Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1220117
J Health Sci Med 2023; 6(1): 183-189

Prognostic role of primary tumor metabolic-volumetric parameters of ^{18}F-fluorodeoxyglucose positron emission tomography in tongue squamous cell carcinoma

Uğuray Aydos[1], Süleyman Cebeci[2]

[1]Department of Nuclear Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey
[2]Department of Otorhinolaryngology, Faculty of Medicine, Gazi University, Ankara, Turkey

Cite this article as: Aydos U, Cebeci S. Prognostic role of primary tumor metabolic-volumetric parameters of ^{18}F-fluorodeoxyglucose positron emission tomography in tongue squamous cell carcinoma. J Health Sci Med 2023; 6(1): 183-189.

ABSTRACT

Aim: It was aimed to evaluate the prognostic role of primary tumor metabolic-volumetric parameters of ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in resectable tongue squamous cell carcinoma (TSCC).

Material and Method: The imaging findings of 44 TSCC patients (23 females, 21 males, mean age: 58±12 years) with resectable tumors who underwent ^{18}F-FDG PET/CT imaging for primary staging before surgery between 2010-2021 were evaluated retrospectively. Maximum standardized uptake value (SUVmax), total lesion glycolysis (TLG), metabolic tumor volume (MTV) of primary tumors were acquired from PET/CT. Histopathological risk factors (pathological tumor and nodal stage, perineural and lymphovascular invasion, depth of invasion, surgical margin positivity) obtained from surgical resection material of primary tumors were also recorded. The prognostic values of imaging and histopathological parameters were assessed by Cox proportional hazards regression models. Survival curves were estimated by using the Kaplan-Meier analysis.

Results: The median follow-up period after diagnosis was 24 months (range: 2-152 months). The univariate and multivariate regression analyses demonstrated that MTV was the only parameter which was significantly related to prognosis for PFS and OS. The patients with higher MTV (> 3.13 cm^3) had lower PFS and OS rates compared to those with lower MTV (≤ 3.13 cm^3) ($p<0.001$, $p=0.002$, respectively).

Conclusion: Primary tumor MTV is an independent prognostic factor in resectable TSCC. PET volumetric features can be used as prognostic biomarker to predict patients with poor prognosis.

Keywords: FDG, metabolic tumor volume, PET/CT, survival, tongue squamous cell carcinoma

INTRODUCTION

Tongue squamous cell carcinoma (TSCC) is the most common malignancy in oral cavity (1). Despite improvements in diagnostic tools and treatment modalities, the mortality rate of TSCC has not diminished in recent years and 5-year survival rate for TSCC is still below 50% (2,3). Tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) is the most commonly used method to determine treatment modalities and to predict patient prognosis. Nevertheless, the prognosis of patients within the same TNM stage may vary (4). In addition to TNM staging system, various histopathological risk factors (depth of invasion, perineural invasion [PNI], surgical margin status, lymphovascular invasion [LVI],) in resectable TSCC can be used to predict patient prognosis (5-9). However, histopathological prognostic markers can only be obtained after surgical resection. New prognostic biomarkers which can be obtained in the preoperative period and allow individualized risk stratification are needed in order to improve patient survival.

Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography / computed tomography (PET/CT) imaging is a hybrid molecular imaging system used in primary staging of head and neck cancers for detection of lymph node and distant metastasis (10-13). FDG PET imaging can also have prognostic role in TSCC patients. The previous studies demostrated that the PET quantitative features of primary tumors, such

Corresponding Author: Uğuray Aydos, uguray23@gmail.com
Received: 16.12.2022 **Accepted:** 02.01.2023

as maximum standardized uptake value (SUVmax), total lesion glycolysis (TLG), metabolic tumor volume (MTV), could contribute to the prediction of survival in TSCC (14-17). However, the studies on this subject are still few and the validation of the previous results with new studies is needed.

The main aim of the study was to investigate the prognostic role of ^{18}F-FDG PET/CT metabolic-volumetric parameters of primary tumor in resectable TSCC. It was also aimed to examine the association between histopathological risk factors and quantitative FDG PET parameters of primary tumors.

MATERIAL AND METHOD

The study was carried out with the permission of Gazi University Clinical Researches Ethics Committee (Date: 05.12.2022, Decision No: 889). Because the study was designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Patients with diagnosed resectable TSCC, who underwent primary staging whole body ^{18}F-FDG PET/CT before surgical resection between April 2010 and November 2021 in our hospital, were reviewed retrospectively. Patients who (a) had distant metastasis, (b) were inoperable, and (c) received neoadjuvant therapy were excluded. Finally, 44 patients (21 males, 23 females, mean age: 58±12 years) were included. Histopathological risk factors (pathological tumor and nodal stage, PNI and LVI, depth of invasion, surgical margin positivity) obtained from surgical resection material of primary tumor were recorded. The median time between preoperative PET/CT and surgical resection was 10 days (range, 2-28 days). After surgical resection, TNM stages were determined by using the AJCC staging guidelines (8th edition) (18).

^{18}F-FDG PET/CT

All patients fasted for 4 to 6 hours prior to the PET/CT scan. Blood glucose levels were less than 150 mg/dl in all patients before ^{18}F-FDG injection (3,7 MBq/kg). PET/CT was performed on a GE Discovery ST PET/CT system (General Electric Medical Systems, Milwaukee, WI, USA) with a spatial resolution of 5 mm, 60 minutes after radiotracer injection. A low dose CT scan without contrast injection (120 keV, 10-90 mA) was acquired. Following the completion of CT scan, a PET scan (from vertex to mid-thigh) with an axial field of view of 15.7 cm was acquired. The CT data were used to obtain the attenuation corrected PET emission data. PET scan duration was 3 minutes per bed position.

Image Analysis

PET/CT images were evaluated quantitatively by one nuclear medicine specialist who was blinded to the patient outcomes. Tumor SUVmax, TLG and MTV were obtained on a dedicated workstation (GE Healthcare, AW Workstation Volume Share 2). The volume of interest (VOI) was drawn on primary tumor by using the software with 42% threshold of SUVmax. TLG was obtained as the product of SUVmean and MTV.

Statistical Analysis

The relationship of PET parameters with histopathological risk groups were analyzed by using the Kruskal-Wallis test and the Mann-Whitney U test. Spearman's rank correlation was used to analyze the correlation levels between FDG PET parameters and histopathological risk factors. Progression-free survival (PFS) time was the time from the diagnosis to the date of disease related clinical relapse, or to the date of last follow-up visit. Overall survival (OS) time was the time from the diagnosis to the date of death or to the date of the final follow-up visit. The prognostic significances of the variables were evaluated by univariate an multivariate analyses using Cox proportional hazards regression models. The optimal cut-off levels of quantitative PET parameters were determined in the receiver operating characteristic (ROC) curve analysis by using the Youden index (sensitivity + specificity-1). Survival curves were estimated by using the Kaplan-Meier analysis and for comparison the log-rank test was used. SPSS 23.0 (IBM, New York) software was used for statistical analyses. For all analyses, p values of <0.05 were considered statistically significant.

RESULTS

Patients

The patient characteristics were shown in **Table 1**. 21 patients were male (47.7%) and the mean age was 58.0±12.0 years at the time of diagnosis. The median pathological tumor size was 2.6 cm. The LVI, PNI, surgical margin were positive in 10 (22.7%), 22 (50%) and 7 (15.9%) patients, respectively. The median depth of invasion was 10.3 mm and median distance from the closest surgical margin was 3 mm. Elective neck dissection was performed in all patients and revealed cervical LN metastasis in 21 patients. According to the AJCC staging system, 6 patients (13.6%) had stage I, 10 (22.7%) had stage II, 14 (31.8%) had stage III and 14 (31.8%) had stage IV disease. All primary tumors had ^{18}F-FDG uptake. The median SUVmax, MTV and TLG were 10.5 (range: 3.5-23.3), 4.3 (range: 0.88-38.2) and 24.9 (2.3-371.3), respectively.

Table 1. The characteristics of patients	
Age (mean±SD)	58.0±12.0 years
	Median (minimum-maximum)
Maximum standardized uptake value (SUVmax)	10.5 (3.5-23.3)
Metabolic tumor volume (MTV, cm³)	4.3 (0.88-38.2)
Total lesion glycolysis (TLG)	24.9 (2.3-371.3)
Histopathological tumor diameter (cm)	2.6 (0.3-7.2)
Depth of invasion (mm)	10.3 (2.0-45.0)
Distance from closest surgical margin (mm)*	3.0 (1.0-8.0)
	N (%)
Gender	
Female	23 (52.3)
Male	21 (47.7)
Pathological tumor stage (pT)	
T1	8 (18.2)
T2	14 (31.8)
T3	16 (26.4)
T4	6 (13.6)
Pathological nodal stage (pN)	
N0	23 (52.3)
N1	9 (20.5)
N2	4 (9.1)
N3	8 (18.2)
AJCC stage (8th)	
I	6 (13.6)
II	10 (22.7)
III	14 (31.8)
IV	14 (31.8)
Tumor differentiation	
Well-differentiated	29 (65.9)
Moderately differentiated	13 (29.5)
Poorly differentiated	2 (4.5)
Lymphovascular invasion	
Negative	34 (77.3)
Positive	10 (22.7)
Perineural invasion	
Negative	22 (50.0)
Positive	22 (50.0)
Surgical margin status	
Negative	37 (84.1)
Positive	7 (15.9)
Tumor Recurrence	
Negative	22 (50.0)
Positive	22 (50.0)
Mortality	
Yes	19 (43.2)
No	25 (56.8)
*In patients with negative surgical margins	

The median follow-up period was 24 months (range: 2-152 months). 22 patients (50%) had tumor recurrence and 19 patients (43.2%) had died during the follow-up.

Relationship Between PET Quantitative Parameters and Histopathological Risk Factors

TLG and MTV were significantly higher in the pT stage T3-T4 group compared to the pT stage T1-T2 group (TLG: 51.6 vs 13.1, respectively, p=0.003; MTV: 6.0 vs 2.4 cm³, respectively, p=0.001). Tumor SUVmax was not significantly different among pT stage categories (p=0.336). FDG PET parameters did not demonstrate significant differences among pN stage categories (p>0.05 for all).

Tumor SUVmax, MTV, TLG had significantly higher values in the patients with LVI than those without LVI (SUVmax: 14.4 vs 9.3, respectively, p=0.028; MTV: 8.0 cm³ vs 3.3 cm³, respectively, p=0.01; TLG: 76.3 vs 18.2, respectively, p=0.005).

Tumor SUVmax, MTV, TLG had significantly higher values in the patients with PNI than those without PNI (SUVmax: 11.9 vs 8.7, respectively, p=0.031; MTV: 5.9 cm³ vs 2.8 cm³, respectively, p=0.005; TLG: 51.6 vs 12.7, respectively, p=0.003).

MTV and TLG had significantly higher median values in patients with positive surgical margin compared to patients with negative surgical margin (MTV: 15.2 cm³ vs 4.0 cm³, respectively, p=0.041; TLG: 91.2 vs 19.3, respectively, p=0.015). However, tumor SUVmax was not significantly different among surgical margin categories (p=0.125).

Tumor SUVmax was significantly but moderately correlated with histopathological tumor diameter (r=0.47, p=0.001) and depth of invasion (r=0.453, p=0.006). However, MTV and TLG had significant stronger positive correlations with histopathological tumor diameter (r=0.70 and 0.717, respectively, p<0.001 for both) and depth of invasion (r=0.70 and 0.727, respectively, p<0.001 for both). While the correlation between tumor SUVmax and the distance from the closest surgical margin was not significant (p=0.37), MTV and TLG had significant moderate negative correlations with the distance from the closest surgical margin (r=-0.408 and -0.465, p<0.05 for both).

Survival Analysis for PFS

The median PFS in all study population was 24 months. On univariate analysis, TLG, MTV, pathological T stage, AJCC stage, LVI and PNI were significant predictors of PFS (p<0.05 for all; **Table 2**). On multivariate analysis, MTV of primary tumor was identified as the only significant parameter for PFS (hazard ratio [HR], 9.2; 95% confidence interval [CI], 1.53-55.2; p=0.015; **Table 2**).

The Kaplan-Meier analysis demonstrated that patients with higher tumor MTV (> 3.13 cm³) had significantly lower PFS rate than the patients with lower MTV (28.6% vs. 87.5%; p<0.001; **Figure 1**).

Table 2. Results of univariate and multivariate Cox regression analyses of progression-free survival (PFS)

Variables	Categories	HR (95% CI) (Univariate)	P	HR (95% CI) (Multivariate)	P
Gender	Male vs Female	1.62 (0.69-3.8)	0.270	-	-
Age	-	1.03 (0.99-1.07)	0.125	-	-
SUVmax	≤ 9.86 vs>9.86	2.07 (0.84-5.12)	0.114	-	-
MTV	≤ 3.13 vs>3.13	8.84 (2.1-38.1)	**0.003**	9.2 (1.53-55.2)	**0.015**
TLG	≤ 18.15 vs>18.15	3.34 (1.23-9.1)	**0.018**	2.1 (0.5-8.54)	0.316
Pathological tumor diameter (cm)	≤ 2.4 vs>2.4	2.12 (0.89-5.1)	0.091	-	-
Pathological T stage	T1-T2 vs T3-T4	3.28 (1.33-8.1)	**0.01**	1.15 (0.36-3.65)	0.813
Pathological N stage	N0 vs N1-N2-N3	1.78 (0.76-4.16)	0.183	-	-
AJCC Stage	I-II-III vs IV	3.28 (1.39-7.72)	**0.007**	2.68 (0.92-7.81)	0.072
Tumor differentiation	Well vs Moderate-Poor	1.77 (0.76-4.11)	0.183	-	-
Lymphovascular invasion	Negative vs Positive	3.53 (1.42-8.76)	**0.006**	1.58 (0.53-4.7)	0.413
Perineural invasion	Negative vs Positive	3.54 (1.42-8.83)	**0.007**	2.24 (0.7-7.17)	0.173
Surgical margin	Negative vs Positive	2.6 (0.95-7.13)	0.062	-	-

The bold entries indicate a significant result. Abbreviations: HR: hazard ratio, CI: confidence interval, SUV: standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis, AJCC: American Joint Committee on Cancer

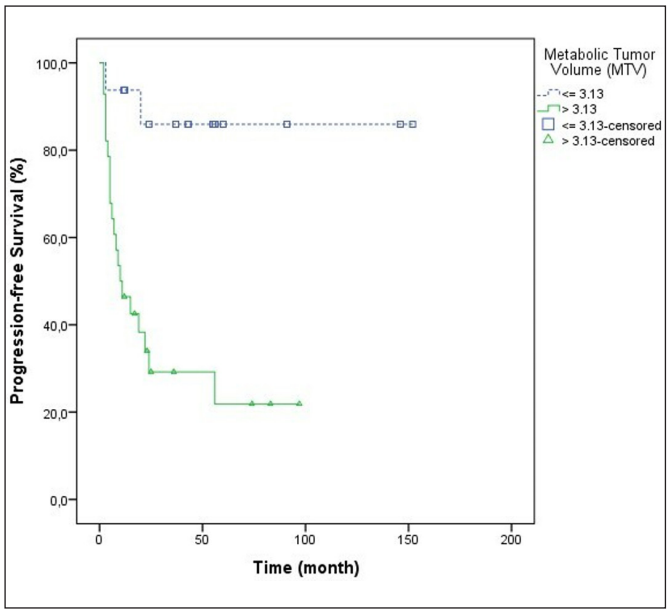

Figure 1. Kaplan-Meier curve of progression-free survival (PFS) of study subjects (n= 44) according to the MTV of primary tumors (Log Rank p<0.001). Patients with higher tumor MTV (> 3.13 cm³) had significantly lower PFS rates compared to those with lower MTV (28.6% vs. 87.5%, respectively).

Survival Analysis for OS

The median OS in all study population was 44 months. On univariate analysis, TLG, MTV, pathological T stage, pathological N stage, AJCC stage, LVI, PNI and surgical margin positivity were significant predictors of OS (p<0.05 for all; **Table 3**). On multivariate analysis, MTV of primary tumor was found as the only significant prognostic parameter for OS (HR, 9.5; 95% CI, 1.5-60.6; p=0.017; **Table 3**).

The Kaplan-Meier curves demonstrated that patients with higher tumor MTV (> 3.13 cm³) had significantly lower OS rate than the patients with lower MTV (39.3% vs. 87.5%; p=0.002; **Figure 2**). PET/CT images of two patients with TSCC were shown in **Figure 3** and **Figure 4**. Tumor SUVmax, MTV and TLG of the patient in **Figure 3** were 21.3, 1.37 cm³ and 20.1, respectively. The patient had no tumor recurrence and is alive at 146 months after cancer diagnosis. Tumor SUVmax, MTV and TLG of the other patient in **Figure 4** were 13.5, 10.37 cm³ and 88.9, respectively. This patient had tumor recurrence at 24 months and had died at 33 months after diagnosis.

Table 3. Results of univariate and multivariate Cox regression analyses of overall survival (OS)

Variables	Categories	HR (95% CI)(Univariate)	P	HR (95% CI)(Multivariate)	P
Gender	Male vs Female	2.58 (1.0-6.6)	0.056	-	-
Age	-	1.03 (0.99-1.1)	0.142	-	-
SUVmax	≤ 9.86 vs>9.86	2.62 (0.94-7.32)	0.066	-	-
MTV	≤ 3.13 vs>3.13	7.5 (1.72-32.7)	**0.007**	9.5 (1.5-60.6)	**0.017**
TLG	≤ 18.15 vs>18.15	3.7 (1.23-11.2)	**0.02**	2.47 (0.49-12.5)	0.276
Pathological tumor diameter (cm)	≤ 2.4 vs>2.4	1.96 (0.77-5.0)	0.157	-	-
Pathological T stage	T1-T2 vs T3-T4	3.1 (1.17-8.2)	**0.023**	1.41 (0.37-5.36)	0.615
Pathological N stage	N0 vs N1-N2-N3	2.84 (1.11-7.3)	**0.03**	1.25 (0.33-4.7)	0.743
AJCC Stage	I-II-III vs IV	5.16 (2.04-13.1)	**0.001**	2.88 (0.64-13.0)	0.169
Tumor differentiation	Well vs Moderate-Poor	2.37 (0.96-5.84)	0.062	-	-
Lymphovascular invasion	Negative vs Positive	4.4 (1.65-11.7)	**0.003**	1.5 (0.38-5.8)	0.565
Perineural invasion	Negative vs Positive	4.87 (1.71-13.9)	**0.003**	2.95 (0.73-11.9)	0.130
Surgical margin	Negative vs Positive	3.46 (1.22-9.8)	**0.019**	2.83 (0.65-12.4)	0.167

The bold entries indicate a significant result.Abbreviations: HR: hazard ratio, CI: confidence interval, SUV: standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis, AJCC: American Joint Committee on Cancer

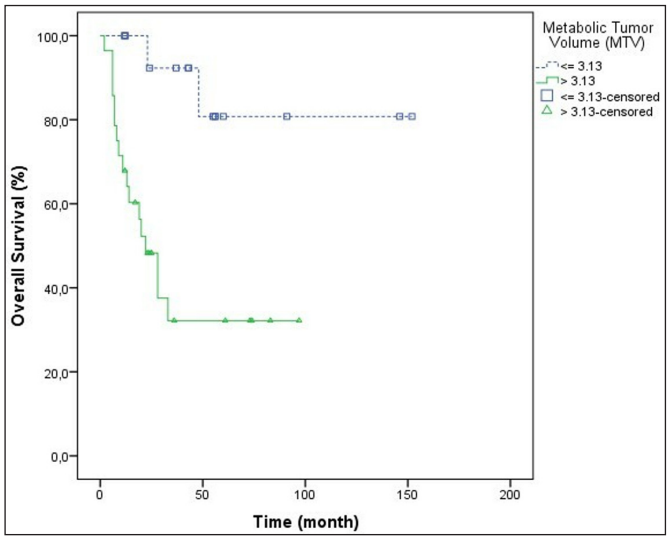

Figure 2. Kaplan-Meier curve of overall survival (OS) of study subjects (n= 44) according to the MTV of primary tumors (Log Rank p = 0.002). Patients with higher tumor MTV (> 3.13 cm³) had significantly lower OS rates compared to those with lower MTV (39.3% vs. 87.5%, respectively).

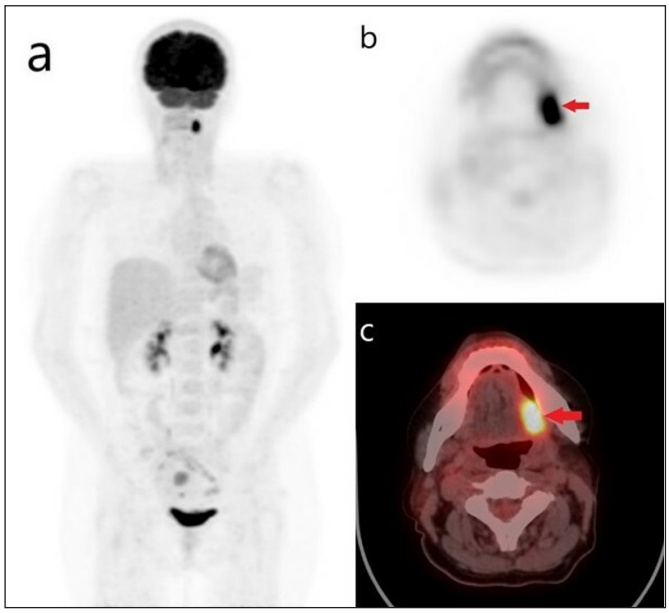

Figure 3. Maximum intensity projection (a), axial ¹⁸F-FDG PET (b) and PET/CT images (c) of a 54-year-old female patient with TSCC. Primary tumor was seen on the left lateral part of the tongue (red arrows). She had pT2-pN0 tumor with LVI and PNI. The surgical margin was positive and the depth of invasion was 5 mm. Tumor SUVmax, MTV and TLG were 21.3, 1.37 cm³ and 20.1, respectively. The patient had no tumor recurrence and is alive at 146 months after initial cancer diagnosis.

DISCUSSION

In this study, it was demonstrated that primary tumor TLG and MTV had significant associations with higher pathological tumor stage (pT3-T4), LVI, PNI and positive surgical margin status. Moreover, MTV and TLG showed higher correlations with histopathological tumor diameter and depth of invasion compared to SUVmax. In patients with negative surgical margins, MTV and TLG showed significant negative correlations with the distance from the closest surgical margin, while SUVmax

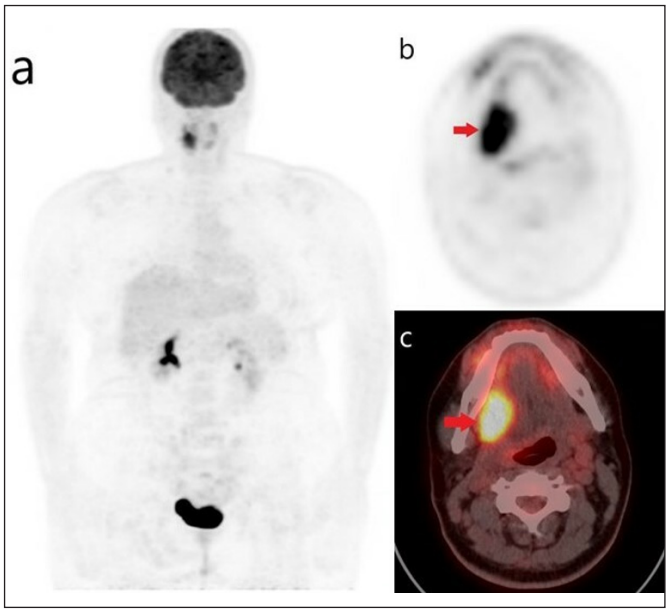

Figure 4. Maximum intensity projection (a), axial ¹⁸F-FDG PET (b) and PET/CT images (c) of a 33-year-old female patient with TSCC. Primary tumor was seen on the right lateral part of the tongue (red arrows). She had pT2-pN0 tumor with PNI but without LVI. The surgical margin was negative, the distance from the closest surgical margin was 2 mm and the depth of invasion was 6 mm. Tumor SUVmax, MTV and TLG were 13.5, 10.37 cm³ and 88.9, respectively. The patient had tumor recurrence at 24 months and had died at 33 months after initial cancer diagnosis.

did not have significant correlation. This study also demonstrated that MTV, as a PET metabolic-volumetric feature, was the only independent prognostic parameter for PFS and OS.

Histopathological tumor and nodal stages, LVI, PNI, surgical margin status and depth of invasion were shown as poor prognostic histopathological risk factors in TSCC (5-9, 19-21). In our study, TLG and MTV were significantly higher in higher pT stage (T3-T4) tumors, in the presence of LVI, PNI and positive surgical margin. While tumor SUVmax had significantly higher values in the presence of LVI and PNI, it did not have a significant association with pathological tumor stage and surgical margin status. These findings suggest that the intensity of FDG uptake in primary tumor may be associated with the tumor aggressiveness and histopathological risk factors. In the study by Yonezawa et al. (15), it was found that tumor SUVmax was higher in patients with the LVI and PNI, similar to the findings of our study. However, while Yonezawa et al. (15) found a significant relationship between tumor SUVmax and advanced T stages, we did not find a similar relationship between SUVmax and T stage groups. This difference between the results of two studies may be related to the use of clinical T stage in this previous study and the use of pathological T stage in our study. In another previous study by Lin et al. (16), it was reported that tumor SUVmax had significant and positive association with depth of invasion. Similar to this finding, we also found a positive correlation between

tumor SUVmax and depth of invasion. Unlike these two previous studies, we also evaluated the relationship of tumor MTV and TLG with histopathological risk factors. While MTV and TLG showed significant relationship with LVI and PNI similar to SUVmax, these parameters also showed significant relationship with pathological T stage and positive surgical margin unlike SUVmax. Furthermore, MTV and TLG showed higher correlations with histopathological tumor diameter, depth of invasion and the distance from the closest surgical margin compared to SUVmax. These findings may be related to the fact that MTV and TLG are metabolic-volumetric quantitative parameters which provide metabolic data about the entire tumor. SUVmax is the single voxel value with highest FDG uptake in tumors, therefore SUVmax may not represent the total tumor metabolic activity.

The present study evaluated the prognostic role of histopathological risk factors and quantitative PET parameters. Our study showed that advanced pathological T stage (pT3-T4), advanced AJCC stage (stage IV), neck lymph node metastasis, LVI, PNI and positive surgical margins were important prognostic factors in the univariate survival analyses. These findings were in accordance with previous studies (14-16). In these previous studies, tumor SUVmax had also significant assocations with patient survival. Unlike these studies, a significant relationship between survival and tumor SUVmax was not found in our study. Although tumor SUVmax did not show significant association with survival, tumor TLG and MTV were also found to have prognostic value in the univariate analyses for both PFS and OS. This result may be related to the fact that SUVmax may not represent the total tumor metabolic activity. On the contrary, TLG and MTV could reflect the total tumor metabolic activity.

Our study demonstrated that tumor MTV was the only significant parameter in the multivariate analyses for PFS and OS. Tumor MTV was also found as independent prognostic parameter of OS in a previous study by Lee et al. (14). We demonstrated that tumor MTV had a prognostic value not only for OS, but also for PFS. Lee et al. used absolute threshold (SUV 2.5) method for the measurement of tumor MTV. Unlike this method, we used relative percentage threshold method (42% of tumor SUVmax) for the measurement of MTV. Despite the differences in the measurement methods, the result of tumor MTV as an independent prognostic factor in both studies suggests that this metabolic-volumetric FDG PET parameter may be an important preoperative imaging biomarker to predict the prognosis in resectable TSCC.

TLG is an important FDG PET parameter that combines SUV and MTV, providing information about the total glycolytic activity of the tumor mass. In our study, tumor TLG had significant associations with survival in univariate analyses. However, TLG did not have independent prognostic role in multivariate analyses. This result was in accordance with the study of Lee et al (14). This result in our study may be associated with the relatively small patient sample size in the multivariate analyses. Further studies with larger patient populations are needed to evaluate the prognostic role of tumor TLG in TSCC.

This study has several limitations. First, this study was a single-center, retrospective study with a small patient size. Second, a single threshold method was used for the measurement of metabolic tumor volume. Prospective multicenter studies with larger sample size are needed to validate the prognostic role of FDG PET metabolic-volumetric parameters in TSCC.

CONCLUSION

Tumor MTV was the only independent prognostic factor for PFS and OS. MTV may be a preoperative prognostic tool to identify patients with poor prognosis in resectable TSCC. The FDG PET metabolic-volumetric features may be used as an indicator for preoperative risk stratification of patients. The validation of these results is necessary in multicenter prospective studies..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gazi University Medical Faculty Clinical Researches Ethics Committee (Date: 05.12.2022, Decision No: 889).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

Author Contributions: The authors declare that they have participated in the design, execution, and analysis of the paper, and they have approved the final version.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34.
2. da Silva Souto AC, Vieira Heimlich F, Lima de Oliveira L, et al. Epidemiology of tongue squamous cell carcinoma: A retrospective cohort study. Oral Dis 2021; 00: 1-9.
3. Moore S, Johnson N, Pierce A, Wilson D. The epidemiology of tongue cancer: a review of global incidence. Oral Dis 2000; 6: 75-84.

4. Li Y, Zhao Z, Liu X, et al. Nomograms to estimate long-term overall survival and tongue cancer-specific survival of patients with tongue squamous cell carcinoma. Cancer Med 2017; 6: 1002-13.
5. Chang B, He W, Ouyang H, et al. A prognostic nomogram incorporating depth of tumor invasion to predict long-term overall survival for tongue squamous cell carcinoma with R0 resection. J Cancer 2018; 9: 2107-15.
6. Huang S, Zhu Y, Cai H, Zhang Y, Hou J. Impact of lymphovascular invasion in oral squamous cell carcinoma: A meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 131: 319-28. e1.
7. Li J, Liu S, Li Z, Han X, Que L. Prognostic value of perineural invasion in oral tongue squamous cell carcinoma: a systematic review and meta-analysis. Front Oncol 2021; 11: 683825
8. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. Oral Oncol 2007; 43: 780-4.
9. Colonia-García A, Salazar-Peláez LM, Serna-Ortiz CA, Álvarez-Sánchez LG, de Andrade CR. Prognostic value of lymphovascular and perineural invasion in squamous cell carcinoma of the tongue. Oral Surg Oral Med Oral Pathol Oral Radiol 2022; 133: 207-15.
10. Pfister DG, Spencer S, Adelstein D, et al. Head and neck cancers, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2020; 18: 873-98.
11. Paleri V, Urbano T, Mehanna H, et al. Management of neck metastases in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016; 130: S161-S9.
12. Yi X, Fan M, Liu Y, Zhang H, Liu S. 18 FDG PET and PET-CT for the detection of bone metastases in patients with head and neck cancer. A meta-analysis. J Med Imaging Radiat Oncol 2013; 57: 674-9.
13. Rohde M, Nielsen AL, Johansen J, et al. Head-to-head comparison of chest x-ray/head and neck MRI, chest CT/head and neck MRI, and ^{18}F-FDG PET/CT for detection of distant metastases and synchronous cancer in oral, pharyngeal, and laryngeal cancer. J Nucl Med 2017; 58: 1919-24.
14. Lee SJ, Choi JY, Lee HJ, et al. Prognostic value of volume-based ^{18}F-fluorodeoxyglucose PET/CT parameters in patients with clinically node-negative oral tongue squamous cell carcinoma. Korean J Radiol 2012; 13: 752-9.
15. Yonezawa N, Minamikawa T, Kitajima K, et al. The maximum standardized uptake value increment calculated by dual-time-point ^{18}F-fluorodeoxyglucose positron emission tomography predicts survival in patients with oral tongue squamous cell carcinoma. Nagoya J Med Sci 2017; 79: 189-98.
16. Lin N-C, Hsu J-T, Chen MY, Tsai K-Y. Maximum standardised uptake value is prognostic in patients with early-stage squamous cell carcinoma of the tongue. Br J Oral Maxillofac Surg 2022; 60: 1209-15.
17. Suzuki-Shibata S, Yamamoto Y, Yoshida T, et al. Prognostic value of volumetric FDG PET/CT parameters in patients with oral tongue squamous cell carcinoma who were treated by superselective intra-arterial chemoradiotherapy. Jpn J Radiol 2017; 35: 740-7.
18. Zanoni DK, Patel SG, Shah JP. Changes in the 8th edition of the American Joint Committee on Cancer (AJCC) staging of head and neck cancer: rationale and implications. Curr Oncol Rep 2019; 21: 52.
19. Ho AS, Kim S, Tighiouart M, et al. Metastatic lymph node burden and survival in oral cavity cancer. J Clin Oncol 2017; 35: 3601-9.
20. Suresh GM, Koppad R, Prakash B, Sabitha K, Dhara P. Prognostic indicators of oral squamous cell carcinoma. Ann Maxillofac Surg 2019; 9: 364-70.
21. Kang C-J, Wen Y-W, Lee S-R, et al. Surgical Margins Status and Prognosis after Resection of Oral Cavity Squamous Cell Carcinoma: Results from a Taiwanese Nationwide Registry-Based Study. Cancers 2021; 14: 15.