Original Article

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in predicting overall survival of oral cavity squamous cell carcinoma: Ongoing controversy

ABSTRACT

We aimed to retrospectively determine if initial staging ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) can predict overall survival (OS) in oral cavity squamous cell carcinoma (OCSCC), which is currently a source of ongoing controversy in the literature. Forty-six consecutive patients with nonmetastatic (Stage M0) OCSCC had ^{18}F-FDG PET/CT prior to definitive surgical treatment followed by observation or adjuvant treatment at our institution between 2006 and 2012. The median follow-up time was 18 months (range 0.1–76 months). Univariate and multivariate analysis were used to determine the ability of imaging, pathologic, and demographic factors to predict OS. ^{18}F-FDG PET/CT parameters were standardized uptake value (SUV) maximum and mean, metabolic tumor volume, and total lesional glycolysis (TLG) of primary tumor and regional nodes. Significant predictors of OS in the multivariate analysis were primary tumor SUV mean, nodal TLG, and age. Two-year OS of patients with primary tumor SUV mean below and above the median of 6.26 was 68% and estimated 28%, respectively. Two-year OS of patients with nodal TLG below and above median of 7.9 was 69% and 34%, respectively. Two-year OS of patients younger and older than median age of 57 was 60% and 43%, respectively. Our results suggest that ^{18}F-FDG PET/CT may be a valuable addition to multifactorial models predicting outcome for OCSCC. Thus, continued research aiming to incorporate ^{18}F-FDG PET/CT parameters in risk-stratification algorithms for OCSCC is warranted and should be conducted using more standardized prognostic models driven by a specific clinical question.

Keywords: Fluorodeoxyglucose, oral cavity squamous cell carcinoma, overall survival, positron emission tomography

INTRODUCTION

Squamous cell carcinoma of the head and neck accounts for 3% of new cancers diagnosed in the United States each year, with an estimated 45,780 in the year 2015.[1] Historically, oral cavity squamous cell carcinoma (OCSCC) has been the most common mucosal site in the head and neck region and is closely associated with tobacco and alcohol use.[2] Surgery is the primary treatment modality for OCSCC, followed by radiation or chemoradiation when indicated.[3] Despite refinement of both surgical techniques and adjuvant treatment, the prognosis of OCSCC is still guarded, with about 60% of patients surviving 5 years.[4,5]

The optimal management of OCSCC requires accurate risk stratification, with early-stage cancer (I and II) being treated by a single modality and patients with late stage (III and IV) tumors undergoing multimodality therapy.[3] ^{18}F-fluorodeoxyglucose

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positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is usually performed prior to the initial surgery for Stage III and IV patients. Performing re-staging ^{18}F-FDG PET/CT following surgery to aid decision on adjuvant treatment is under investigation, but not yet widely utilized.[6-9] The available evidence on the predictive ability of initial staging presurgical ^{18}F-FDG PET/CT in OCSCC is limited and very controversial, ranging from just being predictive for pathologic stage to being predictive of overall survival (OS).[10-15]

Thus, the objective of this study was to determine the value of the initial staging ^{18}F-FDG PET/CT in predicting OS in OCSCC. PET parameters are analyzed along other demographic and pathologic parameters in univariate and multivariate analysis.

MATERIALS AND METHODS

Study population

Forty-six consecutive patients with OCSCC without distant metastatic disease (Stage M0) had initial staging ^{18}F-FDG PET/CT prior to definitive surgical treatment were followed by observation or adjuvant treatment at our institution between 2006 and 2012. The data were censored at the time of last follow-up or death.

Positron emission tomography imaging and analysis

The vertex to mid-thighs ^{18}F-FDG PET/CT studies were acquired on a Philips Gemini Time-of-Flight PET/CT scanner in the standard fashion (at least 6 h fasting, no strenuous exercise for 24 h prior to the study, blood glucose level <200 mg/dL, 0.2 mCi/kg [7.4 MBq/kg] ^{18}F-FDG, 1 h uptake time). PET/CT images were displayed on the Philips IntelliSpace Portal in the standard NM viewer review mode and tumor tracking analysis mode and retrospectively interpreted by board-certified radiologist/nuclear medicine physician with 7 years of experience. Standard uptake value (SUV) was normalized per body weight. Reference SUV mean of the liver was determined in 3 cm circular region of interest placed over the right liver lobe. SUV max, SUV mean, metabolic tumor volume (MTV), and total lesional glycolysis (TLG) for primary tumor and regional nodes were determined using fixed-percentage threshold segmentation method. The voxels were included if they were >40% of the maximum voxel within an operator defined sphere.[16,17] The regional nodes were considered involved by tumor if their SUV max was greater than the SUV mean of the liver. For calculating nodal MTV and TLG, however, regional nodes were considered measurable if their SUV max was 1.5-fold greater than liver SUV mean.[18]

Treatment

The interval between ^{18}F-FDG PET/CT and initial surgery was 13.5 (1–43) days. Primary tumor resection involved wide-local excision, marginal or segmental mandibulectomy. Unilateral nodal dissection was performed for unilateral tumors far from midline, and bilateral neck dissection was performed for tumors approaching midline and bilateral tumors. Frozen section pathological analysis was performed intraoperatively to clear margins. Reconstruction was performed via primary intention, skin grafting, local reconstruction, or free tissue reconstruction based on defect size and location, and surgeon preference. All resected tissue specimens were handled by standard surgical pathology methods according to institutional protocols. Pathologic tumor (pT) and nodal stage (pN) were determined according to the American Joint Commission on Cancer (AJCC) Staging Manual 7th edition.[19] Following initial surgery, per discretion of institutional Head and Neck Tumor Board, the patients were either observed (n = 19) or treated with adjuvant radiation (n = 16) or chemoradiation (n = 11). In principle, postsurgical management was guided by the National Comprehensive Cancer Center (NCCN) guidelines.[3]

Statistical analysis

Primary tumor PET/CT parameters were SUV max, SUV mean, MTV, and TLG. Regional nodal PET/CT parameters were number of involved lymph nodes (# LN involved), SUV max of the most active node, and MTV and TLG of the measurable nodes. Total MTV and TLG were derived by summing primary and nodal MTV and TLG, respectively. Demographic parameters were age, sex, and race. Pathologic variables were pT and pN. Human papillomavirus status in pathologic specimens is not routinely determined or considered in treatment decision for OCSCC at our institution, and could not be analyzed as an outcome predictor. The outcome variable was OS. The significance level α is taken to be 0.05 throughout the analysis. Pearson's correlation coefficients were first obtained for all continuous variables. Primary tumor SUV mean was highly significantly correlated with primary tumor SUV max, primary tumor TLG, total TLG, and significantly correlated with SUV max of the most active lymph node, and primary tumor MTV. To avoid multicollinearity in the model building process, those variables that were significantly correlated with primary tumor SUV mean were excluded from the model building process. Multiple Cox regression was then run with primary tumor SUV mean, # LN involved, nodal MTV, nodal TLG, total MTV, age, pN, and pT, as possible predictors (regressors). To obtain the best model fitted to the data, a backward elimination procedure was used in the multiple Cox regression. The procedure started the model with all above predictors, and then eliminated one predictor at a time starting with the one whose elimination gave the smallest decrease in the Wald Chi-square statistic value. The procedure continues until no more predictors can be deleted from the model. The final Cox regression contained

age ($P = 0.000$), primary tumor SUV mean ($P = 0.023$), and nodal TLG ($P = 0.023$) in the model (more details in multivariate analysis under the results section).

Ethical statement

This study was approved by the Institutional Review Board (IRBNet ID# 611419-17 dated 04/25/2012). All procedures followed were in accordance with the ethical standards of the responsible IRB and with the Helsinki Declaration of 1964 and later versions.

RESULTS

Descriptive statistics

The median postsurgical follow-up was 18 months (range 0.1–76 months). Twenty-six of 46 patients died during the follow-up period; the median time to death was 13.4 months (range 1.5–47.4 months). The median follow-up in 20 survivors was 42.4 months (19.4–76.4 months). All imaging variables and age as continuous (quantitative) predictors were listed in Table 1a, while sex, race, pT, pN as discrete (qualitative) predictors were listed in Table 1b.

Table 1a: Patient characteristics ($n=46$) - descriptive statistics for prognostic factors

Prognostic parameters	Mean	Median	SD	Range
^{18}F-FDG PET/CT - Primary tumor				
Primary tumor SUV max	15.1	13.8	8.7	3.2-44.6
Primary tumor SUV mean	6.7	6.3	2.9	1.9-19.9
Primary tumor MTV	24.2	14.3	28.1	3.7-114.2
Primary tumor TLG	194.4	92.8	317.8	13.9-1851.2
^{18}F-FDG PET/CT - Regional nodes				
Number of LN involved[a]	2.9	2.0	3.6	0-14
SUV max of most active LN	5.1	4.4	5.7	0-32.3
Nodal MTV[a]	6.2	2.9	9.6	0-50.7
Nodal TLG[a]	28.8	7.9	53.9	0-291.2
^{18}F-FDG PET/CT - Primary tumor and regional nodes				
Total MTV	30.5	20.3	31.6	3.6-128.6
Total TLG	223.7	114.8	340.3	15.2-2022.9
Demographic				
Age	59.5	57	11.6	36-84

[a]The nodes were considered involved if SUV max of node was higher than SUV mean of liver. However, for MTV and TLG calculations, the nodes are considered to be measurable if SUV max of node was 1.5 × SUV mean of liver. PET: Positron emission tomography; CT: Computed tomography; TLG: Total lesion glycolysis; MTV: Metabolic tumor volume; SUV: Standardized uptake value; LN: Lymph nodes; ^{18}F-FDG: ^{18}Fluorine-2-fluoro-2-Deoxy-d-glucose; SD: Standard deviation

Table 1b: Patient characteristics ($n=46$) - descriptive statistics for prognostic predictors

Prognostic predictor	*n* (%)
Demographic	
Sex	
Male	33 (71.7)
Female	13 (28.3)
Race	
Black	15 (32.6)
White	30 (65.2)
Other	1 (2.2)
Pathologic parameters	
Pathologic tumor (pT) stage	
T1	6 (13.0)
T2	18 (39.1)
T3	7 (15.2)
T4	15 (32.6)
Pathologic nodal (pN) stage	
N0	12 (26.1)
N1	14 (30.4)
N2b	9 (19.6)
N2c	9 (19.6)
N3	2 (4.3)

Univariate analysis

The results of the univariate analysis were summarized in Table 2. The imaging parameters that were significant predictors of OS in univariate analysis were primary tumor SUV mean ($P = 0.016$), SUV max of the most active node ($P = 0.011$), and nodal TLG ($P = 0.017$). The only demographic parameter that significantly predicted OS was age. pN and pT were not significantly associated with OS, although pN nearly reached the significance ($P = 0.059$).

Multivariate analysis and Kaplan–Meyer survival plots

As expected most imaging parameters were significantly correlated to each other, and backward elimination showed that each of the three variables (primary tumor SUV mean, nodal TLG, age) were significant predictors of OS when the other two variables were in the model. For instance, nodal TLG was a significant predictor of OS [Tables 3a and b] when primary tumor SUV mean and age were present in the model. Figure 1 shows Kaplan–Meyer survival plots for primary tumor SUV mean, nodal TLG, and age. Two-year OS patients with primary tumor SUV mean below and above median of 6.26 was 68% and 28%, respectively [Figure 1a]. Two-year OS of patients with nodal TLG below and above median of 7.9 was 69% and 34%, respectively [Figure 1b]. Two-year OS of patients younger and older than median age of 57 was 60% and 43%, respectively [Figure 1c]. Figure 2 compares two representative patients from the study on ^{18}F-FDG PET/CT. The first patient without nodal disease was alive 72 months after treatment [Figure 2a], while the second patient with the extensive nodal disease died after 6 months despite an aggressive management [Figure 2b].

DISCUSSION

Tumor node metastasis (TNM) staging aims to predict the survival based on local, regional nodal, and distant tumor

Table 2: Cox proportional hazards regression (univariate) for each independent variable

Variables	Coefficient	Hazards ratio (95% CI)	*P**
F-FDG PET/CT - Primary tumor			
Primary tumor SUV max	0.02	1.02 (0.99-1.06)	0.235
Primary tumor SUV mean	0.13	1.14 (1.02-1.27)	0.016
Primary tumor MTV	0.00	1.00 (0.99-1.01)	0.932
Primary tumor TLG	0.00	1.00 (1.00-1.00)	0.585
F-FDG PET/CT - Regional nodes			
# LN involved	0.03	1.03 (0.93-1.13)	0.607
SUV max of most active LN	0.07	1.07 (1.02-1.13)	0.011
Nodal MTV	0.03	1.03 (0.99-1.07)	0.121
Nodal TLG	0.01	1.01 (1.00-1.01)	0.017
F-FDG PET/CT - Primary tumor and regional nodes			
Total MTV	0.00	1.00 (0.99-1.01)	0.730
Total TLG	0.00	1.00 (1.00-1.00)	0.388
Demographic			
Age	0.05	1.05 (1.02-1.09)	0.003
Sex			
Male		Reference group	
Female	−0.43	0.65 (0.26-1.62)	0.357
Race			
Black		Reference group	
White	0.33	1.39 (0.60-3.20)	0.438
Other	−18.88	0.00 (0.00-10,000+)	0.999
Pathologic parameters			
pT stage			
T1, T2		Reference group	
T3, T4	0.55	1.74 (0.80-3.77)	0.163
pN stage			
N0, N1		Reference group	
N2b, N2c, N3	0.75	2.13 (0.97-4.66)	0.059

LN: Lymph nodes; # LN involved: Number of involved LNs; PET: Positron emission tomography; CT: Computed tomography; TLG: Total lesion glycolysis; MTV: Metabolic tumor volume; SUV: Standardized uptake value; ^{18}F-FDG: ^{18}Fluorine-2-fluoro-2-Deoxy-d-glucose; CI: Confidence interval; pT: Pathologic tumor; pN: Pathologic nodal; *P*: *P*-value, **P*-value indicates significance < 0.05

Table 3a: Summary of backward elimination for model time for parameters age, primary tumor, standardized uptake value mean, number of involved lymph nodes, nodal metabolic tumor volume, nodal total lesion glycolysis, total metabolic tumor volume, pathologic nodal, pathologic tumor

Step	Effect removed	Wald (χ^2)	*P*
1	pN	0.23	0.633
2	Nodal MTV	0.67	0.414
3	# LN involved	0.93	0.336
4	Total MTV	0.87	0.352
5	pT	0.53	0.467

pT: Pathologic tumor; pN: Pathologic nodal; LN: Lymph nodes; # LN involved: Number of involved LNs; MTV: Metabolic tumor volume

spread. In OCSCC, AJCC 7th edition 2010, also includes histologic grade (G) as a potential predictor, however, Stages 0 to IVC are assigned solely based on based on T, N, and M.[19] In NCCN guidelines, the initial treatment (surgery in a majority of treatment arms) of OCSCC is chosen solely based on TNM staging parameters estimated by clinical examination, endoscopy, and imaging.[3] Following the initial surgery, the decision on adjuvant treatment (observation, radiation, or chemoradiation) is based on adverse risk features in pathologic specimens, including extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in Levels IV and V, perineural invasion, and vascular embolism.[3] Although additional parameters not routinely incorporated into TNM staging do influence the survival in OCSCC,[20,21] their introduction into treatment algorithms remains challenging. In general, the additional factors should have added independent prognostic value to TNM staging in the multivariate analysis, which is difficult to prove unless the sample is very large.

In our study, the multivariate predictors of OS in OCSCC were age, primary tumor SUV mean, and nodal TLG. The design and results of our study were compared and contrasted in Table 4 with five other studies that evaluated the ability of initial staging presurgical ^{18}F-FDG PET/CT to predict survival.[10,12-15] In all six studies, the initial surgery was followed by observation, radiation, or chemoradiation as per NCCN guidelines. Only 4 of 6 studies found that ^{18}F-FDG PET parameters are independently predictive of OCSCC survival. Hofele *et al.* found that primary tumor SUV max is the only independent predictor of OS in 79 patients with OCSCC.[12] In the study by Abd El-Hafez *et al*., primary tumor TLG, SUV max of the most active node, and pN were independent predictors disease-specific survival in 126°CSCC patients.[10] Ryu *et al.* reported total primary tumor and nodal MTV and TLG and involved resection margin being predictive of OS in 105°CSCC patients.[15] In contrast, Kendi *et al*. ($n = 36$)[13] and Kim *et al*. ($n = 160$)[14] found that ^{18}F-FDG PET parameters were not predictive of OS in OCSCC patients. Our study result that primary tumor SUV mean is a significant predictor of OS is unexpected and could have been caused by the small sample size of our study. However, there was no consistency between ^{18}F-FDG PET parameters predictive of survival in four positive studies [Table 4], suggesting broader study design inconsistencies. For example, there was no consistency in the selection of ^{18}F-FDG PET parameters between all 6 studies, with the discrepancies being greater for regional lymph nodes than for primary tumor. In 4 studies that evaluated regional nodes, the abnormal nodes were identified based on FDG avidity, and potentially false-positive reactive nodes were not excluded based on correlation with surgical pathology. Two studies analyzed only primary tumor and omitted regional lymph nodes on PET. Thus, standardized selection of ^{18}F-FDG PET parameters with pathologic correlation may lead to more consistent results and eventually resolve

current controversy on ^{18}F-FDG PET in predicting OCSCC OS. All studies included demographic age and sex into the multivariate analysis, despite these parameters not being considered by TNM staging system and NCCN guidelines. Pathologic parameters were included in all studies, but also in very inconsistent fashion, with 4 of 6 studies adding additional parameters beyond the scope of TNM staging system and NCCN guidelines. Two studies in which ^{18}F-FDG PET parameters were not predictive of OS, had included additional imaging into the multivariate analysis, which was predictive of OS.[13,14] Since ^{18}F-FDG PET/CT prognostic studies are usually limited with by sample size, unnecessary plethora of analyzed parameters could weaken statistical analysis and lead to erroneous conclusion of no predictive value. This is particularly relevant since ^{18}F-FDG PET parameters are usually highly correlated to each other. Moreover, plethora of parameters may adversely affect practical clinical applicability of positive study. A potentially better approach would be to design a limited standardized prognostic model driven by a specific clinical question. For example, ^{18}F-FDG PET predictive value in OCSCC may be tested in NCCN model (with only a few high-value pathologic parameters) by assessing one routine (i.e., SUV max) and one advanced imaging parameter (i.e., TLG) for primary tumor and dominant lymph node in multi-institutional study (to secure a sufficient sample size).

Table 3b: Multiple cox proportional hazards regression (final model built from Model 1) for parameters age, primary tumor, standardized uptake value mean, nodal total lesion glycolysis

Variables	Coefficient	Hazards ratio (95% CI)	*P*
Age	0.06	1.07 (1.03-1.10)	0.000
Primary tumor SUV mean	0.13	1.13 (1.02-1.26)	0.023
Nodal TLG	0.01	1.01 (1.00-1.02)	0.023

TLG: Total lesion glycolysis; SUV: Standardized uptake value; CI: Confidence interval

Our retrospective study is limited by a small patient cohort, short follow-up, and challenges in selecting the optimal PET parameters from many candidates. Consequently, the optimal PET parameters in our study, primary tumor SUV mean and nodal TLG could be tested for independent predictive value against only a limited number of demographic and TNM parameters. Thus, our results, like results of other similar ^{18}F-FDG PET/CT studies should be considered preliminary. Our study adds to ongoing controversy on the predictive value and the most optimal PET parameters for outcome prediction in OCSCC. It is probably unrealistic to expect ^{18}F-FDG PET/CT predictors to be superior over pathologic and demographic parameters, although PET has a theoretical advantage in depicting the activity and volume of the tumor in addition to its anatomical extent denoted by TNM staging. However, we believe that ^{18}F-FDG PET/CT still may be a valuable addition to multifactorial models predicting outcome for oral cavity cancer. Thus, continued research aiming to incorporate ^{18}F-FDG PET/CT parameters in risk-stratification algorithms for OCSCC is

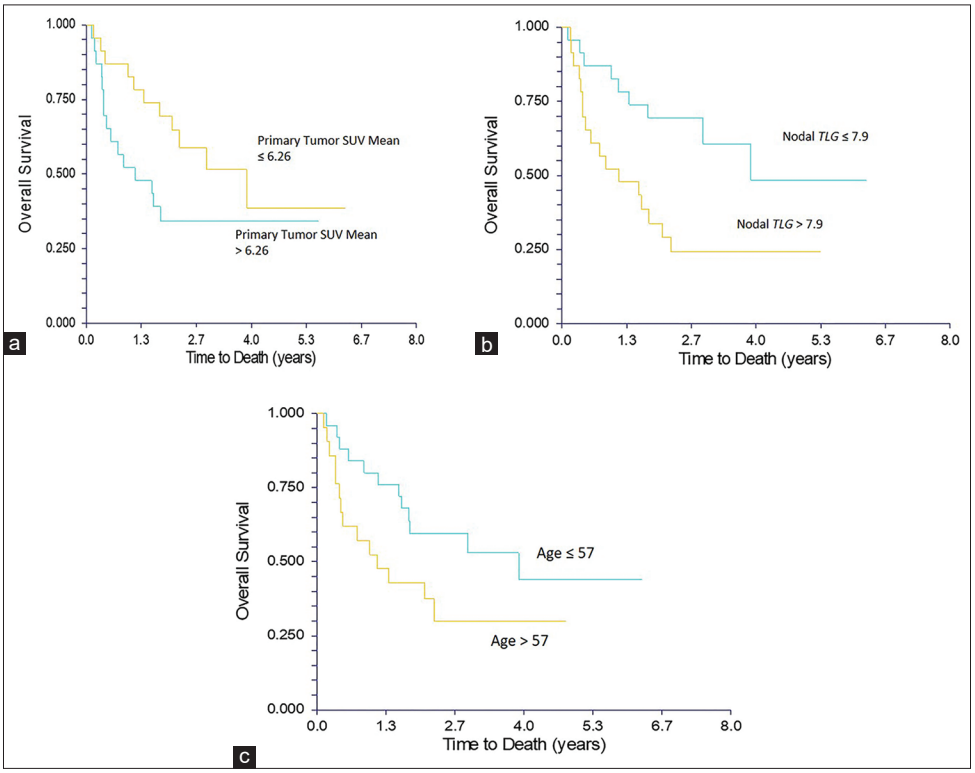

Figure 1: Kaplan–Meier overall survival plots for predictors primary tumor standard uptake value mean (a), nodal total lesional glycolysis (b), and age (c)

Table 4: Comparison of studies evaluating initial staging ^{18}Fluorine-2-fluoro-2-Deoxy-d-glucose positron emission tomography/computed tomography in predicting oral squamous cell carcinoma survival

	Our study	Hofele *et al*.[12]	Abd El-Hafez *et al*.[10]	Ryu *et al*.[15]	Kendi *et al*.[13]	Kim *et al*.[14]
N patients	46	79	126	105	36	160
Follow-up	Median 18 (1-76) months	Median 26 (3-87) months	Until death or ≥24 months	Until death or ≥12 months	Until death or ≥7 months	53 months average
Survival	OS	OS	DSS	OS	OS	OS
PET primary tumor parameters	SUVmax, SUV mean, MTV, TLG	SUVmax	SUVmax, SUV mean, MTV, TLG	NA	SUVmax, SUV mean, SUV peak, MTV, TLG, N SAM, SAM	SUVmax, SUV mean, SUV peak, TLG
PET LNs parameters	# LNs, SUV max (most active LN), MTV, TLG	NA	SUVmax (most active LN)	NA	SUVmax, SUV mean, SUV peak, MTV, TLG, N SAM, SAM	NA
LNs analyzed on PET	SUV max LN >1.5 × SUVmax liver	NA	Not specified	LNs avid on visual analysis	Single hottest LN analyzed	NA
PET total tumor parameters	MTV, TLG	NA	NA	SUVmax, MTV, TLG	NA	NA
Other imaging	NA	NA	NA	NA	Ring pattern on FDG PET, CECT	FAMT PET
Demographic parameters	Age, sex race	Age, sex	Age, sex, smoking, alcohol	Age, sex, smoking, alcohol	Age, sex, smoking, alcohol	Age, sex
Pathologic parameters	pT, pN	Stage	TS, TG, SI, PNI, RM pT, pN, ECS, stage	TS, TG, RM, LVI, PNI, stage	TG, PNI, LVI, pT, pN, ECS	TG, INF, pT, pN, pM, stage
Significant Survival Multivariate Predictors	Primary tumor SUV mean, nodal TLG, age	Primary Tumor SUV max	Primary tumor TLG, nodal SUV max, pN	Total tumor MTV and TLG, RM	Ring pattern on CECT	MTV on FAMT PET, pN

OS: Overall survival; DSS: Disease-specific survival; NA: Not applicable; LN: Lymph node; SAM: Standardized added metabolic activity; N SAM: Normalized standardized added metabolic activity; CECT: Contrast-enhanced CT; FAMT: L-3-[18F]-Fluoro-α-methyl tyrosine; TS: Subsite of primary tumor; TG: Grade of primary tumor; PNI: Perineural invasion of primary tumor; SI: Skin invasion; LVI: Lymphovascular invasion of primary tumor; RM: Resection margin of primary tumor; INF: Infiltrative growth of primary tumor; ECS: Extracapsular nodal spread; PET: Positron emission tomography; CT: Computed tomography; TLG: Total lesion glycolysis; MTV: Metabolic tumor volume; SUV: Standardized uptake value; pT: Pathologic tumor; pN: Pathologic nodal

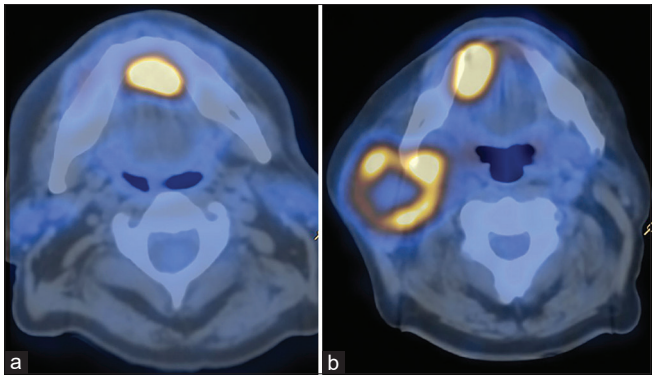

Figure 2: Comparison of two patients with floor of the mouth oral cavity squamous cell carcinoma primary on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. The first patient (a) had no nodal disease, was treated with primary surgery and adjuvant radiation and is alive after 72 months of follow up. The second patient (b) had extensive nodal disease and succumbed to disease after only 6 months despite aggressive management with primary surgery and adjuvant chemoradiation

warranted and should be conducted using more standardized prognostic models driven by a specific clinical question.

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Conflicts of interest

There are no conflicts of interest.

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