotracer uptake (SUVmax) to the tumor centroid (NHOC) and the tumor perimeter (NHOP) have been introduced as novel geometric [^{18}F]FDG PET/CT parameters that could reflect tumor aggressiveness.[12,13] In previous studies, both NHOC and NHOP have been found to have significant correlations with survival outcomes in patients with lung and breast cancers.[12–14] Considering the significant relationship between tumor aggressiveness and clinical outcomes in HNSCC patients treated with CCRT,[6,9,10] it is hypothesized that NHOC and NHOP of primary HNSCC tumors could have significant associations with treatment response and survival outcomes in HNSCC patients. However, the clinical significance of NHOC and NHOP in predicting clinical outcomes for patients with HNSCC remained unreported.

Thus, the current study was designed to evaluate the prognostic significance of NHOC and NHOP, as derived from pre-treatment and post-treatment [^{18}F]FDG PET/CT scans, for predicting treatment response and progression-free survival (PFS) in HNSCC patients treated with CCRT.

Materials and methods

Patients

We retrospectively reviewed the medical records of patients diagnosed with biopsy-proven HNSCC at two medical centers from May 2012 to December 2021. Among these patients, those who met the following inclusion criteria were enrolled in the study: (1) absence of distant metastasis on staging imaging examinations, (2) have undergone CCRT treatment, and (3) completion of both initial staging [^{18}F]FDG PET/CT (PET1) and a follow-up [^{18}F]FDG PET/CT three months after completing CCRT (PET2). Patients were excluded if they (1) had a previous history of malignant disease, (2) presented with neck lymph node metastasis from an unknown primary tumor site, (3) had a primary tumor in the mobile tongue, (4) received any treatment prior to PET1, (5) had a small primary tumor size of less than 1.0 cm, and (6) exhibited low [^{18}F]FDG uptake in the primary tumor, impeding differentiation from background tissue. Based on the inclusion and exclusion criteria, a total of 116 patients with HNSCC were finally enrolled in this study.

All patients underwent staging examinations, including blood tests, contrast-enhanced CT and magnetic resonance imaging (MRI) of the head and neck area, as well as [^{18}F]FDG PET/CT. From differential counts in the blood tests, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated. The median interval between PET1 and the start of CCRT was 14.0 days (range, 1–38 days). In both medical centers, patients received chemotherapy with platinum-based agents concurrently with radiotherapy. Following CCRT, treatment response was evaluated using PET2 findings. The median interval between the completion of CCRT and PET2 was 3.0 months (range, 1.8–6.3 months). According to the PET response criteria in solid tumors (PERCIST) 1.0, metabolic responses to CCRT were classified as complete metabolic response (CMR), partial metabolic response (PMR),

Table 1
Characteristics of patients (n = 116).

Characteristics		Number of patients (%)
Age (years)		62 (18–88)*
Sex	Men	95 (81.9%)
	Women	21 (18.1%)
Smoking	Current or former	69 (59.5%)
	Never	47 (40.5%)
Primary site	Nasopharynx	30 (25.9%)
	Oropharynx	43 (37.1%)
	Hypopharynx	31 (26.7%)
	Larynx	12 (10.3%)
Clinical T stage	T1–T2	46 (39.7%)
	T3–T4	70 (60.3%)
Clinical N stage	N0	27 (23.3%)
	N1–N3	89 (76.7%)
TNM stage	Stage I–II	19 (16.4%)
	Stage III–IV	97 (83.6%)
Tumor size (cm)		3.5 (1.3–13.0)*
C-reactive protein (mg/dL)		1.93 (0.03–120.57)*
Neutrophil-to-lymphocyte ratio		2.88 (0.79–47.00)*
Platelet-to-lymphocyte ratio		164.58 (14.85–1409.31)*
CCRT response	Complete metabolic response	60 (51.7%)
	Partial metabolic response	28 (24.1%)
	Stable metabolic disease	7 (6.0%)
	Progressive metabolic disease	21 (18.1%)

CCRT, concurrent chemoradiotherapy.
* Median (range).

stable metabolic disease (SMD), or progressive metabolic disease (PMD).[15] Routine clinical follow-ups were conducted every 3–6 months after treatment, including direct laryngoscopy and imaging studies.

This study was approved by the Institutional Review Board of each medical center. Due to the retrospective nature of the study, the requirement for informed consent was waived.

[^{18}F]FDG PET/CT protocol

Patients were instructed to fast for at least 6 h before the [^{18}F]FDG PET/CT scan, ensuring a serum glucose level below150 mg/dL prior to [^{18}F]FDG administration. At both medical facilities, PET/CT scans extended from the vertex to the proximal thigh using the Biograph mCT 128 scanner (Siemens Healthineers, Knoxville, TN, USA). A dose of either 4.07 MBq/kg or 5.18 MBq/kg was intravenously administered, and, after approximately 60 min of [^{18}F]FDG uptake time, an unenhanced CT scan was initially performed with a slice thickness of 5 mm utilizing an automated dose modulation. Subsequently, a PET scan was carried out, allocating 1.5 min per bed position, employing a three-dimensional acquisition mode. The PET images were reconstructed using an ordered subset expectation maximization algorithm that integrated point spread function, time-of-flight modeling, and attenuation correction on a 128 × 128 matrix (2 iterations and 21 subsets).

PET/CT parameter measurements

Two experienced nuclear medicine physicians retrospectively assessed PET1 and PET2 images and measured PET/CT parameters through consensus using the LIFEx software (version 7.6.0; www.lifexsoft.org).[16] All PET images were reconstructed into a voxel size of 4.07 × 4.07 × 2.5 mm. A volume-of-interest (VOI) was manually delineated surrounding the primary tumor, and, metabolically active primary tumor lesion was automatically outlined using Nestle's adaptive threshold method[17,18]: (SUV threshold) = 0.3 × (mean SUV within a tumor volume containing voxels exhibiting [^{18}F]FDG uptake of >70% of SUVmax) + (mean SUV of background). From the metabolically active primary tumor, five PET parameters, including SUVmax, MTV, TLG, NHOC, and NHOP were measured. NHOC and NHOP represent the distances from the SUVmax voxel to the tumor centroid and perimeter, respectively, each divided by the radius of a hypothetical sphere having the same volume with the tumor lesion.[13] For analyzing PET2 images, measurement of PET parameters was limited to patients who exhibited residual primary tumor lesions on PET2 images. For patients with calculated PET2 parameters, the percent change in each parameter between PET1 and PET2 was determined: (ΔPET parameter) = [(PET parameter on PET2) – (PET parameter on PET1)]/(PET parameter on PET1) × 100 (%).

Statistical analysis

The Mann–Whitney *U* test and Kruskal–Wallis test were utilized to assess differences in PET parameters based on clinical factors. Spearman's correlation coefficients were generated to explore the associations between PET parameters, tumor size, and serum inflammatory markers. The predictive capability of the PET1 parameters for CMR was evaluated using the receiver operating characteristic (ROC) curve. Sensitivity and specificity for the PET1 parameters were determined using optimal cut-off values established by the Youden index. Univariate and multivariate logistic regression analyses were conducted to ascertain the effectiveness of PET1 parameters in predicting CMR. Univariate and multivariate Cox proportional hazard regression analyses were undertaken to determine the prognostic significance of PET parameters in predicting PFS. PFS was defined as the interval from the initiation of CCRT to the identification of disease progression detection, death, or the final clinical follow-up. For the survival analysis, PET parameters were transformed into binary data based on cut-off values determined by ROC curve analysis. In the multivariate logistic regression and survival analyses, only those PET parameters that demonstrated statistical significance in the univariate analysis were included, with the addition of age, sex, and TNM stage as covariates. PFS curves were generated using the Kaplan-Meier method, and differences between patient groups were analyzed using the log-rank test. In subgroup patients with residual primary tumors evident on PET2, the prognostic significance of the ΔPET parameter for predicting PFS was further investigated. All statistical analyses were conducted with MedCalc Statistical software (version 22.021, MedCalc Software Ltd, Ostend, Belgium). A *P*-value of <.05 was deemed indicative of statistical significance.

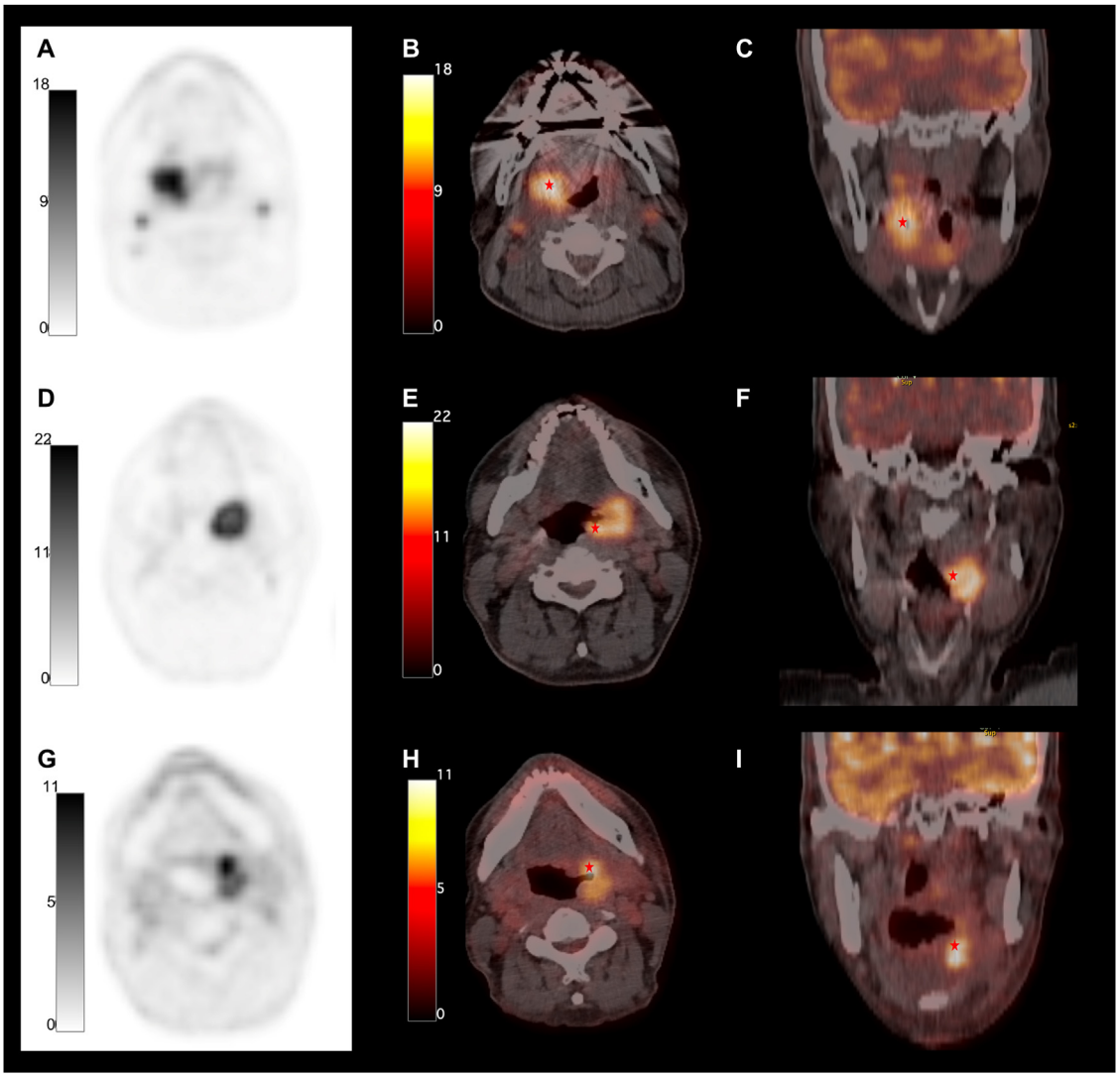

Figure 1. Transaxial PET (A) and transaxial (B) and coronal (C) fused PET/CT images of pre-treatment [^{18}F]FDG PET/CT in a 51-year-old man with right tonsillar cancer. Values of SUVmax, TLG, and NHOC were 18.1, 173.6 g, and 0.11, respectively. The patient achieved a complete metabolic response following concurrent chemoradiotherapy, and has not experienced a cancer progression event during 41.9 months of follow-up. Transaxial PET (D) and transaxial (E) and coronal (F) fused PET/CT images of pre-treatment [^{18}F]FDG PET/CT in a 57-year-old man with left tonsillar cancer. Values of SUVmax, TLG, and NHOC were 22.2, 215.0 g, and 0.66, respectively. In transaxial PET (G) and transaxial (H) and coronal (I) fused PET/CT images of [^{18}F]FDG PET/CT images conducted 4 months after the completion of CCRT, the patient showed the residual primary tumor with ΔSUVmax of −50.7%, ΔTLG of −63.3%, and ΔNHOC of 21.2%, indicating partial metabolic response. The cancer progressed 4.9 months after the treatment. The position of SUVmax is denoted by a red star.

Results

Patient characteristics

The baseline characteristics of the enrolled 116 patients with HNSCC are presented in Table 1. The median age was 62 years (range, 18–88 years), and men comprised 81.9% of the participants. Among these patients, 89 (76.7%) had regional lymph node metastases and 97 (83.6%) were diagnosed with TNM stage III–IV disease. Assessment of CCRT response using PET2 classified 60 patients (51.7%) as achieving CMR, while the remaining 56 (48.3%) were identified as having residual tumor lesions (PMR, SMD, or PMD) (Fig.1). The median follow-up duration was 36.0 months (range, 4.8–132.9 months). During this period, 63 patients (54.3%) experienced PFS events.

Correlation analysis of NHOC and NHOP with clinical factors and CCRT response

The results of correlation analysis between NHOC and NHOP on PET1 and clinical factors are shown in Table 2. Patients with T3–T4 stage exhibited significantly higher values of NHOC than those with T1–T2 stage ($P = .002$), while patients with lymph node metastasis displayed significantly lower values of NHOP compared to those without lymph node metastasis ($P = .020$). These trends were also observed for TNM stage, but lacked statistical significance ($P > .05$). NHOC demonstrated significant positive, but weak, correlations with tumor size, and also with serum inflammatory markers including NLR and PLR ($P < .05$).

In comparisons of NHOC and NHOP according to CCRT response, patients achieving CMR demonstrated significantly lower values of

Table 2
Correlation analysis of NHOC and NHOP on PET1 with clinical factors.

Clinical factors		NHOC	NHOP
Primary site	Nasopharynx	0.61 (0.41–0.85)	0.23 (0.12–0.33)
	Oropharynx	0.63 (0.33–0.78)	0.21 (0.14–0.35)
	Hypopharynx	0.56 (0.31–0.79)	0.19 (0.16–0.32)
	Larynx	0.43 (0.25–0.81)	0.22 (0.18–0.27)
	P-value	.578	.961
Clinical T stage	T1–T2	0.48 (0.29–0.63)	0.21 (0.15–0.34)
	T3–T4	0.68 (0.40–0.85)	0.20 (0.13–0.30)
	P-value	.002	.315
Clinical N stage	N0	0.56 (0.25–0.84)	0.27 (0.18–0.35)
	N1–N3	0.60 (0.36–0.81)	0.19 (0.14–0.31)
	P-value	.594	.020
TNM stage	Stage I–II	0.48 (0.29–0.67)	0.28 (0.15–0.39)
	Stage III–IV	0.62 (0.37–0.84)	0.19 (0.14–0.30)
	P-value	.125	.106
CCRT response	CMR	0.48 (0.29–0.70)	0.23 (0.15–0.34)
	PMR, SMD, and PMD	0.66 (0.47–0.85)	0.19 (0.13–0.32)
	P-value	.007	.102
Tumor size	Correlation coefficient (95% confidence interval)	0.239 (0.059–0.404)	0.069 (−0.115 to 0.248)
	P-value	.010	.460
C-reactive protein	Correlation coefficient (95% confidence interval)	0.076 (−0.107 to 0.255)	0.040 (−0.143 to 0.221)
	P-value	.416	.669
NLR	Correlation coefficient (95% confidence interval)	0.241 (0.062–0.406)	−0.045 (−0.225 to 0.139)
	P-value	.009	.635
PLR	Correlation coefficient (95% confidence interval)	0.218 (0.037–0.385)	−0.082 (−0.261 to 0.102)
	P-value	.019	.381

Data are median (interquartile range).
CCRT, concurrent chemoradiotherapy; CMR, complete metabolic response; NHOC, normalized distance from the hot spot of radiotracer uptake to the tumor centroid; NHOP, normalized distance from the hot spot of radiotracer uptake to the tumor perimeter; NLR, neutrophil-to-lymphocyte ratio; PET, positron emission tomography; PLR, platelet-to-lymphocyte ratio; PMD, progressive metabolic disease; PMR, partial metabolic response, SMD; stable metabolic disease.

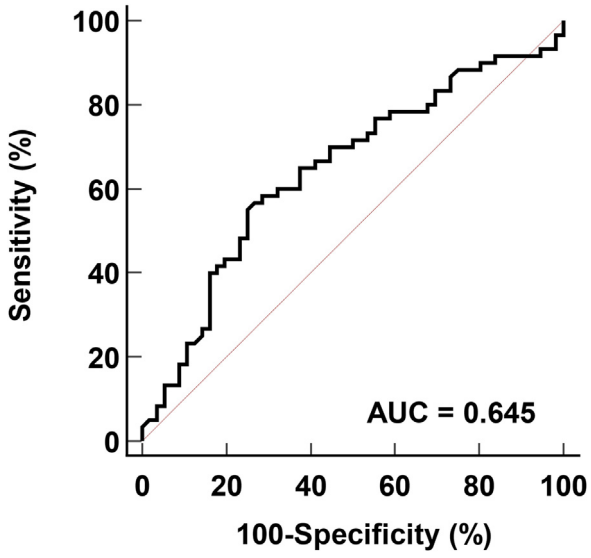

Figure 2. ROC curve analysis of NHOC for predicting CMR.

NHOC than other patients ($P = .007$; Table 2). In ROC curve analysis, NHOC showed the best performance for predicting CMR with an area under the ROC curve (AUC) of 0.645 [95% confidence interval (CI), 0.550–0.731] among the PET1 parameters (Supplementary Table 1; Fig. 2). However, no significant differences were found in the AUC values between NHOC and other PET1 parameters ($P > .05$). For NHOC, a cut-off value of 0.48 was proposed by the Youden index, resulted in a sensitivity of 75.0% and a specificity of 55.0%. In multivariate logistic regression analysis, NHOC on PET1 emerged as the sole independent predictor of CMR after adjustment for age, sex, and TNM stage ($P = .028$; Table 3). A lower value of NHOC was significantly associated with a higher rate of CMR.

Survival analysis for PFS

The prognostic significance of PET1 parameters for predicting PFS was assessed after categorizing into two groups according to specific cut-off values (Table 4). Results from the univariate analysis demonstrated that SUVmax, MTV, TLG, and NHOC were significantly associated with PFS ($P < .05$). Given the significant strong correlation between MTV and TLG ($P < .001$; correlation coefficient, 0.941) and the weak correlations among SUVmax, TLG, and NHOC (correlation coefficient < 0.400), SUVmax, TLG, and NHOC were further included in the multivariate survival analysis. In the multivariate analysis adjusted for age, sex, and TNM stage, both TLG ($P = .017$; hazard ratio, 2.308; 95% CI, 1.369–3.893) and NHOC ($P = .006$; hazard ratio, 2.529; 95% CI, 1.308–4.889) remained as significant predictors for PFS. The Kaplan-Meier survival analysis revealed that patients with an NHOC ≥ 0.49 experienced significantly worse PFS compared to those with an NHOC < 0.49 ($P < .001$; 1-year PFS rate, 52.3% vs. 80.4%; Fig. 3).

The patients were classified as two subgroups according to T stage (T1–T2 stage subgroup, 46 patients; T3–T4 stage subgroup, 70 patients), and the prognostic value of PET1 parameters for predicting PFS was further evaluated in both subgroups (Supplementary Table 2). In the univariate survival analysis, NHOC as well as TLG significantly predicted PFS in both subgroups ($P < .05$ for all). In the Kaplan-Meier survival analysis, patients with high NOC consistently exhibited worse PFS than those with low NHOC in both T1–T2 stage ($P = .021$) and T3–T4 stage ($P = .002$) subgroups (Fig. 4).

Subgroup survival analysis with ΔPET parameter

Among 56 patients classified as PMR, SMD, and PMD, 46 patients (24 with PMD, 7 with SMD, and 15 with PMD) exhibited residual primary tumors on PET2. Therefore, ΔPET parameters were calculated for these 46 patients. In the comparative analysis, patients with SMD and PMD demonstrated significantly higher values of ΔSUVmax [$P = .031$; median, −50.8% (interquartile range, −65.2% to −8.3%) vs. median, −65.1% (interquartile range, −72.1% to −52.3%)],

Table 3
Univariate and multivariate logistic regression analyses of PET1 parameters for predicting CMR.

Parameter	Univariate analysis		Multivariate analysis*	
	P-value	Odds ratio (95% confidence interval)	*P*-value	Odds ratio (95% confidence interval)
SUVmax	.036	0.938 (0.884–0.996)	.120	0.952 (0.895–1.013)
MTV	.107	0.976 (0.948–1.005)		
TLG	.044	0.997 (0.994–1.000)	.291	0.998 (0.995–1.002)
NHOC	.014	0.173 (0.042–0.704)	.028	0.195 (0.045–0.840)
NHOP	.151	10.481 (0.394–278.87)		

CMR, complete metabolic response; MTV, metabolic tumor volume; NHOC, normalized distance from the hot spot of radiotracer uptake to the tumor centroid; NHOP, normalized distance from the hot spot of radiotracer uptake to the tumor perimeter; PET, positron emission tomography; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.
* Multivariate analysis was performed with adjusting for age, sex, and TNM stage.

Table 4
Univariate and multivariate survival analysis of PET1 parameters for predicting PFS.

Parameter	Univariate analysis		Multivariate analysis*	
	P-value	Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)
SUVmax (<17.4 vs. ≥17.4)	.032	1.750 (1.050–2.918)	.417	1.265 (0.718–2.228)
MTV (<8.6 vs. ≥8.6)	.011	1.904 (1.157–3.134)		
TLG (<66.7 vs. ≥66.7)	.002	2.170 (1.316–3.579)	.017	2.308 (1.369–3.893)
NHOC (<0.49 vs. ≥0.49)	.001	2.984 (1.706–5.219)	.006	2.529 (1.308–4.889)
NHOP (<0.15 vs. ≥0.15)	.387	1.293 (0.723–2.313)		

MTV, metabolic tumor volume; NHOC, normalized distance from the hot spot of radiotracer uptake to the tumor centroid; NHOP, normalized distance from the hot spot of radiotracer uptake to the tumor perimeter; PET, positron emission tomography; PFS, progression-free survival; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.
* Multivariate analysis was performed with adjusting for age, sex, and TNM stage.

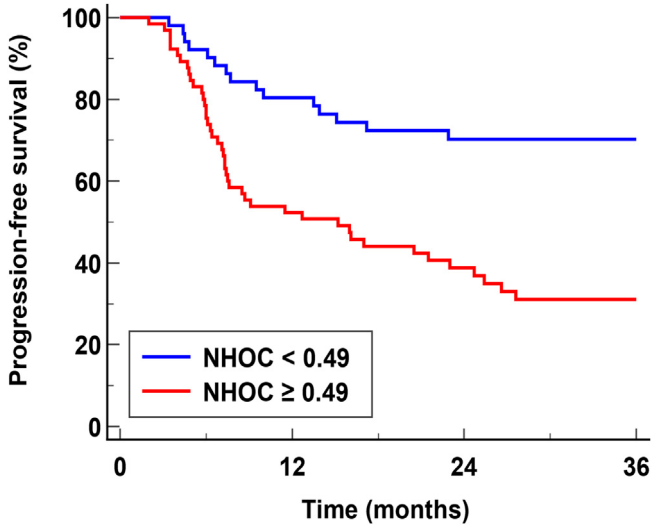

Figure 3. Kaplan-Meier PFS curve stratified by NHOC.

ΔTLG [*P* = .014; median, −52.6% (interquartile range, −87.9% to 0.8%) vs. median, −81.3% (interquartile range, −88.1% to −72.4%)], and ΔNHOC [*P* = .017; median, 4.9% (interquartile range, −17.8% to 68.1%) vs. median, −22.7% (interquartile range, −50.9% to 18.0%)] compared to those with PMR. However, no significant differences in ΔMTV and ΔNHOP were observed between the groups (*P* > .05).

ΔPET parameters were categorized into two groups based on the optimal cut-off values, and the prognostic significance of ΔPET parameters for predicting PFS was assessed in these 46 patients with residual primary tumors (Table 5). In the univariate analysis, ΔNHOC (*P* = .048) and ΔNHOP (*P* = .041) were significant predictors for PFS, whereas all other ΔPET parameters did not achieve statistical significance (*P* > .05). In the Kaplan-Meier survival analysis, patients with high ΔNHOC and low ΔNHOP showed significantly worse PFS than those with low ΔNHOC and high ΔNHOP. The 1-year PFS rates were 66.7% and 52.4% for patients with ΔNHOC < −34.6% and ΔNHOP ≥ 12.6%, respectively, while the rates were 29.7% and 24.0% for patients with ΔNHOC ≥ −34.6% and ΔNHOP < 12.6%, respectively (Fig. 5).

Discussion

It is well-known that cancer tissue consists of subclones of cancer cells with diverse genetic profiles.[19,20] This genetic diversity results in phenotypic and metabolic differences among cells within a cancer lesion, consequently leading to heterogeneous [^{18}F]FDG uptake.[12,19,20] A recent study employed nonlocal Fisher–Kolmogorov model to examine how the location of cancer cells with aggressive features shifts over time.[12] The findings from this study indicated that cancer cells with high rates of proliferation, aggressive phenotypes, and elevated metabolic activity displaced from the tumor center towards the boundary as the cancer develops, primarily due to the increased cancer cell density in the tumor center.[12] Thus, as the tumor advances, the distance between the site of highest metabolic activity (i.e., SUVmax) and the tumor centroid increases, while the distance between the SUVmax and the tumor perimeter decreases.[12] To mitigate inter-tumoral variation, these distances were normalized by the radius of a hypothetical sphere having the same volume as the tumor and were termed NHOC and NHOP, respectively.[12,13] In a prior study involving lung cancer patients, the reproducibility of NHOC and NHOP measurements was found to be excellent, and both parameters showed less variation with changes in image spatial resolution and sampling compared to SUVmax, demonstrating their robustness.[13] In our study, patients with advanced T stage exhibited significantly higher NHOC values than those at an early stage, while those with clinical regional nodal disease displayed significantly lower NHOP values compared to patients without lymph node metastases. Although not reaching statistical significance, patients with stage III−−IV disease also demonstrated higher NHOC values and lower NHOP values than those with stage I−−II disease. Additionally, NLR and PLR, which are known as serum inflammatory biomarkers associated with tumor aggressiveness and poor prog-

Table 5
Univariate survival analysis of ΔPET parameter for predicting PFS in subgroup patients.

Parameter	*P*-value	Hazard ratio (95% confidence interval)
ΔSUVmax (<−64.9% vs. ≥−64.9%)	.174	1.631 (0.806–3.300)
ΔMTV (<−72.5% vs. ≥−72.5%)	.243	1.764 (0.681–4.571)
ΔTLG (<−71.4% vs. ≥−71.4%)	.152	1.640 (0.833–3.229)
ΔNHOC (<−34.6% vs. ≥−34.6%)	.048	2.872 (1.007–8.186)
ΔNHOP (<12.6% vs. ≥12.6%)	.041	0.476 (0.234–0.969)

ΔPET parameter, the percent change in positron emission tomography parameters between pre-treatment and post-treatment scans; MTV, metabolic tumor volume; NHOC, normalized distance from the hot spot of radiotracer uptake to the tumor centroid; NHOP, normalized distance from the hot spot of radiotracer uptake to the tumor perimeter; PFS, progression-free survival; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.

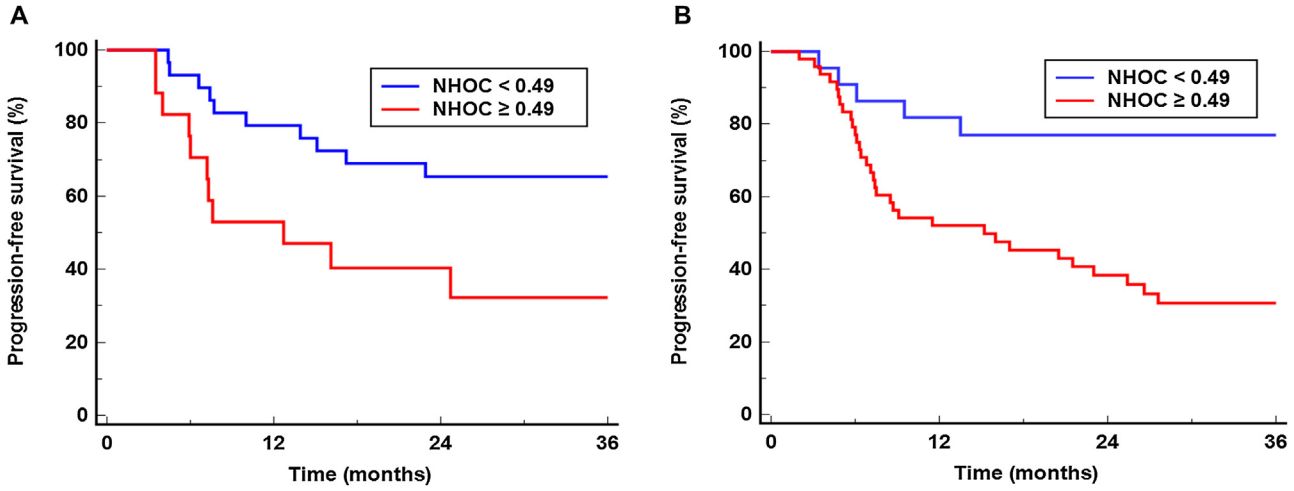

Figure 4. Kaplan-Meier PFS curve stratified by NHOC in 46 subgroups patients with T1–T2 stage (A) and 70 subgroup patients with T3–T4 stage (B).

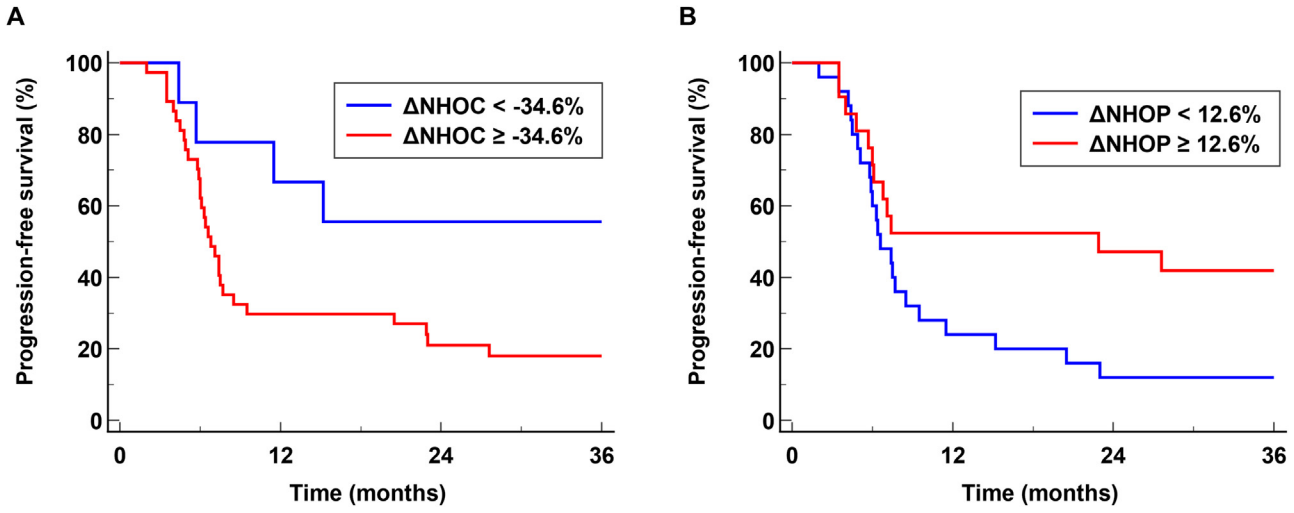

Figure 5. Kaplan-Meier PFS curve stratified by ΔNHOC (A) and ΔNHOP (B) in 46 subgroup patients with residual primary tumors on PET2.

nosis in HNSCC,[21] showed significant positive correlations with NHOC. These findings support the notion that simple geometric parameters related to the location of SUVmax may serve as innovative imaging parameters for evaluating the aggressiveness of malignant diseases, including HNSCC.[12]

In the present study, NHOC measured from pre-treatment PET images demonstrated the most effective performance in predicting CMR among PET parameters, and served as independent predictors for both CMR and PFS in the multivariate analysis after adjusting for age, sex, and TNM stage. Moreover, NHOC showed prognostic significance for predicting PFS in both patient subgroups with early and advanced T stages. Since cancer cells are unable to growth when situated in the tumor center densely populated with cells, while they possess greater capacity for progression and invasion when located at the periphery, it is logical to anticipate a significant association between NHOC and clinical outcomes.[12,14] In previous studies, high NHOC in primary tumors on pre-treatment [^{18}F]FDG PET/CT was significantly associated with poor survival in patients with lung and breast cancers, aligning with our results.[12,13] A previous study involving a breast cancer patient cohort reported a cut-off NHOC value of 0.499 as the optimal threshold for distinguishing between two distinct survival profiles.[12] Similarly, in this study, a cut-off NHOC value of 0.49 was determined, indicating that a cancer lesion displaying the location of SUVmax in the

outer half of the lesion is likely associated with a higher risk of disease progression. In the literature, conventional parameters on pre-treatment PET images including SUVmax, MTV, and TLG have consistently been identified as significant predictors for survival in HNSCC patients[9,22]; however, conflicting results have been shown regarding their predictive capacity for CCRT response.[23,24] Our study suggests that NHOC could be a significant additional [^{18}F]FDG PET/CT biomarker for predicting clinical outcomes in patients with HNSCC, necessitating an aggressive management strategy with careful follow-up surveillance for those with high NHOC values. However, given the moderate predictive ability of NHOC for CMR, relying solely on NHOC for predict CCRT response might have limited utility.

Previous studies with lung cancer patients also demonstrated significant value of NHOP for predicting survival, along with NHOC.[13,14] Contrastingly, NHOP failed to show statistical significance for predicting both PMR and PFS in this study. These conflicting results might result from different methods of delineating primary tumors, since the delineation method could affect the determination of the tumor perimeter. The previous studies employed a fixed relative threshold (40% of SUVmax) method and gradient-based algorithm method for delineation.[13,25] Meanwhile, we used the Nestle's method, which also relies on relative thresholding, but, considers both tumor and background [^{18}F]FDG uptake.[17,26] Nestle's method was initially developed in the field of radiation oncology to more accurately delineate target volumes, but, in numerous studies, PET radiomic parameters extracted using Nestle's method have successfully demonstrated their clinical significance.[17,18,27] Recently, Nestle's method demonstrated the highest segmentation accuracy and strong inter-patient stability in delineating primary tumor lesions in HNSCC patients compared to other methods including fixed relative threshold and algorithm-based methods.[26] However, further studies are required to define the optimal delineation method for calculating NHOP from [^{18}F]FDG PET/CT images.

In addition to NHOC and NHOP on PET1 images, we further investigated the prognostic significance of ΔNHOC and ΔNHOP. Since CMR on post-treatment PET images has been recognized as a significant predictor of survival outcomes,[15,28] we assessed the prognostic value of ΔNHOC and ΔNHOP exclusively in subgroup patients who exhibited residual primary tumors on PET2 images to prevent overestimation of their prognostic value. In our study, patients with SMD and PMD had significantly higher values of ΔNHOC than those with PMR, and both ΔNHOC and ΔNHOP emerged as significant predictors for PFS in these subgroup patients, indicating better survival in patients with markedly decreased ΔNHOC and increased ΔNHOP. These findings imply that a further shift of the location of SUVmax to the tumor edge after CCRT was associated with poor survival outcomes, and the extent of the decline in these two geometric PET parameters could serve as imaging biomarkers for clinical outcomes in patients with HNSCC. Previous studies involving HNSCC patients have identified changes in [^{18}F]FDG PET parameters between pre-treatment and interim PET/CT scans as valuable imaging biomarkers for early prediction of response to radiotherapy or CCRT.[29,30] Similarly, changes in NHOC and NHOP on interim [^{18}F]FDG PET/CT during treatment might aid in the early prediction of response, warranting further investigation.[12]

This study has several limitations. First, this study was conducted retrospectively and involved a relatively small sample size. A study involving a larger patient population is required to validate the results of this study. Second, HNSCC in our analysis included heterogeneous disease entities, and the prognostic value of NHOC and NHOP should be further assessed based on the anatomical location of HNSCC and HPV status. Third, it is recommended to perform post-treatment PET/CT at a minimum of 12 weeks after CCRT completion to assess treatment response in patients with HNSCC.[5] However, because of the retrospective nature of this study, a significant number of patients underwent their PET2 earlier than 12 weeks, which might lead to classification errors of PET response to CCRT. Finally, measurements of NHOC and NHOP were made from the primary tumor only, and residual or recurrent cancer lesions might have originated from a subclone of cancer cells in metastatic lymph nodes that exhibited different characteristics from the primary tumors.[30]

Conclusions

NHOC on PET1 demonstrated the most effective performance in predicting CCRT response, and was an independent significant predictor for CMR and PFS in patients with HNSCC. Patients with high NHOC showed a lower CMR rate and poor PFS. Additionally, ΔNHOC and ΔNHOP between PET1 and PET2 were significantly associated with PFS, indicating worse survival in patients with increased ΔNHOC and decreased ΔNHOP. NHOC on pre-treatment [^{18}F]FDG PET/CT images and the percent changes of NHOC and NHOP after treatment could be potential imaging biomarkers for predicting CCRT response and PFS in patients with HNSCC. Further studies are necessary to confirm their clinical relevance in HNSCC.

Ethical statement

All procedures performed in the study were in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Institutional Review Board of CHA Bundang Medical Center (reference number: CHA2024-07-011) and Soonchunhyang University Cheonan Hospital (reference number: SCHA2024-07-017). The requirement to obtain informed consent was waived by the Institutional Review Board of CHA Bundang Medical Center and Soonchunhyang University Cheonan hospital due to the retrospective nature of this study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.remnie.2025.500103.

Declaration of competing interest

None.

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