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18F-FDG-PET/CT parameters as imaging biomarkers in oral cavity squamous cell carcinoma, is visual analysis of PET and contrast enhanced CT better than the numbers?

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Abstract

Purpose—This study was designed to seek associations between positron emission tomography/computed tomography (PET/CT) parameters, contrast enhanced neck computed tomography (CECT) and pathological findings, and to determine the potential prognostic value of PET/CT and CECT parameters in oral cavity squamous cell carcinoma (OCSCC).

Materials and method—36 OCSCC patients underwent staging PET/CT and 30/36 of patients had CECT. PET/CT parameters were measured for the primary tumor and the hottest involved node, including maximum, mean, and peak standardized uptake values (SUV max, SUV mean, and SUV peak), metabolic tumor volume (MTV), total lesion glycolysis (TLG), standardized added metabolic activity (SAM), and normalized standardized added metabolic activity (N SAM). Qualitative assessment of PET/CT and CECT were also performed. Pathological outcomes included: perineural invasion, lymphovascular invasion, nodal extracapsular spread, grade, pathologic T and N stages. Multivariable logistic regression models were fit for each parameter and outcome adjusting for potentially confounding variables. Multivariable Cox proportional hazards models were used for progression free survival (PFS), locoregional recurrence free survival (LRFS), overall survival (OS) and distant metastasis free survival (DMFS).

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Results—In multivariable analysis, patients with high ($\geq$ median) tumor SUV max (OR 6.3), SUV mean (OR 6.3), MTV (OR 19.0), TLG (OR 19.0), SAM (OR 11.7) and N SAM (OR 19.0) had high pathological T-stage (T3/T4) ($p < 0.05$). Ring/heterogeneous pattern on CECT qualitative assessment was associated with worse DMFS and OS.

Conclusion—High PET/CT parameters were associated with pathologically advanced T stage (T3/T4). Qualitative assessment of CECT has prognostic value. PET/CT parameters did not predict clinical outcome.

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer worldwide and eighth most common malignancy among males in the United States [1].

Recent studies implemented the use of not only TNM staging but also some of the pathological parameters to predict outcome in oral cavity squamous cell carcinoma (OCSCC) [2,3]. These pathological risk factors are nodal extracapsular spread (ECS), perineural invasion (PNI), advanced T stage (T3/T4), and (lymphovascular invasion) LVI [2,3].

The limitations of the TNM staging as the sole prognostic tool become more accentuated when non-surgical therapies are considered in some SCCHN patients. The study of novel imaging techniques could help in the development of reliable non-invasive tools for risk stratification.

¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging provides both anatomical and functional information. Functional data can also provide quantitative information known as PET/CT parameters that can potentially be used as imaging biomarkers to assess both prognostic and diagnostic information [4-8]. Maximum standardized uptake value (SUV max), the most widely used PET/CT parameter is the maximum SUV for a voxel in volume of interest (VOI). SUV mean is the average SUV of all the voxels in VOI [9] SUV peak is the local average of a 1 ml spherical volume centered on SUV max [9]. MTV is the volume of all visually positive FDG uptake. Total lesion glycolysis (TLG) is the multiplication of MTV and SUV mean, incorporating both the tumor's size and activity [9].

Each of these PET/CT parameters has some limitations. Partial volume may result in errors in SUV max and SUV peak especially for small tumors [10,11]. SUV mean, MTV and TLG vary according to the method used to calculate the VOI. A recently reported measurement, standardized added metabolic activity (SAM), attempts to overcome some of these limitations by avoiding partial volume effects and the influence of VOI size [8]. SAM is calculated by measuring all of the activity due to tumor that is above the activity concentration of surrounding tissue. However, SAM is still affected from calibration of the scanner, injected dose of the radiotracer and patient's body weight. For this reason Mertens et al [8] introduced N SAM (SAM/mean background activity). The sources of error associated with SAM may be avoided by using N SAM as these are affecting both SAM and mean background activity similarly.

Presence of tumor necrosis before therapy is associated with tumor hypoxia. Tumor hypoxia is suggested as one of the causes of treatment failure [12]. Therefore qualitative assessment of PET/CT and associated contrast enhanced CT (CECT) may have prognostic value.

In this retrospective study we assessed the study cohort for associations of PET/CT parameters in OCSCC with pathological findings and also assessed the prognostic value of these PET/CT parameters and available CECT qualitative evaluations. Our goal was to explore the relationship of PET/CT and CECT with clinical/pathological parameters in OCSCCs.

Methods and materials

Patients

After institutional review board (IRB) approval, retrospective chart review of patients treated at our cancer institute between January 2010 and March 2013 for newly diagnosed OCSCC was performed. All patients had a baseline PET/CT examination performed before oral surgery as part of our standard of care.

Collected information included, gender, smoking history, alcohol use (current or past), age at diagnosis, primary OC subsite, initial TNM staging, and information about cancer treatment including date of treatment and treatment modality (chemotherapy, radiation therapy, surgery, or a combination thereof) as well as the pathological findings after surgery. Patients were excluded if they had distant metastatic disease (M1) at initial presentation, were less than 18 years of age, had received prior local and/or systemic therapy, including local surgery for current OCSCC presentation. Patients for who follow up after surgery was not available were also excluded from study. All surviving patients had at least 7 months of follow-up.

FDG-PET/CT Protocol

All PET/CT and CECT studies were performed using one of 3 PET/CT systems at our institution. Patients fasted at least 4 hours before the scan. Scans were obtained from skull vertex to mid thigh with arms down. All PET data was reconstructed with and without CT-based attenuation correction. The emission scan lasted for 2-4 minutes for each bed position. Following PET/CT, dedicated neck CECT was acquired in 26/36 cases after administration of intravenous contrast (110 ml, Isovue 370) (kVp 120, mA 100-440 (auto mA), pitch 0.938/1, slice thickness: 2.5 mm, recon interval: 2.5 mm). An additional 4 patients had CECTs performed at outside institutions, and images were available for interpretation. Six patients did not have any CECT available.

Image Analysis

All PET/CT studies were reviewed on a MIM workstation (software version 6.1; MIM Software Inc) by two board certified radiologists (ATK, AC) in consensus. One (ATK) had subspecialty training in Nuclear radiology and in Neuroradiology and the other (AC) had a Certificate of Additional Qualification in Neuroradiology with expertise in head and neck imaging. Reviewers were blinded to patient name and clinical information. PET and fused

PET/CT images were reviewed in multiple planes. Volume of Interest (VOI_{PET}) was determined as the volume of hypermetabolic FDG uptake using a gradient technique from commercially available software (PETedge; MIM Software, Inc.; Cleveland, Ohio). The imaging biomarker measurements performed were SUV max, SUV mean, SUV peak, MTV, TLG, SAM and N SAM. All SUVs used in this study are normalized to body weight. After automatic segmentation of the primary tumor and/or regional nodal disease, SUV max, SUV mean, SUV peak, MTV and TLG were automatically calculated by the MIMvista software for the primary lesion and for the hottest lymph node, or if there were many nodes with similar FDG activity, the node with the largest linear dimension was analyzed (Figure 1).

To calculate SAM the VOI_{PET} was determined. A second VOI (VOI_{SAM}) was created automatically by expanding VOI_{PET} by 3mm in three dimensions. VOI_{SAM} should contain all of the counts due to the tumor but also includes some counts from surrounding tissue. A third VOI (VOI_{BKG}) was created automatically by expanding VOI_{SAM} , again by 3 mm. Two readers (ATK, AC) reviewed the cases and excluded other structures with high activity from VOI_{BKG} manually. Average normal tissue SUV in the volume between VOI_{SAM} and VOI_{BKG} was calculated and used to subtract the SUVs that would be present in VOI_{SAM} in the absence of tumor. SAM represents the total SUVs above background for the tumor. Normalized SAM (N SAM) is calculated as $SAM / (\text{Average normal tissue SUV})$ [8].

The nodal PET/CT parameters were considered to be zero for patients with undetectable nodal disease at PET/CT.

Qualitative uptake pattern assessment was also performed by two readers (ATK and AC) in consensus. Qualitative qualities evaluated included: pattern of enhancement of the tumor and the lymph nodes on CECT and pattern of uptake by the tumor on PET. Lesion pattern was described as one of the following: ring, heterogeneous or sphere [12]. PET images were evaluated in gray-scale and as a hot-iron color map overlay of the corresponding CT. PET display windows were adjusted to allow the readers to best evaluate each tumor for qualitative assessment. When the FDG uptake showed a central area of low uptake, the PET/CT pattern was defined as ring pattern. When the circular uptake was partial but more than two thirds was complete, this was also accepted as ring pattern (Figure 2). When FDG uptake is heterogeneous, it is accepted as heterogeneous pattern. If uptake of at least one lesion was ring shaped or heterogeneous whether primary or node, we categorized it as a ring or heterogeneous pattern. The sphere shaped pattern was defined as uniform uptake without any areas of lower uptake. For the statistical analysis the ring and heterogeneous uptake groups were combined.

We also evaluated enhancement pattern at corresponding CECTs. A ring shaped enhancement with central non-enhancement (necrosis) at primary or nodal site was defined as a ring pattern (Figure 3), non-uniform enhancement at the primary or nodal site was accepted as a heterogeneous pattern. Uniform or homogeneous enhancement of the nodal or primary disease was placed in the sphere category. For the statistical analysis the ring and heterogeneous uptake groups were combined.

Measures

Chart review of each case was performed to document the investigated variables. Pathological outcomes included PNI, LVI, T stage, N stage, and tumor grade; and for the lymph nodes, ECS (when available),

Progression free survival (PFS) was defined as the number of days from treatment initiation to locoregional recurrence, distant metastasis, or death due to any cause, whichever occurred first, or the last follow-up if the patient did not experience an event. Locoregional recurrence free survival (LRRFS) was defined as the number of days from treatment initiation to locoregional recurrence or death due to any cause, whichever occurred first, or the last follow-up if the patient did not experience an event. Distant metastasis free survival (DMFS) was defined as the number of days from treatment initiation to distant metastasis or death due to any cause, whichever occurred first, or the last follow-up if the patient did not experience an event. Overall survival (OS) was defined as the number of days from treatment initiation to death due to any cause, or the last follow-up if the patient did not experience an event.

Statistical Analysis

Statistical analysis was conducted using SAS Version 9.3. PET/CT parameters were examined as both continuous and categorical variables. PET/CT parameters other than the nodal parameters were dichotomized using the median as the cut point. Nodal parameters were categorized into 0 vs. >0 since more than half of the observations were zero. Post-operative treatment was categorized into radiation therapy (XRT), chemoradiation therapy (CRT), and none/refused. Neck dissection procedure was categorized into modified radical neck dissection (MRND), selective neck dissection (SND) and none.

Descriptive statistics were reported for all variables. The unadjusted associations of the PET/CT parameters with each pathological outcome were assessed, using both parametric and non-parametric statistics. The chi-square test and Fisher's exact test were used for categorical covariates; and ANOVA and the Kruskal-Wallis test for numerical covariates.

Separate multivariable logistic regression models were fit for each PET/CT parameter and outcome. Binary logit models were fit for all outcomes except grade, which used a cumulative logit model. Gender, use of alcohol, smoking status, and age were included in the models if they had a marginal association with the outcome (p-value <0.20) in unadjusted analysis. Firth's penalized maximum likelihood estimation was used in the binary logit models to reduce bias in the parameter estimates and handle empty cells.

To assess associations with PFS, LRRFS, DMFS, and OS, univariate survival analysis for each variable was carried out using the Cox proportional hazards model. Separate multivariable survival models were fit for each PET/CT parameter. Gender, use of alcohol, smoking status, grade, age, PNI, LVI, pathological T stage, pathological N stage, post-operative treatment (including both CRT and XRT), and neck dissection procedure were included in the models if they had a marginal association with PFS, LRRFS, DMFS, or OS (p-value <0.20) in univariate analysis.

Results

Patients

Thirty-six patients were eligible for the study. Patient characteristics are listed in detail in Table 1. The average age was 66 years and 44% of the patients were male. With respect to pathologic tumor grade, 19% were well-differentiated, 67% moderately differentiated, and 14% poorly differentiated. Fifty-six % or 20 patients were stage T3 or T4, and 71% (12/17) of stage T3/T4 patients had primary lesion with largest dimension less than 4 cm in the corresponding CECT. The majority of patients were pathologic stage N0 (57%). Forty-three percent of the patients had pathological N1 or N2 stage. Pathologic ECS was present in 6/15 patients with nodal disease. LVI was observed in 11 patients (31%) and PNI in 21 patients (58%).

Patients were followed starting from the initiation of therapy to death or to the most recent inpatient/outpatient follow up. Follow-up time ranged from 8 to 44.5 months for the surviving patients. Median follow-up time was 24.1 months using the reverse Kaplan-Meier method [13].

PET/CT

Seven patients were analyzed with GE Discovery 690 Elite in 3D mode. 16/36 were analyzed with GE Discovery 600 in 3D mode, and 13/36 were analyzed with GE Discovery ST (General Electric, Milwaukee, Wis.) The average patient blood glucose level was 109 (SD $\pm$ 26) mg/dl. Patients were injected with an average of 14.75 (SD $\pm$ 1.85) mCi of 18F-FDG and incubated for 1 hour.

CECT

Twenty-six patients had a CECT acquired in our department either immediately following PET/CT or within 3 weeks of the PET/CT. Four patients had CECTs performed at outside institutions prior to departmental PET/CT, and these images were available for interpretation. Six patients did not have a CECT available.

Unadjusted analysis

PET ring/heterogeneous pattern (either nodal or primary or both) was associated with ECS. Except nodal MTV, high nodal PET/CT parameters were significantly associated with LVI. Higher values for both tumor and nodal PET/CT parameters (continuous not categorical nodal parameters) as well as PET and CECT ring/heterogenous patterns were associated with high pathological T-stage (T3/T4) as compared to T1/T2. Higher nodal SUV mean and SAM, when used as continuous variables, were significantly associated with high N-stage (N1/N2) as compared to N0. However, no such association was found when using the categorical version of the PET/CT parameters. Alcohol use and PET ring/heterogeneous pattern were significantly associated with LVI. There were no significant associations found between any of the PET/CT parameters and PNI or tumor grade. Smoking was associated with having a higher grade lesion.

Adjusted analysis

High tumor SUV max, tumor SUV mean, tumor MTV, tumor TLG, tumor N SAM, tumor SAM, and CT ring/heterogeneous pattern had significantly higher odds of having a high pathological T-stage (T3/T4) (Table 2). Higher tumor SUV peak was also significantly associated with high pathological T-stage (T3/T4) when looking at it as continuous, but not as a categorical variable. No other significant associations between the other PET/CT parameters and pathological outcomes were found in adjusted analysis.

None of the PET/CT parameters, including the PET/CT ring/heterogeneous pattern were significantly associated with PFS or LRRFS in unadjusted or adjusted analysis. The CECT ring/heterogeneous pattern was associated with poorer DMFS and OS in adjusted analysis (Table 3).

Discussion

We found a statistically significant association between high tumor PET/CT SUV max, SUV mean, MTV, TLG, N SAM, and SAM with pathological advanced T stage (T3/T4) OCSCC. Ring/heterogeneous enhancement pattern at CECT was also associated with advanced T stage, but ring/heterogeneous pattern at PET/CT was not. High primary tumor quantitative PET/CT parameters as well as enhancement pattern at corresponding CECT can be incorporated into cases where conventional imaging findings are equivocal in differentiating early versus advanced stage OCSCCs. PET/CT ring/heterogeneous pattern was associated with LVI and ECS in unadjusted analysis, but was not in adjusted analysis.

The other important finding in this study which may have a significant impact on patients' management was the association between ring/heterogeneous enhancement pattern at CECTs with clinical outcome.

OCSCC is treated with surgery when the tumor is at early stage, but advanced stage OCSCC cannot be treated with a single modality and requires multimodality treatment [1,14]. Our main role as imagers during staging of OCSCC patients is to identify whether a patient has advanced (T3/T4) versus early stage disease (T1/T2) [1,14]. There are two common challenges during interpretation of both anatomic CECT and magnetic resonance imaging (MRI). These are identification of bone invasion (especially mandible or maxillary marrow invasion, as cortical bone involvement does not upstage the patient) and invasion of extrinsic tongue muscles. Each of these two features will upstage any OCSCC to T4a [1,14]. Identification of extrinsic tongue muscle involvement and bone invasion can be even more difficult in cases presenting with small tumor size or in patients with significant dental amalgam artifact. In our study 60% of patients with T3/T4 had tumor size less than 4 cm. In these circumstances presence of high PET/CT parameters and ring/heterogeneous type enhancement pattern at the CECT of the primary tumor will be more suggestive for an advanced T stage.

Abd el-Hafez et al [15] is the only study published in the literature to date investigating the association between pathological risk factors and PET/CT parameters including primary tumor TLG and nodal SUV max in OCSCCs. Similar to our findings, they found an

association between high TLG values of the primary tumor and advanced pathological T stage in OCSCCs. They also noted an association of high nodal SUV max with nodal ECS. In our investigation we did not find any statistically significant association between PET/CT parameters (primary or nodal) and PNI, LVI, or ECS. Although our number of patients was lower (36 vs 126), we also investigated the role of newly introduced PET/CT parameters of SAM and N SAM.

This study also addressed the question of association between PET/CT parameters and prognosis. There was significant association of clinical outcome with CECT enhancement pattern, however, no association between any of the primary or nodal qualitative/quantitative PET/CT parameters and clinical outcome was found.

Lim et al [16] reported that MTV and TLG might provide important prognostic information in oropharyngeal SCC. Dibble et al [17] also reported MTV and TLG as potential prognostic markers in oral cavity and oropharyngeal SCC. Abd el-Hafez et al [15] also suggested TLG as an independent prognostic marker in OCSCCs. In contrast, Higgins et al [18] did not find a significant association between TLG and outcome, however the referenced study suggested that tumor SUV mean has superior prognostic value. Koyasu et al [12] determined that the PET/CT qualitative uptake pattern provided better prognostic information to clinical staging of SCCHN. Unlike our study, they grouped sphere and heterogeneous pattern together and compared it to the ring pattern. In our study we grouped ring and heterogeneous patterns in the same group. We thought heterogeneous uptake at PET/CT and enhancement at CECT are more suggestive for small foci of necrosis. Koyasu et al [12] also did not evaluate the enhancement pattern with CECT.

Our findings contradict most other studies [12, 15-18] as we did not find any association between quantitative/qualitative PET/CT parameters and clinical outcome in OCSCCs. This could be related to the different grouping of uptake pattern, the low number of patients, and low event rates in our study compared to these studies [12, 15-17].

At our institution most patients have CECT performed for staging during their PET/CT unless there is any contraindication to iodinated contrast or patient has had a staging neck magnetic resonance imaging scan performed. We found the ring/heterogeneous pattern of primary tumor enhancement at CECT was significantly associated with poorer OS and DMFS. CECT has advantages over PET/CT for detection of ring/heterogeneous pattern. Small areas of necrosis that are seen by CECT may not be appreciated in the corresponding PET/CT (Figure 3). This particular association needs to be further validated in a larger population study with more events.

Limitations of our investigation include the small patient cohort meeting inclusion criteria, relatively short follow up period, small number of events (i.e. death and recurrences) and the retrospective nature of the study. The small number of patients could be related to the selection criteria, as staging PET/CT imaging is only performed in patients presenting with advanced clinical stage as defined by the National Comprehensive Cancer Network (NCCN) guidelines. Median follow up in our study was 24.1 months. Our low event rate could be related to the high number of cases with post surgery radiation or chemoradiation therapy.

The statistical analysis did not use a procedure to make corrections for multiple comparisons, e.g. Bonferroni and therefore, should be considered exploratory (19).

It is understood that TNM staging should not be used as a sole predictor of prognosis or as the sole consideration in treatment decision-making in SCCHN [2,3] The addition of clinical comorbidities as well as pathological risk factors like ECS, PNI and LVI produce better prognostication in OCSCCs [2,3]. For patients where surgery is contraindicated, the use of non-invasive imaging biomarkers may help improve the risk stratification. PET parameters can be helpful in surgical planning too, since if high values are associated with advanced T stage, a more aggressive surgery can be planned.

Our finding of a significant association of ring/heterogeneous enhancement patterns at CECTs with DMFS and OS is striking as it may provide insight for management of SCCHN. The ring/heterogeneous pattern most likely originates from intratumoral heterogeneity which may be from necrosis and hypoxia [12]. Inadequate oxygen supply can be a direct reason for therapeutic resistance [12]. Koyasu et al [12] recently studied the ring pattern at PET/CT in 108 SCCHN patients and found an association with poor prognosis. While our study did not find any significant association between clinical outcome and PET/CT ring/heterogeneous pattern, we did find the CECT ring/heterogeneous enhancement pattern to be an indicator of poor prognosis.

Conclusion

Recognition of high tumoral FDG activity can be potentially beneficial in identifying advanced pathological stage OCSCCs. Qualitative CECT may also play an important role in prognosis that needs to be further validated in a larger patient population.

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Figure 1.

61 year old male with T4aN2bM0 OCSCC. Images demonstrate the left buccal/gingival hypermetabolic mass, poorly seen on CECT on the edentulous atrophic mandible. Axial PET/CT fused image.

The figure shows the primary VOI (red) and two outer VOIs (light blue and dark blue). SUV max, SUV mean, MTV, and TLG were calculated from VOI_{PET} (defined by a gradient method using the PET uptake, red contour). SUV peak was centered on the voxel defined by SUV max. SAM was calculated as the total SUVs from VOI_{SAM} less the normal tissue SUVs calculated from the volume between VOI_{SAM} (light blue contour) and VOI_{BKG} (dark blue contour).

Figure 2.
Sagittal PET/CT fused image shows right level 2A lymph node with ring/heterogeneous pattern.

Figure 3a **Figure 3b****Figure 3.**

Axial (A) PET image shows homogeneous FDG activity of the left level 2A lymph node. Corresponding axial (B) CECT image shows ring/heterogeneous pattern enhancement consistent with central necrosis.

Table 1
Patient Characteristics (n=36)

Variable	Level	N = 36 (%)
Gender	Female	20 (55.6)
	Male	16 (44.4)
Age	Mean (SD)	66 (12.71)
Alcohol	No	27(75.0)
	Yes	9 (25.0)
Smoking	No	15 (41.7)
	Yes	21 (58.3)
Grade	Moderate	24 (66.7)
	Poor	5 (13.9)
	Well	7 (19.4)
PNI	No	15 (41.7)
	Yes	21 (58.3)
LVI	No	24 (68.6)
	Yes	11 (31.4)
	Missing	1
ECS	No	9 (60)
	Yes	6 (40)
	Missing	21
Pathology T Stage	T1/T2	16 (44.4)
	T3/T4	20 (55.6)
Pathology N Stage	N0	20 (57.1)
	N1/N2	15 (42.9)
	Missing	1
Post-surgical Treatment	None	8 (22.2)
	CRT	10 (27.8)
	CRT (incomplete)	2 (5.6)
	XRT	12 (33.3)
	XRT(incomplete)	2 (5.6)
	Refused	2 (5.6)
PET/CT ring/heterogeneous pattern	No	19 (52.8)
	Yes	17 (47.2)
CECT ring/heterogeneous pattern	No	12 (40)
	Yes	18 (60)
	Missing	6
Neck dissection procedure	L MRND	4 (11.1)
	R MRND	4 (11.1)
	B MRND	3 (8.3)
	L SND	11 (30.6)
	R SND	6 (16.7)

Variable	Level	N = 36 (%)
	B SND	6 (16.7)
	None	2 (5.6)
Tumor SUV max	Median (Range)	13.49 (3.4-29.3)
Tumor SUV mean	Median (Range)	6.65 (2.2-15.6)
Tumor SUV peak	Median (Range)	9.3 (2.1-19)
Tumor MTV	Median (Range)	8.7 (1-94)
Tumor TLG	Median (Range)	74.85 (2.1-1014)
Tumor N SAM	Median (Range)	34.35 (1.2-554)
Tumor SAM	Median (Range)	71 (1.5-927)
Nodal SUV max	Median (Range)	0 (0-14.63)
Nodal SUV mean	Median (Range)	0 (0-7.2)
Nodal SUV peak	Median (Range)	0 (0-11.7)
Nodal MTV	Median (Range)	0 (0-6.9)
Nodal TLG	Median (Range)	0 (0-49.5)
Nodal N SAM	Median (Range)	0 (0-53)
Nodal SAM	Median (Range)	0 (0-58)

SD, standard deviation; PNI, perineural invasion; LVI, lymphovascular invasion; ECS, extracapsular spread; SUV, standardized uptake values; MTV, metabolic tumor volume; TLG, total lesion glycolysis; N SAM, normalized standardized added metabolic activity; SAM, standardized added metabolic activity; MRND: modified radical neck dissection (L for left, R for right and B for bilateral); SND (selective neck dissection (L for left, R for right and B for bilateral))

Table 2
Multivariable association with pathological T stage

Imaging Biomarker	T Stage =T3/T4 ^I
	OR (95% CI)
PET/CT ring/heterogeneous pattern (yes vs. no)	4.23 (0.98-18.30)
CECT high/heterogeneous pattern (yes vs. no)	9.17 (1.54-54.62)
Tumor PET/CT parameters:	
SUV max (high vs. low)	6.34 (1.38-29.02)
SUV mean (high vs. low)	6.34 (1.38-29.02) *
SUV peak (high vs. low)	3.74(0.89-15.74)
MTV (high vs. low)	18.98 (3.25-110.8) *
TLG (high vs. low)	18.98 (3.25-110.8)
N SAM (high vs. low)	18.98 (3.25-110.8) *
SAM (high vs. low)	11.7 (2.2-82.2)
Nodal PET/CT Parameters (yes vs. no)	3.87 (0.82-18.2)

OR, Odds ratios; CI, confidence interval; SUV, standardized uptake values; MTV, metabolic tumor volume; TLG, total lesion glycolysis; N SAM, normalized standardized added metabolic activity; SAM, standardized added metabolic activity.

* P-value < 0.05.

^I Adjusted for smoking. N=30 for CECT ring/heterogeneous pattern model; N=36 for all other models

Table 3
Multivariable association with OS

Imaging Biomarker	Multivariable HR (95% CI) ^I	P-value
PET/CT ring/heterogeneous pattern (yes vs. no)	1.42 (0.18-11.22)	0.742
CECT ring/heterogeneous pattern (yes vs. no)	30.10 (1.04-874.77)	0.048
Tumor PET/CT parameters:		
SUV max (high vs. low)	1.33 (0.16-11.15)	0.790
SUV mean (high vs. low)	1.33 (0.16-11.15)	0.790
SUV peak (high vs. low)	4.68 (0.28-77.68)	0.281
MTV (high vs. low)	0.40 (0.05-3.18)	0.385
TLG (high vs. low)	1.74 (0.29-10.49)	0.544
N SAM (high vs. low)	0.37 (0.05-3.00)	0.352
SAM (high vs. low)	1.59 (0.28-9.64)	0.614
Nodal PET/CT Parameters (yes vs. no)	3.23 (0.35-29.99)	0.200

HR, Hazard ratio; CI, confidence interval; SUV, standardized uptake values; MTV, metabolic tumor volume; TLG, total lesion glycolysis; N SAM, normalized standardized added metabolic activity; SAM, standardized added metabolic activity.

^I Adjusted for smoking, grade, pathologic N stage. N=29 for CECT ring/heterogeneous pattern model; N=35 for all other models.