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FDG Volumetric Parameters and Survival Outcomes After Definitive Chemoradiotherapy in Patients With Recurrent Head and Neck Squamous Cell Carcinoma

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Abstract

OBJECTIVE—The purpose of this study was to establish the predictive value of ¹⁸F-FDG parameters for overall survival in biopsy-proven recurrent head and neck squamous cell cancer (HNSCC) patients after definitive chemoradiotherapy.

MATERIALS AND METHODS—We conducted a retrospective study including 34 patients with HNSCC who had biopsy-proven recurrence between April 2004 and March 2012 and underwent FDG PET/CT at our institution at the time of recurrence. Maximum standardized uptake value (SUV_{max}), peak SUV (SUV_{peak}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured. The primary outcome measure was overall survival. ROC analysis, univariate and multivariate Cox regression models, and Kaplan-Meier survival curves were performed.

RESULTS—In univariate analyses, human papillomavirus (HPV) status ($p = 0.04$), primary site recurrence of MTV ($p = 0.03$), metastasis of MTV ($p = 0.02$), metastasis of TLG ($p = 0.02$), total MTV ($p = 0.002$), and total TLG ($p = 0.04$) were significantly associated with overall survival outcome. Total MTV remained as significant independent prognostic factor when adjusted for all other covariates except for primary site recurrence SUV_{max} and SUV_{peak} and lymph node SUV_{max} and SUV_{peak}. There was a significant difference in time to survival between patients with total MTV above and below the 50th percentile (Mantel-Cox log-rank test, $p = 0.05$ and Gehan-

Breslow-Wilcoxon test, $p = 0.03$) and the optimum threshold of 16.8 mL (Mantel-Cox log-rank test, $p = 0.01$ and Gehan-Breslow-Wilcoxon test, $p = 0.01$; hazard ratio [HR], 0.25).

CONCLUSION—FDG PET/CT-based total MTV and clinical HPV status may be significant prognostic markers for overall survival of patients with recurrent HNSCC after definitive chemoradiotherapy.

Keywords

head and neck squamous cell carcinoma recurrence; human papillomavirus; metabolic tumor volume

Head and neck cancer is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide each year [1]. Up to 50% of head and neck squamous cell carcinoma (HNSCC) patients will experience recurrence or residual disease even after therapy with curative intent [2]. Locoregional recurrence remains the most common cause of failure in head and neck cancer and accounts for approximately 40–60% of head and neck cancer related deaths [3–5]. The majority of recurrences occur within 3 years of completion of treatment [2, 6, 7]. Recurrence in the neck offers a distinctly higher risk of mortality as opposed to local failure [8]. Historically, patients with recurrence had a poor survival of 4–7 months [9, 10]. However, recent studies suggest that there is improvement in survival for these patients with new treatment options [11].

Over the past decade, ^{18}F -FDG PET/CT has evolved as a valuable imaging modality for staging, treatment response evaluation, and surveillance for recurrence in patients with many human solid tumors [12–20]. Studies have shown that FDG PET/CT is highly sensitive and specific [21–23] in the posttreatment setting. Various FDG parameters have been tested in the pre- and postradiotherapy settings as potential prognostic factors for outcome in HNSCC. Maximum standardized up-take value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) are the common FDG quantitative parameters that have been studied along with qualitative assessments. The purpose of our study was to establish the prognostic value of the volumetric FDG PET parameters of MTV and TLG in recurrent head and neck cancer after definitive chemoradiotherapy.

Materials and Methods

Patient Characteristics

This is a retrospective study approved by the Johns Hopkins institutional review board (IRB). HIPAA guidelines were followed, and an informed consent waiver was obtained from the IRB. Inclusion criteria included biopsy-proven or follow-up imaging confirmation of recurrence of head and neck squamous cell carcinoma (HNSCC) after definitive chemoradiotherapy. We excluded patients with previously treated recurrences or distant metastases at initial presentation or treated primarily with surgery. The study group was composed of 34 patients (13 women and 21 men; mean age [$\pm$ SD], 57 ± 14 years) who presented with recurrence between April 2004 and March 2012 and underwent FDG PET/CT at our institution.

All patients received radiation therapy with or without chemotherapy. The radiation therapy regimen included a total dosage of 70 Gy that was given in 35 fractions at a dose of 200 cGy per fraction over a course of 50 days. Most patients were treated with an intensity modulated radiation therapy approach. The chemotherapy regimen was variable and included either concurrent chemotherapy alone ($n = 24$) or induction chemotherapy followed by concurrent chemotherapy ($n = 6$). Patients receiving induction chemotherapy were treated with 2–3 cycles of cisplatin, taxotere, and 5-fluorouracil or cisplatin and cetuximab. Patients treated with concurrent chemotherapy were treated either with cisplatin or with cetuximab started within 3–7 days of radiation therapy commencement. Carboplatin was used instead of cisplatin in patients with an elevated creatinine or those who developed side effects precluding continuation of cisplatin during treatment.

Outcome Endpoints

Data collection included patient age, sex, and overall stage at presentation; risk factors; treatment received; and mortality data at last follow-up. Overall mortality was determined from the Social Security database or hospital electronic medical records. Time to overall survival was measured from the date of the original positive PET/CT to diagnosis of recurrence or to the last follow-up in patients who were still alive or to the date of death for patients who had died. For all patients, including those who died, the mean length of follow-up was 27.03 ± 25.58 months and the median length of follow-up was 17.5 months (interquartile range [IQR], 8.0–37.5).

PET/CT Protocol

All PET/CT studies were performed using either a Discovery LS (2D) or a Discovery RX VCT (3D) scanner (both scanners, GE Healthcare). All patients were scanned using a dedicated head and neck protocol as part of the standard clinical protocol at our institution. Patients were scanned from skull vertex to mid thigh in two separate acquisitions starting from mid thigh to chin and then from carina to skull vertex. Head and neck images were acquired with the arms down and body images were obtained with the arms up. The average patient blood glucose level was 91 mg/dL (range, 70–114 mg/dL). Mean height and weight of the study population were 171 ± 12 cm and 67 ± 17 kg, respectively. Patients were injected with an average of 15.02 ± 3.58 mCi of FDG and the mean uptake time was 67 ± 10 minutes.

The ordered-subsets expectation maximization algorithm was used to reconstruct all PET images. The 2D implementation on the Discovery LS scanner used two iterations, 28 subsets, a 5.5-mm postreconstruction gaussian filter, and 3.9-mm pixels. The fully 3D implementation on the Discovery RX VCT used two iterations, 21 subsets, a 3.0-mm reconstruction gaussian filter, and 4.7-mm pixels. All PET data were reconstructed with and without CT-based attenuation correction. Helical CT images were obtained with a matrix of 512×512 . Beam collimation was 10 mm with a pitch of 0.984. Table speed was 9.84 mm/rotation and the slice thickness was 0.625 mm; 120 kV and 440 mAs were used.

PET/CT Image Analysis

All PET/CT studies were electronically retrieved and reviewed on a Mobile MIM workstation (MIM Software) by a board-certified nuclear medicine fellow. The reader was blinded to the clinical outcome. PET, CT, and fused PET/CT images were displayed in axial, coronal, and sagittal planes. For this study, the relevant imaging parameters were the maximum SUV (SUV_{max}), peak SUV (SUV_{peak}), MTV, and TLG. All parameters were measured for each primary site recurrence (SUV_{max} , SUV_{peak} , MTV, and TLG), lymph nodal recurrence (SUV_{max} , SUV_{peak} , MTV, and TLG), and distant metastasis (SUV_{max} , SUV_{peak} , MTV, and TLG). We only included positive lymph nodes with SUV_{max} more than 2.0. MTV was defined as the tumor volume with FDG uptake segmented by a gradient-based method. The MIM-vista software analysis suite, version 5.2 (MIM Software) includes a contouring PET/CT suite. Once the ROI was segmented, SUV_{max} and MTV were semi-automatically calculated by the MIMvista software. The gradient segmentation methods of volume measurement available in MIMvista software rely on an operator-defined starting point near the center of the lesion. As the operator drags the cursor out from the center of the lesion, six axes extend, providing visual feedback for the starting point of gradient segmentation. Spatial gradients are calculated along each axis interactively, and the length of an axis is restricted when a large gradient is detected along that axis. The six axes define an ellipsoid that is then used as an initial bounding region for gradient detection. The MTV, TLG, SUV_{peak} , and SUV_{max} within the bounding region are automatically calculated [24]. We further calculated the total tumor burden by combining the activity at the primary site recurrence, lymph node recurrence, and distant metastasis and measured the following metabolic parameters: total MTV and total TLG. We used gradient-based segmentation because our previous studies have suggested that MTV measured by gradient-based segmentation may be a superior prognostic marker [24].

Statistical Analysis

We present central tendencies as mean $\pm$ SD or as median (IQR) when data were skewed or as frequency and percentage for categorical variables. ROC analysis was performed for identifying the optimum thresholds. Survival is presented as Kaplan-Meier survival curves with analysis performed using the Mantel-Cox log-rank test and Gehan-Breslow-Wilcoxon Test. Cox multivariate analyses were performed to adjust for important prognostic factors. Multicollinearity was established using Pearson correlation coefficients ($r > 0.70$). A Mann-Whitney U test was performed to compare distribution of parameters between those who survived and those who died. We used the Prism 5 (GraphPad Software) and SPSS 20 (IBM) statistical packages for all analyses, and all hypothesis tests are two-sided with a significance level of 0.05.

Results

The mean age ($\pm$ SD) of our study population was 57 ± 14 years. Twenty-one (62%) patients were men and 13 (38%) were women. Twenty-seven (79%) patients had American Joint Commission on Cancer stage IV cancer at the time of initial diagnosis. Human papillomavirus (HPV) status for 13 (38.2%) patients was available, and among those, eight of 13 (61.5%) were positive for HPV and five of 13 (38.5%) were negative. Eighteen (53%)

patients had died and 16 (47%) were alive at the end of follow-up. The median length of follow-up for the study population was 17.5 months (IQR, 8.0–37.5 months).

Among the 34 patients included in this study, all the recurrences occurred within 3 years of completion of treatment. Of these recurrences, 21 of 34 (61.8%) were noted in the first year, 10 of 34 (29.4%) in the second year, and three of 34 (8.8%) in the third year after completion of treatment. Tumor recurred at the primary site in 23 of 34 (67.6%) patients, lymph nodes in 16 of 34 (47.1%) patients, and distant sites in 15 of 34 (44.1%) patients. There was a significant difference in median total MTV ($p = 0.025$) and total TLG ($p = 0.004$) between those patients who were alive and those who were dead at the end of follow-up (Table 1). There was also a significant difference in the overall survival time of those who were HPV positive (mean rank, 8.75) versus those who were HPV negative (mean rank, 4.2) ($p = 0.04$).

Univariate Cox Regression Model

Age, sex, stage, site of recurrence, HPV status, FDG metabolic parameters of primary site recurrence (primary SUV_{max}, primary SUV_{peak}, primary MTV, and primary TLG), lymph nodal recurrence (nodal SUV_{max}, nodal SUV_{peak}, nodal MTV, and nodal TLG), distant metastasis (metastasis SUV_{max}, metastasis SUV_{peak}, metastasis MTV, and metastasis TLG), and total tumor (total MTV and total TLG) were included in the univariate and multivariate Cox regression models for overall survival outcome. In univariate analyses, when stratified by overall survival status at the end of follow-up, HPV status, primary site recurrence MTV, metastasis MTV, metastasis TLG, total MTV, and total TLG were significantly associated with overall survival outcome (Table 2).

Multivariate Cox Regression Model

Given the strong correlation between MTV and TLG (0.98, $p < 0.001$), we further studied only total MTV and primary site recurrence MTV with exploratory multivariate models to identify whether the univariate results were an artifact due to confounding variables. We tested the association between total recurrence MTV and outcome (Table 3) while controlling for each covariate individually. Total MTV remained a significantly independent prognostic factor associated with overall survival when adjusted for age, sex, stage and site of recurrence, HPV status, metastasis SUV_{max}, and SUV_{peak} but not when adjusted for primary site recurrence SUV_{max}, SUV_{peak}, lymph node SUV_{max}, and SUV_{peak}.

ROC Analysis

ROC curve analysis was performed to determine the accuracy of total MTV to differentiate those living at 24 months from those who died (AUC, 0.66; 95% CI, 0.48–0.85; $p < 0.09$). The median cut point of 9.69 mL of total MTV had sensitivity, specificity, and likelihood ratio (LR) of 67.7%, 63.2%, and 1.81, respectively. An optimum threshold of 27.8 mL had 46.7% sensitivity, 84.2% specificity, and LR of 2.96 in identifying patients who died within 2 years. ROC analysis was also performed for overall survival. The AUC for total MTV was 0.72 (0.55–0.90, $p = 0.03$) for differentiating those who had died at the end of follow-up from those still alive. The median cut point of 9.69 mL had sensitivity, specificity, and LR

of 66.7%, 68.8%, and 2.13, respectively. For an optimum cut point of 16.8 mL, the sensitivity, specificity, and LR were 55.6%, 87.5%, and 4.44, respectively.

Kaplan-Meier Survival Curves

Overall survival curves were compared using the Mantel-Cox log-rank test and Gehan-Breslow-Wilcoxon test. A significant difference in time to survival was observed between patients with total metabolic tumor volume above and below the optimum threshold of 16.8 mL (Mantel-Cox log-rank test, $p = 0.01$ and Gehan-Breslow-Wilcoxon test, $p = 0.01$; HR, 0.25; 0.09–0.72). A significant difference in time to survival was also observed between patients with total metabolic tumor volume above and below the median threshold total metabolic volume of 9.69 mL (Mantel-Cox log-rank test, $p = 0.05$ and Gehan-Breslow-Wilcoxon test, $p = 0.03$) (Fig. 1). Illustrative cases are provided in Figures 2 and 3.

Discussion

Our study showed that the total metabolic tumor volume is a significant prognostic marker for patients with recurrent HNSCC after definitive chemoradiotherapy. We found that patients with large total MTV above the 50th percentile at the time of diagnosis of recurrence had a significantly worse overall survival even when adjusted for all the clinical covariates in the Cox regression analysis.

A review of the literature shows that 30–50% of HNSCC patients treated with curative intent will develop residual disease or recurrence [2]. Recurrent head and neck cancers are particularly challenging to physicians because we have to consider resectability, prior treatment, age, performance status, and patient wishes in the overall management strategy. Moreover, the cost of treatment may need to be considered because most therapies may fail to provide overall survival benefit [25]. However, in the past few years there have been many emerging alternative treatment options for patients with recurrent HNSCC. These treatment options have shown promising results with improved survival [26–28]. The value of PET/CT in detecting recurrence is already established [23], including identifying the distant metastasis before salvage surgery [29]. Risk stratifying patients at the time of recurrence may allow modifying treatment strategies to individualize patient management using quantitative imaging parameters, such as MTV or TLG of the total tumor burden.

Several studies have shown that baseline SUV_{max} [30], MTV [31, 32], and TLG [33] are significant independent prognostic factors for survival in HNSCC. Studies have evaluated posttreatment SUV_{max} [34–36] and posttreatment MTV [37] for prediction of disease-free survival and overall survival. Wong et al. [34] suggested that for every one unit increase in posttreatment SUV_{max} , the relative risk of death increases by 14%. Similarly, Murphy et al. [37] suggested that an increase in posttreatment MTV of 21 cm³ measured by the threshold segmentation method was associated with an increased risk of death (HR = 2.0, $p = 0.003$). In our study we focused on those with biopsy-proven recurrence. We included patients who were stage III and stage IV at initial staging, treated with definitive chemoradiotherapy, and developed a recurrence, and we investigated the FDG volumetric parameters as well as SUV_{max} and SUV_{peak} . Our study suggests total MTV is a marker for prognosis in patients with recurrent HNSCC after treatment with chemoradiation. Our study results are consistent

with recent reports supporting the emerging value of metabolic tumor volume as a prognostic marker [24, 38–41].

HPV status was a significant factor associated with overall survival both in univariate and multivariate analyses adjusted for imaging variables in our study. HPV-positive HN-SCC patients have improved survival in comparison with HPV-negative patients [42, 43]. A recent study by O’Sullivan et al. [44] reported that HPV-positive patients have high local and regional control but similar distant control in comparison with HPV-negative patients. Our preliminary results suggest that HPV status is associated with the prognosis of patients with recurrence of HNSCC.

This study has several limitations, including its retrospective design and relatively small sample size of 34 patients. The findings are therefore only hypothesis-generating and will need to be validated in a larger prospective study. Because of the small numbers within each stage, we did not stratify within each stage, but we performed Cox regression analysis adjusting the clinical parameters, including stage. Because of the small number of patients with HPV-positive status, we could not perform stratification analyses to establish the value of total MTV among these patients. We used segmentation from only one commercial vendor’s software workstation for analysis and need to investigate multiple vendor-provided segmentation algorithms.

In conclusion, our study suggests that total metabolic tumor volume (gradient-based segmentation) and clinical HPV status are potential markers for overall survival in patients with recurrent advanced HNSCC treated with chemoradiotherapy. Total MTV and HPV status may be valuable in risk-stratifying patients to individualize therapy.

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Fig. 1.
Kaplan Meir survival curves.

A and **B**, Kaplan-Meier plots for total metabolic tumor volume were generated using 50th percentile (9.69 mL) (**A**) and optimum (16.8 mL) (**B**) cutoff thresholds. Significant difference in time to survival was observed between patients with total metabolic tumor volume above and below median threshold (Mantel-Cox log-rank test, $p = 0.05$ and Gehan-Breslow-Wilcoxon test, $p = 0.03$) as well as optimum threshold (Mantel-Cox log-rank test, $p = 0.01$ and Gehan-Breslow-Wilcoxon test, $p = 0.01$).

Fig. 2.

59-year-old man with history of human papillomavirus–associated T2N2M0 squamous cell carcinoma of right tonsil.

A and B, Initial staging PET/CT images show intense ^{18}F -FDG uptake in right tonsil and right level IIA nodes. Patient was treated with cisplatin and erlotinib with 70 Gy radiation over 6 weeks followed by neck dissection and remained disease free for 3 years. **C and D,** Restaging PET/CT images at 3 years after completion of treatment show intense FDG uptake in right side of tongue base (maximum standardized uptake value [SUV], 4.7; peak SUV, 3.1; total metabolic tumor volume, 1.77 mL; total lesion glycolysis, 5.14 g). There was no evidence of regional nodal or distant metastatic disease. Patient was treated with transoral robotic surgery for recurrence and was alive at 33 months after PET/CT at time of last follow-up.

Fig. 3.

32-year-old man with history of human papillomavirus–negative T3N1M0 squamous cell carcinoma of right tonsil.

A and B, Initial staging PET/CT images show intense ^{18}F -FDG uptake in right tonsil. Patient was treated with cetuximab and 70-Gy radiotherapy over 6 weeks. Cisplatin was stopped after 5 days because of fever and cytopenia. Patient remained disease-free for 2 years. **C and D,** Restaging PET/CT images at 2 years after completion of treatment show intense FDG uptake in right side of tongue base (maximum standardized uptake value [SUV], 25.5; peak SUV, 19.4; total metabolic tumor volume, 37.97 mL; total lesion glycolysis, 379.9 g). There was no regional or distant metastatic disease. Patient died 19 months after PET/CT.

TABLE 1
FDG Parameters of Local Recurrence, Nodal Recurrence, Distant Metastasis, and Total Tumor Burden

Parameter	Dead		Alive		p
	Median	Interquartile Range	Median	Interquartile Range	
Total MTV (mL)	11.25	5.07–18.75	3.84	2.25–9.34	0.03
Total TLG (g)	59.64	11.93–141.50	8.86	5.70–31.27	0.00
Primary SUV _{max}	7.17	4.56–9.73	4.49	3.20–6.71	0.10
Primary SUV _{peak}	4.80	3.09–8.66	3.20	2.40–4.10	0.10
Primary MTV (mL)	6.17	1.79–11.23	2.80	2.23–5.40	0.24
Primary TLG (g)	24.51	4.49–75.66	8.86	5.47–49.69	0.15
Lymph node SUV _{max}	7.41	3.86–14.02	5.80	4.12–6.21	0.52
Lymph node SUV _{peak}	6.70	2.80–9.40	3.95	2.75–4.48	0.57
Lymph node MTV (mL)	4.06	2.21–7.85	4.45	2.21–16.71	0.77
Lymph node TLG (g)	19.88	6.08–36.84	13.53	7.50–64.12	0.77
Metastasis SUV _{max}	6.72	6.33–10.04	8.79	4.81–11.29	0.78
Metastasis SUV _{peak}	5.00	3.35–7.35	4.75	1.83–7.9	1.00
Metastasis MTV (mL)	14.69	3.06–43.41	2.62	1.74–5.17	0.46
Metastasis TLG (g)	90.82	7.36–181.50	13.23	4.81–19.66	0.46

Note—MTV = metabolic tumor volume, TLG = total lesion glycolysis, SUV_{max} = maximum standardized uptake value (SUV), SUV_{peak} = peak SUV.

TABLE 2

Cox Univariate Analysis for Clinical and Imaging Parameters and Overall Mortality

Parameters	Overall Mortality		<i>p</i>
	Hazard Ratio	95% CI	
Age	1.03	0.99–1.07	0.14
Sex	1.19	0.47–3.02	0.72
Stage	2.23	0.78–6.39	0.14
Site	0.62	0.24–1.60	0.31
HPV status	6.21	1.08–35.84	0.04
Primary SUV _{max}	1.06	0.97–1.15	0.20
Primary SUV _{peak}	1.08	0.97–1.21	0.17
Primary MTV (mL)	1.05	1.01–1.10	0.03
Primary TLG (g)	1.00	1.00–1.01	0.11
Lymph node SUV _{max}	1.05	0.93–1.19	0.39
Lymph node SUV _{peak}	1.13	0.94–1.36	0.20
Lymph node MTV (mL)	1.01	1.00–1.02	0.21
Lymph node TLG (g)	1.00	1.00–1.00	0.14
Metastasis SUV _{max}	0.97	0.79–1.19	0.78
Metastasis SUV _{peak}	1.04	0.80–1.34	0.77
Metastasis MTV (mL)	1.01	1.00–1.02	0.02
Metastasis TLG (g)	1.00	1.00–1.00	0.02
Total MTV (mL)	1.01	1.00–1.01	0.00
Total TLG (g)	1.00	1.00–1.00	0.00

Note—Human papillomavirus (HPV) status, primary tumor metabolic tumor volume (MTV), metastasis MTV, metastasis total lesion glycolysis (TLG), maximum standardized uptake value (SUV_{max}), peak SUV (SUV_{peak}), total MTV, and total TLG were significantly associated with overall survival outcome.

TABLE 3

Cox Multivariate Analysis Model of Total Metabolic Tumor Volume (MTV) of Recurrence as Predictor of Overall Survival Adjusted for Other Covariates

Parameters	Hazard Ratio	95% CI	<i>p</i>
Total MTV	1.01	1.00–1.01	0.00
Age (per y)	1.02	0.99–1.06	0.23
Total MTV	1.01	1.00–1.01	0.00
Male	1.06	0.40–2.79	0.91
Total MTV	1.01	1.00–1.01	0.00
Stage (stage III vs stage IV)	2.15	0.74–6.22	0.16
Total MTV	1.01	1.00–1.01	0.01
Site (locoregional recurrence vs distant metastasis)	0.82	0.30–2.23	0.70
Total MTV	1.02	1.00–1.04	0.04
HPV (positive vs negative)	9.03	1.25–65.25	0.03
Total MTV	1.014	0.99–1.04	0.21
Primary SUV _{max}	1.031	0.93–1.15	0.57
Total MTV	1.02	0.99–1.04	0.21
Primary SUV _{peak}	1.05	0.91–1.20	0.52
Total MTV	1.00	1.00–1.01	0.15
Lymph node SUV _{max}	1.00	0.86–1.16	0.98
Total MTV	1.00	1.00–1.01	0.32
Lymph node SUV _{peak}	1.03	0.80–1.34	0.80
Total MTV	1.01	1.00–1.01	0.01
Metastasis SUV _{max}	0.89	0.70–1.12	0.30
Total MTV	1.00	1.00–1.01	0.02
Metastasis SUV _{peak}	0.88	0.65–1.19	0.41

Note—Total MTV remained as a significant independent prognostic factor when adjusted for all other covariates individually except for primary site recurrence maximum standardized uptake value (SUV_{max}) and lymph node recurrence SUV_{max} and peak SUV (SUV_{peak}). HPV = human papillomavirus.