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Original Article

Pretreatment nodal SUVmax predicts neck progression in hypopharyngeal cancer undergoing definitive chemoradiotherapy, while higher radiotherapy dose improves regional control particularly in the high SUV-N subgroup: a long-term outcome study

Wing-Keen Yap[1], Chia-Hsin Lin[1], Ken-Hao Hsu[2], Po-Yuan Chen[1], Chien-Yu Lin[1], Shin-Nan Lin[3], Nai-Ming Cheng[4], Kai-Ping Chang[2], Chung-Jan Kang[2], Chi-Kuang Young[2], Chi-Ting Liau[5], Yi-An Lu[2], Yu-Feng Hu[2], Chia-Chi Yeh[2], Ting-Shiuan Yeh[6], Tsung-You Tsai[2]

[1]Department of Radiation Oncology, Proton and Radiation Therapy Center, Linkou Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan City 333, Taiwan; [2]Department of Otolaryngology-Head and Neck Surgery, Linkou Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan City 333, Taiwan; [3]Department of Medical Imaging and Intervention, Linkou Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan City 333, Taiwan; [4]Department of Nuclear Medicine, Linkou Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan City 333, Taiwan; [5]Department of Medical Oncology, Linkou Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan City 333, Taiwan; [6]Department of Otolaryngology, Head and Neck Surgery, New Taipei Municipal Tu-Cheng Hospital, New Taipei City 236, Taiwan

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Abstract: This retrospective study evaluated the prognostic significance of pretreatment maximum standardized uptake value of the primary tumor (SUV-T) and the metastatic lymph nodes (SUV-N) in 146 patients with lymph node-positive hypopharyngeal squamous cell carcinoma (HPSCC) treated with definitive chemoradiotherapy between 2005 and 2013. Pretreatment ^{18}F-FDG PET/CT was utilized to calculate the SUV-T and SUV-N, with clinical correlations assessed via Gamma statistic and survival outcomes analyzed using Kaplan-Meier methods and multivariable Cox regression. The results were further strengthened using multivariable Fine-Gray competing risk regression analysis, considering death as a competing risk when appropriate. After a median follow-up of 9.0 years (95% CI: 7.7-10.2), SUV-N correlated significantly with N category (Gamma coefficient = 0.63, P < 0.001), AJCC stage (Gamma coefficient = 0.53, P = 0.005), and radiologic extranodal extension (Gamma coefficient = 0.80, P < 0.001). SUV-N ≥ 13 predicted worse 5-year regional control (51.8% vs 86.1%, P < 0.001) and showed a borderline significant association with overall survival (26.3% vs 42.6%, P = 0.074). Multivariable analysis confirmed SUV-N ≥ 13 as an independent predictor of regional progression (HR = 4.59, P < 0.001). Competing risk analysis further confirmed that SUV-N ≥ 13 remained a robust predictor of regional progression (subdistribution hazard ratio [SHR] = 4.65; 95% CI: 2.23-9.69; P < 0.001), even after accounting for death as a competing risk. Conversely, radiotherapy dose escalation to 72-74 Gy (EQD2) significantly reduced the risk of regional progression (multivariable Cox regression: HR = 0.41, P = 0.047; multivariable competing risk regression: SHR = 0.37; 95% CI: 0.17-0.84; P = 0.017). Exploratory subgroup analysis revealed that this therapeutic benefit was primarily driven by the high SUV-N subgroup (SUV-N ≥ 13), where dose escalation significantly reduced regional progression (Fine-Gray P = 0.018), whereas no such benefit was observed in the low SUV-N subgroup (Fine-Gray P = 0.740). In contrast, SUV-T was not prognostic for survival outcomes. In conclusion, high pretreatment SUV-N is an independent prognostic factor for regional progression in node-positive HPSCC undergoing definitive chemoradiotherapy. Integrating SUV-N into treatment planning may guide intensified therapies for high-risk patients.

Keywords: Hypopharyngeal squamous cell carcinoma, definitive chemoradiotherapy, nodal SUVmax, ^{18}F-FDG PET/CT, prognostic factor, regional control, dose-escalation, survival outcomes

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Introduction

Head and neck cancer encompasses a variety of malignancies located in the oral cavity, sinonasal tract, nasopharynx, oropharynx, larynx, and hypopharynx, ranking as the seventh most common cancer globally [1-3]. Hypopharyngeal squamous cell carcinoma (HPSCC) is particularly notorious for its poor prognosis, characterized by a high propensity for metastasis to cervical lymph nodes and distant organs, as well as elevated recurrence rates following the current standard radical treatment [4, 5]. With advancements in imaging techniques for staging and prognosticating HPSCC, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has emerged as a pivotal tool, owing to its unique capability to detect tumor metabolic activity [6-10].

The maximum standardized uptake value (SUVmax) is a quantitative parameter commonly used in PET/CT to evaluate tumor metabolic activity [7, 11]. While numerous studies have demonstrated the prognostic significance of the SUVmax of the primary tumor (SUV-T) across various cancers [12-16], findings in patients with head and neck cancers treated with definitive chemoradiotherapy (CRT) have been inconsistent [7]. The most recent meta-analysis published in 2018 concluded that there was no statistically significant association between the SUV-T and oncological outcome measures in patients with locally advanced head and neck squamous cell carcinoma undergoing definitive CRT [7].

In recent years, research has increasingly focused on the prognostic value of the SUVmax of nodal metastases (SUV-N) rather than the primary tumor, yielding positive results across multiple cancers [12, 16-27], including head and neck cancers [28-39]. However, since HPSCC accounts for only 3% to 5% of all head and neck cancers [1, 2], previous studies on the prognostic value of SUV-N have primarily focused on other subsites, such as the oral cavity [29], oropharynx [35], larynx [38], nasopharynx [28, 30, 37], and salivary glands [36]. Even in studies that included all head and neck cancer subsites, the number of HPSCC patients was very limited [31-34, 39].

To date, no studies have thoroughly investigated the prognostic significance of the pre-treatment SUV-N specifically in HPSCC, highlighting a critical knowledge gap that warrants further exploration. Thus, this study aims to evaluate the prognostic significance of pre-treatment SUV-N, as measured by ^{18}F-FDG PET/CT, in patients with lymph node-positive (cN+) HPSCC undergoing definitive CRT.

Material and methods

Patient selection and treatment

Our hospital's institutional review board approved this study (IRB No.: 202400858B0). We evaluated hypopharyngeal cancer patients treated at our hospital between January 2005 and December 2013 from our cancer registry. Inclusion criteria were: biopsy-confirmed HPSCC, staging 18F-FDG-PET/CT scan, staging MRI or CT of the head and neck, cN+ staging, and initial treatment with definitive CRT of ≥ 66 Gy in 2 Gy per fraction, without induction chemotherapy. Per institutional guidelines, the standard concurrent regimen during the study period (2005-2013) was high-dose cisplatin (100 mg/m^2 every three weeks for three cycles). For patients ineligible for cisplatin due to renal insufficiency or other contraindications, carboplatin or cetuximab was administered as an alternative concurrent agent. Patients with prior or simultaneous malignancy or M1 disease were excluded. Clinical staging was based on the AJCC 7th edition. The multidisciplinary tumor board reviewed and confirmed the pre-treatment stage for all patients using two imaging modalities, either CT or MRI combined with PET/CT. In cases where imaging results were inconsistent, fine-needle aspiration or core-needle biopsy was performed to resolve discrepancies. The prescribed radiation dose to the GTVs, including primary tumor and gross metastatic lymph nodes, was converted into an equivalent dose in 2 Gy fractions (EQD2) with an alpha/beta ratio of 10 for further analyses. Per institutional guidelines, the standard prescribed dose to the GTV was 66-70 Gy (EQD2). However, our institutional guidelines allowed for dose escalation to the gross tumor at the discretion of the treating physician. This dose intensification was primarily reserved for patients presenting with bulky lymphadenopathy or those exhibiting a poor response, either

clinically or on CT-simulation for adaptive plan, observed near the completion of the radiotherapy course, rather than being determined by patient fitness alone.

^{18}F-FDG-PET/CT

Pretreatment ^{18}F-FDG-PET/CT scans were done for staging. Patients fasted for at least six hours before the scan. Serum glucose was checked before the PET study and rescheduled if above 200 mg/dL. Scans were done using a Discovery ST system (GE Healthcare) with bismuth germanate detectors and a 16-slice CT, covering from the skull vertex to mid-thigh. Regions of interest (ROIs) were marked over lesions showing ^{18}F-FDG uptake. An experienced nuclear medicine physician drew ROIs using edge-finding techniques, and SUVmax was calculated as follows: PET count at the most intense point × calibration factor (MBq/kg)/injection dose (MBq)/bodyweight (kg). SUV-T represented the SUVmax of the primary tumor, while SUV-N was the highest SUVmax of the regional neck lymph nodes. While routine maintenance and calibration were performed to ensure consistency, no major hardware replacements or fundamental reconstruction algorithm changes occurred during the study period (2005-2013) that would significantly alter SUV quantification.

Post-therapy surveillance

According to our institution's surveillance protocol [40], follow-up visits were scheduled every 1-3 months in the first year, every 3-4 months in the second and third years, and every 4-6 months afterward. Each visit included a flexible nasopharyngeal fiberscopy and a physical examination. Post-treatment imaging was done three months after treatment and then every 6-12 months or as needed. If residual disease or recurrence was suspected, more frequent clinical follow-ups and imaging studies like MRI, CT, and PET were performed. Recurrence was confirmed by biopsy when possible. If a biopsy was not possible or was negative, close clinical and imaging follow-up continued. Recurrences without a biopsy required positive findings in at least two imaging modalities (usually CT or MRI plus PET) along with relevant clinical symptoms and signs.

Statistical analysis

Categorical variables were described by absolute frequency and percentage, and numerical variables by median and range. Median follow-up time was calculated using the reverse Kaplan-Meier estimator [41]. Receiver operating characteristic (ROC) curve analysis was utilized for examining the predictive performance of SUV-T and SUV-N on local progression, regional progression and distant metastasis after CRT [42]. We utilized the Youden Index to determine the optimal cutoff values when the ROC analysis yielded statistically significant results. The Youden Index, calculated as sensitivity + specificity - 1, identifies the point on the ROC curve that maximizes the balance between sensitivity and specificity, thus providing the most accurate threshold for diagnostic purposes. If the ROC analysis results were not statistically significant, we selected the median value as the cutoff to balance the number of patients in each group.

For time-to-event analysis, our study evaluated the following endpoints: the primary endpoint was regional control (RC) and local control (LC), while the secondary endpoints included freedom from distant metastasis (FFDM) and overall survival (OS). Time to progression was measured from the date of radiotherapy (RT) completion to the date of the event or the last follow-up. Overall survival time was measured from the date of RT initiation to the date of death or the last follow-up. Actuarial survival data and curves were generated using the Kaplan-Meier method. The Log Rank test compared survival curves between groups. Univariable and multivariable Cox proportional hazard regression models to assess the effect of various prognostic factors. We employed the stepwise backward conditional selection method for the multivariable model, beginning with a model that included all potential predictor variables (age, T category, N category, AJCC stage, radiologic extranodal extension, SUV-T, SUV-N, and EQD2 of RT). Variables were retained in the final model based on a removal probability threshold of 0.15 and an entry probability threshold of 0.05. All *p*-values were two-sided, with $P < 0.05$ considered statistically significant. To assess for potential multicollinearity among the variables included in the

Table 1. Patient characteristics (n = 146)

Characteristics	No. (%)
Median age, years (range)	53.0 (37.2-78.6)
Male sex	144 (98.6)
Cigarette smoking	
No	8 (5.5)
Yes	138 (94.5)
Betel quid chewing	
No	36 (24.7)
Yes	110 (75.3)
Alcohol drinking	
No	43 (29.5)
Yes	103 (70.5)
T category	
T1	8 (5.5)
T2	21 (14.4)
T3	23 (15.8)
T4a	78 (53.4)
T4b	16 (11.0)
N category	
N1	24 (16.4)
N2a	6 (4.1)
N2b	65 (44.5)
N2c	27 (18.5)
N3	24 (16.4)
AJCC stage	
III	7 (4.8)
IVA	104 (71.2)
IVB	35 (24.0)
Presence of rENE	
No	59 (40.4)
Yes	87 (59.6)
SUV-T	
Median (SD)	14.5 (5.4)
Range	3.5-28.9
SUV-N	
Median (SD)	10.1 (5.2)
Range	1.0-23.9
Median EQD2 of RT, Gy (range)	72 (66-74)
Median RT duration, days (range)	53 (46-70)
Concurrent Chemotherapy	
High-dose Cisplatin	136 (93.2)
Carboplatin	1 (0.7)
Cetuximab	4 (2.7)
5-Fluorouracil	5 (3.4)

Abbreviations: rENE, radiologic extranodal extension; SUV-T, the maximal standardized uptake value of the primary tumor; SUV-N, the maximal standardized uptake value of metastatic lymph nodes; SD, standard deviation; EQD2, equivalent dose in 2 Gy fractions; RT, radiotherapy.

multivariable models, Variance Inflation Factors (VIF) were calculated. A VIF value of < 5 was considered to indicate the absence of significant multicollinearity. Statistical analyses were performed using SPSS® v. 29.0 (IBM Corp., New York, NY, USA).

Results

Patient characteristics

A total of 146 newly diagnosed cN+ non-metastatic HPSCC patients treated with definitive CRT were included in this study. Detailed patient characteristics are provided in **Table 1**. The median age was 53.0 years (range, 37.2-78.6), and the cohort was predominantly male (98.6%). A high prevalence of cigarette smoking (94.5%), betel quid chewing (75.3%), and alcohol consumption (70.5%) was observed. Most patients had advanced disease, with 64.4% classified as T4 and 88.4% as N2 or N3 categories. According to the AJCC stage, 4.8% were stage III, 71.2% were stage IVA, and 24.0% were stage IVB. Radiologic extranodal extension (rENE) was present in 59.6% of patients. The median SUV-T and SUV-N were 14.5 (range, 3.5-28.9) and 10.1 (range, 1.0-23.9), respectively. The median EQD2 of RT was 72 Gy (range, 66-74). Regarding concurrent chemotherapy, the vast majority of patients (93.2%) received high-dose cisplatin administered on a tri-weekly schedule, while a small proportion was treated with 5-fluorouracil (3.4%), cetuximab (2.7%), or carboplatin (0.7%).

Receiver operating characteristic (ROC) analyses

After a median follow-up of 9.0 years (95% CI: 7.7-10.2), there were 105 deaths (71.9%). Disease progression was observed in 77 patients (52.7%), with 40 patients (27.4%) experiencing local progression, 27 patients (18.5%) experiencing regional progression, and 43 patients (29.5%) developing distant metastasis. Receiver operating characteristic (ROC) analyses were performed to evaluate the predictive value of SUV-T and SUV-N for local progression, regional progression, and distant metastasis following CRT. The results were summarized in Table S1. ROC analyses revealed that SUV-N had a significant predictive value for regional progression, with an AUC of 0.660 (P = 0.007), while SUV-T did not show significant predictive

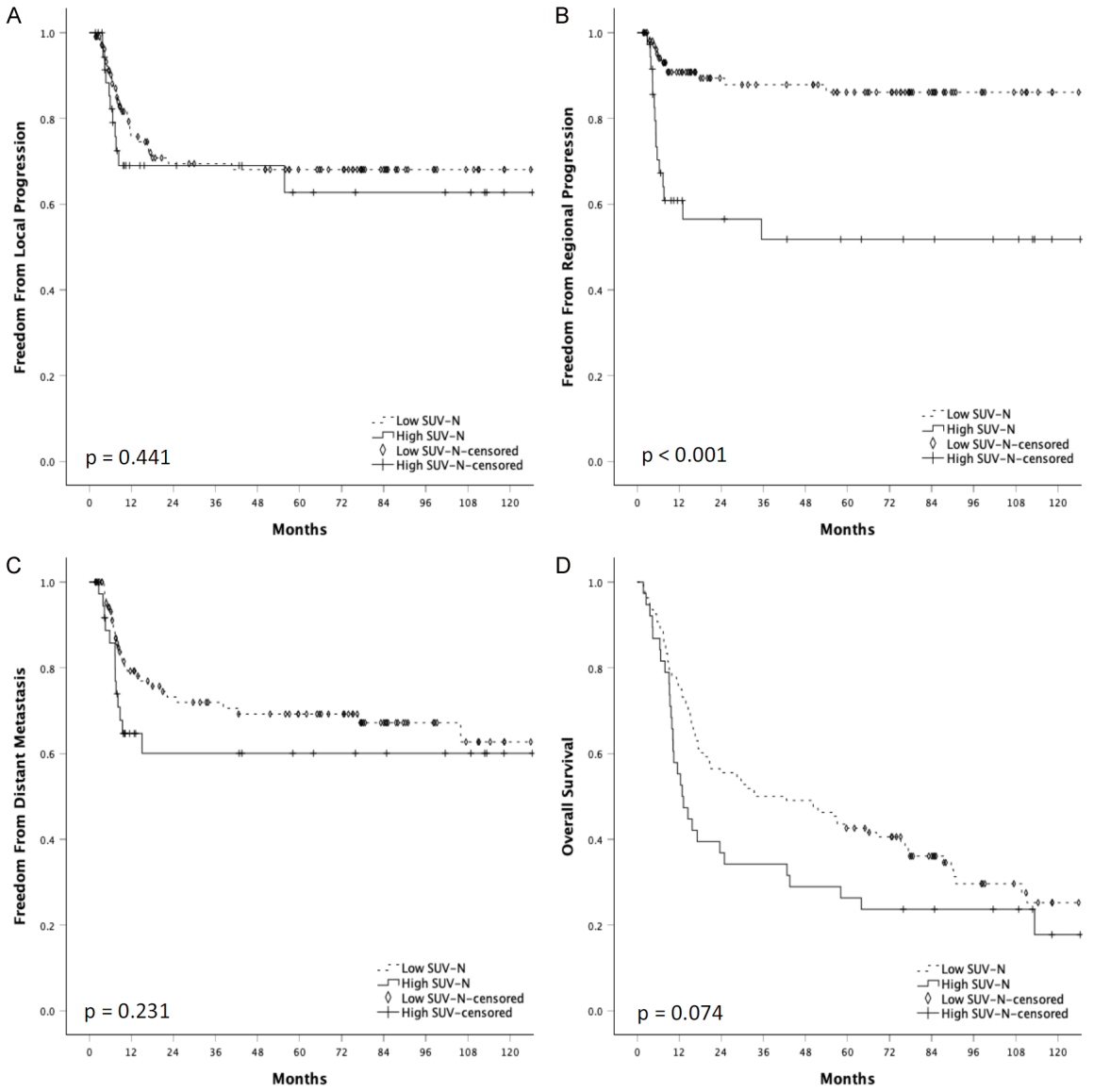

Figure 1. Kaplan-Meier estimates of (A) LC, (B) RC, (C) FFDM, and (D) OS for patients with high SUV-N (≥ 13) versus low SUV-N (< 13). High SUV-N was associated with significantly worse RC (5-year: 51.8% vs 86.1%, P < 0.001) and a trend toward significantly worse OS (5-year: 26.3% vs 42.6%, P = 0.074), while no significant difference was observed in LC (5-year: 62.7% vs 68.1%, P = 0.441) and FFDM (5-year: 60.1% vs 69.2%, P = 0.231).

power for local progression, regional progression, or distant metastasis. The optimal cutoff value for SUV-N to predict regional progression after CRT was determined to be 13.0, based on the highest Youden index. This cutoff value resulted in a specificity of 81.7%, a sensitivity of 55.6%.

Kaplan-Meier survival analysis

In this cohort, the 5-year LC, RC, FFDM, and OS rates were 66.7%, 77.6%, 66.7%, and 38.4%, respectively. The median OS of the cohort was 24.9 months (95% CI, 6.2-43.6). Kaplan-Meier analysis revealed no significant differences in 5-year LC (P = 0.441) or FFDM (P = 0.231) between patients with SUV-N ≥ 13 and < 13. However, a significant difference in RC (P < 0.001) and a near-significant difference for OS (P = 0.074) were observed (**Figure 1**). Patients with SUV-N ≥ 13 had significantly worse 5-year RC (51.8% vs 86.1%) and OS (26.3% vs 42.6%). The median OS for patients with SUV-N ≥ 13

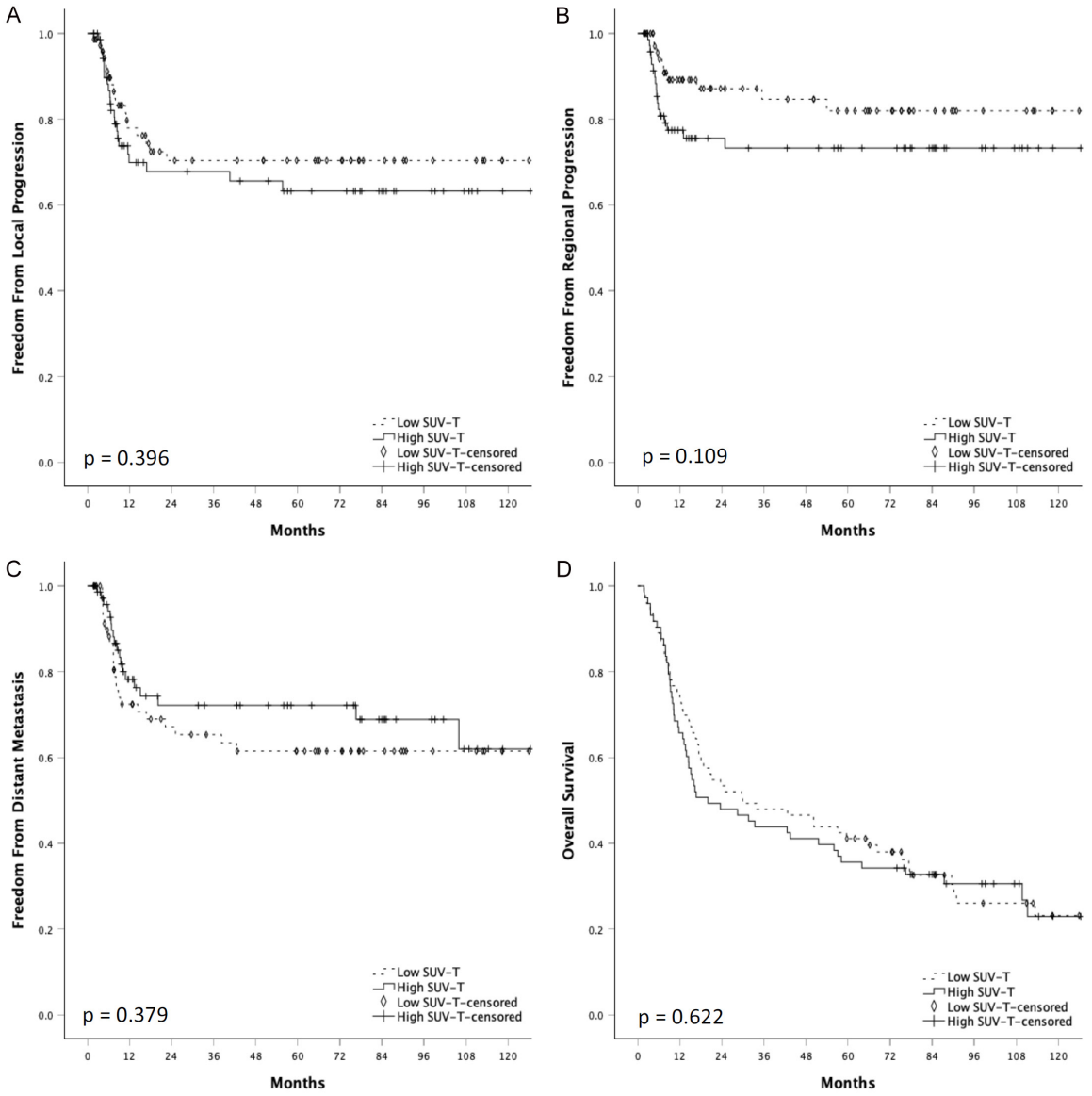

Figure 2. Kaplan-Meier estimates of (A) LC, (B) RC, (C) FFDM, and (D) OS for patients with high SUV-T (≥ 14.5) versus low SUV-T (< 14.5). No significant differences were observed in LC (5-year: 63.2% vs 70.4%, P = 0.396), RC (5-year: 73.3% vs 81.9%, P = 0.109), FFDM (5-year: 72.2% vs 61.5%, P = 0.379), or OS (5-year: 35.6% vs 41.1%, P = 0.622).

was 12.9 months, significantly worse than that of patients with SUV-N < 13, whose median OS was 33.9 months. For SUV-T, no significant differences were observed in LC, RC, FFDM, or OS between patients with SUV-T ≥ 14.5 and < 14.5 (**Figure 2**).

Correlations between the SUV-T, SUV-N, and clinical characteristics

The correlations between the SUV-T, SUV-N, and various clinical factors were analyzed, revealing significant associations in several categories. The detailed results are summarized in **Table 2**. High SUV-N exhibited strong positive associations with a more advanced N category (Gamma coefficient = 0.63, P < 0.001), more advanced AJCC stage (Gamma coefficient = 0.53, P = 0.005), and the presence of rENE (Gamma coefficient = 0.80, P < 0.001). In contrast, SUV-T demonstrated a moderate strength of significant correlation only with the T category (Gamma coefficient = 0.32, P = 0.013). Additionally, a moderate positive correlation was observed between SUV-N and SUV-T (Gamma coefficient = 0.475, P = 0.007).

Table 2. Correlations between the SUV-T, SUV-N, and clinical characteristics

Characteristics	No.	SUV-T ≥ 14.5			SUV-N ≥ 13		
		No. (%)	Gamma coefficient[a]	*p*-value	No. (%)	Gamma coefficient[a]	*p*-value
Age			-0.11	0.507		0.05	0.780
< 53	72	38 (52.8%)			18 (25.0%)		
≥ 53	74	35 (47.3%)			20 (27.0%)		
T category			0.32	0.013		-0.13	0.356
T1	8	1 (12.5%)			1 (12.5%)		
T2	21	8 (38.1%)			5 (23.8%)		
T3	23	12 (52.2%)			10 (43.5%)		
T4a	78	41 (52.6%)			20 (25.6%)		
T4b	16	11 (68.8%)			2 (12.5%)		
N category			0.18	0.146		0.63	< 0.001
N1	24	9 (37.5%)			0 (0.0%)		
N2a	6	2 (33.3%)			1 (16.7%)		
N2b	65	33 (50.8%)			15 (23.1%)		
N2c	27	17 (63.0%)			7 (25.9%)		
N3	24	12 (50.0%)			15 (62.5%)		
AJCC stage			0.19	0.284		0.53	0.005
III	7	4 (57.1%)			0 (0.0%)		
IVA	104	48 (46.2%)			23 (22.1%)		
IVB	35	21 (60.0%)			15 (42.9%)		
Presence of rENE			0.03	0.866		0.80	< 0.001
No	59	29 (49.2%)			4 (6.8%)		
Yes	87	44 (50.6%)			34 (39.1%)		
EQD2 of RT, Gy			0.18	0.399		0.28	0.231
66-70	28	12 (42.9%)			5 (17.9%)		
72-74	118	61 (51.7%)			33 (28.0%)		
SUV-N			0.475	0.007			
< 13	108	47 (43.5%)					
≥ 13	38	26 (68.4%)					

Abbreviations: SUV-T, standardized uptake value of the primary tumor; SUV-N, the highest standardized uptake value of neck lymph nodes; rENE, radiologic extranodal extension. [a]Gamma correlation test was applied to measures the strength and direction of association for ordinal data. The Gamma coefficient indicates the strength of association as follows: less than 0.3 is weak, 0.3 to 0.5 is moderate, and greater than 0.5 is strong.

Univariate and multivariable analyses

Results of the univariable analysis of the influence of various clinical factors on LC, RC, FFDM, and OS are shown in **Table 3**. The T4 category was significantly associated with worse LC (HR = 2.59; P = 0.012) and OS (HR = 2.33; P < 0.001). The N3 category significantly impacted RC (HR = 4.55; P < 0.001) and FFDM (HR = 2.38; P = 0.014). AJCC stage IVB was a significant predictor for worse RC (HR = 3.67; P < 0.001), FFDM (HR = 2.49; P = 0.004), and OS (HR = 1.98; P = 0.002). Both rENE (HR = 2.73; P = 0.030) and SUV-N (HR = 4.81; P < 0.001) were significantly associated with worse RC.

Multivariable Cox regression analyses confirmed the independent prognostic significance of several factors (**Table 4**). The T4 category was independently associated with worse LC (HR = 2.59; 95% CI, 1.23-5.46; P = 0.012) and OS (HR = 2.38; 95% CI, 1.53-3.70; P < 0.001). AJCC stage IVB was an Independent predictor for worse RC (HR = 2.88; 95% CI, 1.29-6.43; P = 0.010), FFDM (HR = 2.66; 95% CI, 1.40-5.08; P = 0.003), and OS (HR = 1.74; 95% CI, 1.12-2.69; P = 0.013). SUV-N ≥ 13 was the

Table 3. Univariable Cox regression analysis of clinical factors on LC, RC, FFDM, and OS

Characteristic	No	LC		RC		FFDM		OS	
		HR	*p*	HR	*p*	HR	*p*	HR	*p*
Age, years									
< 53 (ref)	72								
≥ 53	74	0.71	0.288	0.86	0.702	0.55	0.062	0.85	0.408
T category									
T1-3 (ref)	52								
T4	94	2.59	0.012	1.90	0.146	1.51	0.212	2.33	< 0.001
N category									
N1-2 (ref)	122								
N3	24	1.30	0.526	4.55	< 0.001	2.38	0.014	1.77	0.023
AJCC stage									
III-IVA (ref)	111								
IVB	35	1.64	0.156	3.67	< 0.001	2.49	0.004	1.98	0.002
rENE									
Absence (ref)	59								
Presence	87	1.11	0.751	2.73	0.030	1.76	0.088	1.36	0.131
SUV-T									
< 14.5 (ref)	73								
≥ 14.5	73	1.31	0.398	1.87	0.115	0.76	0.381	1.10	0.622
SUV-N									
< 13 (ref)	108								
≥ 13	38	1.31	0.443	4.81	< 0.001	1.49	0.234	1.47	0.074
EQD2 of RT, Gy									
66-70 (ref)	28								
72-74	118	0.79	0.537	0.66	0.345	0.86	0.682	0.95	0.818

Abbreviations: HR, hazard ratio; LC, local control; RC, regional control; FFDM, freedom from distant metastasis; OS, overall survival; rENE, radiologic extranodal extension; SUV-T, the maximal standardized uptake value of the primary tumor; SUV-N, the maximal standardized uptake value of metastatic lymph nodes; EQD2, equivalent dose in 2 Gy fractions; RT, radiotherapy.

strongest independent predictor for worse RC (HR = 4.59; 95% CI, 2.06-10.26; P < 0.001) and showed a trend towards impacting OS (HR = 1.42; 95% CI, 0.91-2.19; P = 0.120). Higher RT dose (EQD2 72-74 Gy) was associated with improved RC (HR = 0.41; 95% CI, 0.17-0.99; P = 0.047). While both T4 category and AJCC stage IVB are significant predictors of poor outcomes, SUV-N ≥ 13 emerges as a robust marker for assessing the risk of regional progression after CRT in patients with cN+ HPSCC.

Furthermore, collinearity diagnostics verified the robustness and mathematical stability of the final multivariable models, with all retained predictors demonstrating VIF values between 1.000 and 1.081 (**Table 4**). These results indicate negligible collinearity among the independent variables, ensuring that the model estimates were not compromised by redundant covariates and confirming the high reliability of the reported prognostic outcomes.

Given the high mortality rate in this cohort, a Fine-Gray competing risk regression model was performed to verify the predictors of regional progression, treating death from any cause as a competing risk (**Table 5**). The analysis confirmed that pretreatment SUV-N ≥ 13 remained a robust and independent predictor of regional progression, with a subdistribution hazard ratio (SHR) of 4.65 (95% CI: 2.23-9.69; P < 0.001). Additionally, AJCC Stage IVB was associated with an increased risk of regional progression (SHR = 2.97; 95% CI: 1.36-6.46; P = 0.006). Conversely, dose escalation to 72-74 Gy (EQD2) significantly reduced the risk of regional progression (SHR = 0.37; 95% CI: 0.17-0.84; P = 0.017), suggesting a protective benefit even

Table 4. Multivariable Cox regression analysis of clinical factors on LC, RC, FFDM, and OS

Clinical Factors	Multivariable Analyses*			
	HR	95% Confidence Interval	*P*-value	VIF
Local Control				
T4 category	2.59	1.23-5.46	0.012	1.000
Regional Control				
SUV-N ≥ 13	4.59	2.06-10.26	< 0.001	1.065
AJCC stage IVB	2.88	1.29-6.43	0.010	1.068
EQD2 of RT (72-74 Gy)	0.41	0.17-0.99	0.047	1.018
T4 category	2.16	0.90-5.17	0.084	1.019
Freedom From Distant Metastasis				
AJCC stage IVB	2.66	1.40-5.08	0.003	1.033
Age ≥ 53	0.53	0.29-1.00	0.050	1.030
SUV-T ≥ 14.5	0.56	0.29-1.06	0.073	1.035
T4 category	1.78	0.91-3.49	0.093	1.039
Overall Survival				
T4 category	2.38	1.53-3.70	< 0.001	1.030
AJCC stage IVB	1.74	1.12-2.69	0.013	1.081
SUV-N ≥ 13	1.42	0.91-2.19	0.120	1.064
Age ≥ 53	0.74	0.50-1.10	0.136	1.030

Abbreviations: HR, hazard ratio; SUV-T, the maximal standardized uptake value of the primary tumor; SUV-N, the maximal standardized uptake value of metastatic lymph nodes; EQD2, equivalent dose in 2 Gy fractions; RT, radiotherapy; VIF, variance inflation factor. *Stepwise backward conditional selection method, starting with a model that includes all potential predictor variables (age, T category, N category, AJCC stage, radiologic extranodal extension, SUV-T, SUV-N, and EQD2 of RT). VIF values < 5 indicate the absence of significant multicollinearity among predictors retained in the final model.

Table 5. Multivariable fine-gray competing risk regression analysis of clinical factors predicting regional progression

Clinical Factors*	SHR	95% Confidence Interval	*P*-value
SUV-N ≥ 13	4.65	2.23-9.69	< 0.001
AJCC Stage IVB	2.97	1.36-6.46	0.006
EQD2 of RT (72-74 Gy)	0.37	0.17-0.84	0.017
T4 Category	1.91	0.83-4.41	0.130

Abbreviations: SHR, subdistribution hazard ratio; SUV-N, the maximal standardized uptake value of metastatic lymph nodes; EQD2, equivalent dose in 2 Gy fractions; RT, radiotherapy. *The Fine-Gray subdistribution hazard model was employed to estimate the risk of regional progression, accounting for death as a competing risk. Variables included in the final model were selected using a stepwise backward approach.

after adjusting for tumor burden and metabolic activity.

Exploratory subgroup analyses

Exploratory subgroup analyses were conducted for the primary endpoint of RC stratified by SUV-N. As shown in **Figure 3**, patients in the high SUV-N subgroup (SUV-N ≥ 13) exhibited a non-significant trend toward improved regional control with dose escalation (higher EQD2), with RC curves separating early and remaining distinct over time (Log-rank P = 0.054). The non-significant trend observed in the high SUV-N subgroup likely reflects limited statistical power to detect a definitive difference due to the relatively small sample size in this exploratory analysis. Notably, when a Fine-Gray competing risk regression was performed to rigorously account for the high mortality rate in this population, the analysis confirmed that dose escalation (EQD2 of 72-74 Gy) significantly reduced the risk of regional progression in the high SUV-N subgroup (SHR = 0.27; 95% CI: 0.09-0.80; P = 0.018).

In contrast, no apparent benefit of dose escalation was observed in the low SUV-N subgroup (Log-rank P = 0.730). This lack of benefit was further confirmed by competing risk regression, which showed no significant reduction in regional progression risk (SHR = 0.80; 95% CI:

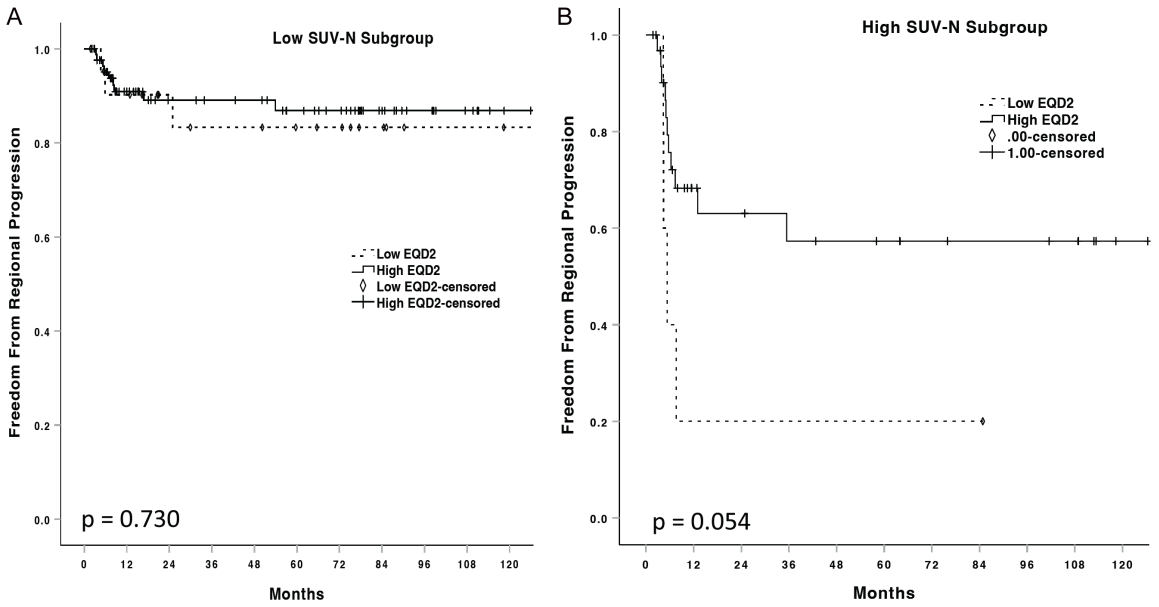

Figure 3. Kaplan-Meier estimates of RC for low EQD2 versus high EQD2 in subgroups with (A) low SUV-N (< 13) and (B) high SUV-N (≥ 13). No significant differences were observed in the low SUV-N subgroups (5-year RC: 83.3% vs 86.9%, P = 0.730). In the high SUV-N subgroup, patients receiving higher EQD2 showing a non-significant trend toward better regional control against patients receiving lower EQD2 (5-year RC: 20.0% vs 57.3%, P = 0.054).

0.22-2.92; P = 0.740). These findings suggest that the regional control advantage associated with higher radiation dose was primarily derived from patients with high SUV-N.

Discussion

Pretreatment ^{18}F-FDG PET/CT scans not only play a critical role in the diagnosis and initial staging of head and neck carcinomas but have also been shown to indirectly measure the expression of various biological markers of tumor aggressiveness, thereby serving as a valuable prognostic tool [7, 43-45]. PET/CT imaging provides valuable metabolic tumor parameters, including SUV, metabolic tumor volume (MTV), and total lesion glycolysis (TLG), which have been widely studied for their clinical relevance in head and neck cancers [7, 46, 47]. While volumetric parameters such as MTV and TLG offer comprehensive biological insights, this study focused on SUVmax for its specific advantages in clinical reproducibility. In clinical practice worldwide, SUVmax remains the most commonly used parameter because it is independent of ROI definition, less observer-dependent, and more reproducible compared to SUVmean, MTV and TLG [48-51]. Although SUVmax is more susceptible to image noise than volumetric metrics, its robustness and ease of implementation across different institutional settings justify its use as a standard prognostic tool in HPSCC [48-51].

Nevertheless, the prognostic value of pretreatment SUV-T in patients with head and neck carcinomas undergoing definitive CRT has been questioned, as studies on this topic have yielded contradictory results, with the most recent meta-analysis reporting a negative finding [7]. In contrast, the studies on the prognostic value of pretreatment SUV-N have consistently yielded positive outcomes across various subsites of head and neck cancers [28-39]. However, the prognostic value of pretreatment SUV-N in the specific setting of patients with HPSCC undergoing definitive CRT remains underexplored, with very limited data published due to the disease's low incidence [1, 2, 31-34, 39]. Notably, HPSCC is known for its aggressive nature and significant risk of early metastasis to cervical lymph nodes, with neck metastasis observed in approximately 65% to 80% of cases at diagnosis [4]. Consequently, assessing the prognostic significance of pretreatment SUV-N specifically in HPSCC holds substantial clinical value.

To the best of our knowledge, this is the first study to specifically evaluate the prognostic significance of pretreatment SUV-N in HPSCC undergoing definitive CRT, with a study sample size of 146 cases and a long follow up time. Our findings demonstrated that SUV-N is significantly correlated with clinical parameters, including N category, advanced AJCC stage, and rENE (**Table 2**). These correlations support the hypothesis that patients with high SUV-N exhibit more aggressive tumor biology and greater resistance to treatment, leading to poorer prognoses. Although our study utilized the AJCC 7th edition staging system, our findings have significant implications for the current AJCC 8th edition, which formally incorporates clinically overt extranodal extension (ENE) - unequivocal evidence of gross ENE on physical examination supported by strong radiographic findings - into clinical N-staging. We observed a strong correlation between high SUV-N and radiologic ENE (Gamma = 0.80). Interestingly, while both variables showed significance in univariable analysis, only SUV-N was retained as a significant independent predictor of regional progression in the final multivariable model, with rENE being excluded during the stepwise backward conditional selection process. This suggests that SUV-N may serve as a more sensitive metabolic surrogate for aggressive biological behavior - including subclinical ENE - that anatomic imaging alone may miss. High SUV-N could thus identify patients who behave like clinical ENE-positive (cN3b in AJCC 8th edition) even in the absence of overt radiological signs. Consequently, high pretreatment SUV-N may identify a subset of patients with 'metabolic ENE' who are at an exceptionally high risk for regional failure, potentially justifying more intensive local interventions even in the absence of overt radiological ENE.

The key findings of this study are that a pretreatment SUV-N ≥ 13 was significantly associated with worse RC (HR = 4.81, P < 0.001) and showed a trend toward worse OS (HR = 1.47, P = 0.074) in univariable analysis. Furthermore, multivariable Cox regression analysis confirmed SUV-N ≥ 13 as a strong independent predictor of regional progression (HR = 4.59, P < 0.001) and as showing a non-significant trend for worse OS (HR = 1.42, P = 0.120). The increased rate of regional progression may translate into worse OS due to delays in salvage surgery and the heightened technical complexity of post-chemoradiation salvage procedures, resulting in a low salvageable rate (15%-30%), a high incidence of postoperative complications (40%-70%), and ultimately poor survival outcomes, with 5-year overall survival rates of only 20%-30% for those undergoing salvage surgery after definitive CRT as reported in previous studies [52].

In this study, among the 27 patients who experienced regional progression, 11 (41%) had isolated regional recurrence at the time of first failure, 12 (44%) experienced regional progression concurrently with or following primary tumor progression, and 4 (15%) developed regional progression alongside or after the onset of distant metastasis. Fourteen patients (52%) underwent salvage surgery consisting of neck dissection with or without pharyngolaryngectomy. However, within one year of salvage surgery, 5 patients (43%) developed further locoregional recurrence without distant metastasis, and 6 patients (43%) developed distant recurrence (including one patient who experienced both distant and locoregional failure). One patient developed distant metastasis three years after salvage treatment, and only two patients remained disease-free at the time of last follow-up or death. For the entire cohort of patients with regional failure, the median survival after regional progression was 7.4 months (95% CI: 3.4-11.4), with only one patient surviving beyond 5 years (5-year OS = 3.7%), highlighting the grave prognosis associated with regional progression.

Nevertheless, the borderline statistical significance for OS in the univariable and multivariable analyses may be attributable to the relatively small sample size (n = 146) of the current study, which lacked sufficient power to detect a difference. Interestingly, a higher EQD2 of RT was identified as an independent protective factor for RC (HR = 0.41, P = 0.047) in multivariable analysis. Exploratory subgroup analysis further demonstrated that this therapeutic benefit was primarily driven by the high SUV-N subgroup (SUV-N ≥ 13), where dose escalation significantly reduced regional progression (Fine-Gray P = 0.018), compared to no observed benefit in the low SUV-N subgroup (Fine-Gray P = 0.740). These findings suggest that a

dose-escalation strategy may be particularly advantageous for patients at high risk of regional progression following definitive CRT.

In the current study, pre-treatment SUV-T was not associated with OS, RC, LC, or FFDM, consistent with the conclusions of the meta-analysis by Bonomo et al. [7]. Notably, previous studies focusing primarily on other subsites of head and neck cancers undergoing definitive CRT also support the prognostic value of pretreatment SUV-N, in addition to its critical role in cancer staging [28, 30, 31, 34, 37]. For instance, Inokuchi et al. analyzed 178 head and neck cancer patients with nodal metastasis treated with definitive CRT, of whom only 15% (n = 27) had HPSCC [34]. They concluded that a high pretreatment SUV-N was a significantly unfavorable prognosticator for disease-free survival, nodal progression-free survival, and distant metastasis-free survival [34]. Furthermore, among patients with high SUV-N, those who underwent planned neck dissection had better nodal progression-free survival [34]. These findings are consistent with our study results and further support the idea that escalating neck treatment (e.g., RT dose escalation or planned neck dissection) guided by pretreatment SUV-N may improve treatment outcomes in patients receiving definitive CRT. Similarly, another study by Werner et al. investigated 90 patients with head and neck cancers treated with definitive CRT, of whom 21 (23.3%) had HPSCC, and found that SUV-N was independently predictive of disease-specific survival [31]. In addition, three separate studies on nasopharyngeal cancer patients undergoing CRT concluded that high pretreatment SUV-N values were independent poor prognostic factors for OS and PFS [28, 30, 37]. Collectively, these findings underscore the prognostic significance of SUV-N in patients with head and neck cancers treated with definitive CRT.

Interestingly, the optimal SUV-N cutoff of 13.0 identified in this study is notably higher than thresholds reported in other head and neck subsites [28-39]. This is likely attributable to the distinct biological aggressiveness of HPSCC. HPSCC typically presents with a higher burden of nodal disease (88.4% N2-N3 in our cohort) and large lymph nodes, which exhibit intense metabolic activity. Consequently, a higher metabolic threshold may be necessary to effectively stratify risk in this specific malignancy compared to oral cavity, oropharyngeal, or nasopharyngeal cancers [28-39].

Limitations

Although this study is the first to examine SUV-N as a prognostic marker in HPSCC using the largest cohort to date, it has several limitations. The retrospective design may introduce selection and information biases, and confounding factors could not be fully controlled, which may limit the generalizability of the findings. Additionally, being conducted at a single institution, the results require validation in independent, multicenter cohorts to confirm their robustness. The relatively small sample size, despite a lengthy follow-up period, may also reduce the statistical power of certain analyses. To address these limitations, large-scale, multicenter prospective studies are needed to validate the findings. Finally, while SUVmax is clinically practical, it cannot fully characterize intratumoral heterogeneity and remains susceptible to image noise. Future research should incorporate AI-based radiomics models using multi-modality PET/CT and CT imaging to enhance risk stratification [53-55]. Such advanced computational approaches could facilitate personalized adaptive strategies, such as metabolic-guided dose painting, further optimizing regional control and long-term survival in HPSCC.

Conclusion

In this study, SUV-N demonstrated a significant correlation with key clinical parameters, including N category, advanced AJCC stage, and rENE. Furthermore, the findings identified high pre-treatment SUV-N as an independent unfavorable prognostic factor for regional progression in HPSCC patients. These findings are supported by a robust median follow-up period of 9.0 years, providing a rigorous assessment of long-term oncological outcomes. Integrating SUV-N into treatment planning and prognostic assessments may facilitate the identification of high-risk patients who could benefit from intensified therapeutic strategies. Additionally, these results provide valuable insights for the design of future studies.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Tsung-You Tsai, Department of Otolaryngology-Head and Neck Surgery, Linkou Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan City 333, Taiwan. Tel: +886-3-3281200 Ext. 7000; Fax: +886-3-3280797; E-mail: J-acky_101@hotmail.com

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Table S1. Receiver operating characteristic analyses of SUV-T and SUV-N for predicting local progression, regional progression, and distant metastasis after chemoradiotherapy

Total N = 146	SUV-T		SUV-N	
	AUC (SE)	*p*-value	AUC (SE)	*p*-value
Local Progression (n = 40)	0.558 (0.053)	0.268	0.529 (0.053)	0.578
Regional Progression (n = 27)	0.564 (0.058)	0.265	0.660 (0.059)	0.007
Distant Metastasis (n = 43)	0.431 (0.054)	0.206	0.545 (0.054)	0.402

Abbreviations: AUC, area under the curve; SUV-T, the maximal standardized uptake value of the primary tumor; SUV-N, the maximal standardized uptake value of metastatic lymph nodes.