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Pretreatment quantitative ^{18}F-FDG PET/CT parameters as a predictor of survival in adenoid cystic carcinoma of the salivary glands

Mehmet Gencturk[a], Kerem Ozturk[a], Yasemin Koksel[a], Faqian Li[b], Zuzan Cayci[a,*]

[a] Department of Radiology, University of Minnesota Medical Center, Minneapolis, MN 55455, USA
[b] Department of Pathology and Laboratory Medicine, University of Minnesota Medical Center, Minneapolis, MN 55455, USA

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ABSTRACT

Purpose: The aim of this study was to determine the unique prognostic value of quantitative ^{18}F-FDG PET/CT parameters to assess progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) in patients with salivary gland adenoid cystic carcinoma (ACC).

Methods: We performed a retrospective study including 23 patients (15 men, 8 women; median age, 58 years; range, 21–91 years) with salivary gland ACC between January 2009 and October 2017 who underwent ^{18}F-FDG PET/CT scan prior to treatment. Maximum, mean, peak, tumor-to-mediastinal blood pool and tumor-to-liver standardized uptake values (SUV_{max}, SUV_{mean}, SUV_{peak}, $SUV_{ratio[med]}$ and $SUV_{ratio[liver]}$), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were obtained from ^{18}F-FDG PET/CT. The prognostic value of quantitative ^{18}F-FDG PET/CT parameters and other clinicopathological variables were evaluated utilizing the Cox proportional regression analysis.

Results: The 3-year and 5-year OS for all the patients were 90.9%, and 62.3%, respectively. Log rank test determined that the $SUV_{ratio[med]}$, $SUV_{ratio[liver]}$, MTV and TLG were predictive factors of DMFS, PFS, and OS ($p < 0.05$), furthermore, SUV_{max}, minor salivary gland tumors and DM at initial diagnosis (M1 stage) were predictor for PFS; M1 stage and overall stage 3–4 predicted DMFS (all $p < 0.05$). Cox regression analyses confirmed that the higher $SUV_{ratio[med]}$, $SUV_{ratio[liver]}$, MTV, and TLG values predicted DMFS, PFS and OS independently, whereas SUV_{max} was an independent predictor of only PFS ($p < 0.05$).

Conclusions: The pretreatment metabolic ^{18}F-FDG PET/CT parameters may reflect tumor aggressiveness in patients with salivary gland ACC and may potentially be utilized as a prognostic biomarker.

1. Introduction

Adenoid cystic carcinoma (ACC) of the salivary glands is a rather uncommon tumor accounting for 1% of all head and neck malignancies [1,2]. The behavior of these tumors is quite unique along with their infrequent occurrences [3]. ACC is characterized by slow local growth and frequent development of local recurrences after treatment, high incidence of perineural invasion (PNI) [4], and indolent distant metastases. ACC is associated with a poor prognosis due to the high tendency of local invasion to the surrounding vital anatomical structures [5] and delayed diagnosis [6,7]. Distant metastases (DM), as well as locoregional recurrences, impact the prognosis of ACC patients [8], with a gradual decrease in survival beyond 5 years, suggesting the importance of long-term surveillance following treatment [9]. Because of its rarity, some controversy exists about the clinicopathological variables which may have an impact on the survival of patients with ACC of the minor and major salivary glands [10,11]. Consequently, there is a crucial demand to identify the risk factors related to DMs and locoregional recurrences, to enhance the prediction and early recognition of at-risk patients.

Over the past decade, fluorine-18-deoxy-glucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been widely utilized for initial staging, follow-up, and treatment response evaluation in head and neck cancers including salivary gland cancers [12,13]. The relationship between the ^{18}F-FDG uptake and the degree of metabolic tumor activity has been documented to be related with the incidence of loco-regional and distant recurrences in ACC of the salivary glands [14,15]. Therefore, analyses of metabolic parameters on ^{18}F-FDG PET/CT may offer an attractive opportunity to predict individual tumor behavior independently from morphologic changes. These parameters

* Corresponding author.
E-mail addresses: genct003@umn.edu (M. Gencturk), keremozturk@uludag.edu.tr (K. Ozturk), ykksel@umn.edu (Y. Koksel), lif@umn.edu (F. Li), cayci001@umn.edu (Z. Cayci).

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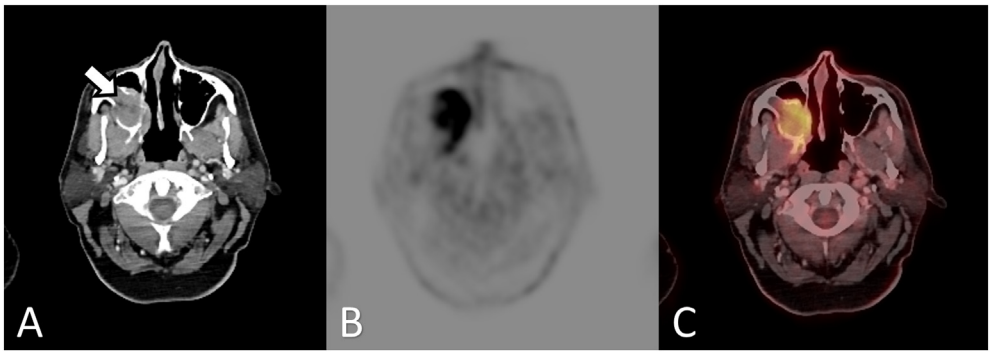

Fig. 1. 57 year old male with newly diagnosed maxillary sinus mass (A). Mass centered in the right maxillary sinus causes erosion of the lateral sinus osseous wall and extends to the retromaxillary fat pad. ^{18}F-FDG PET image demonstrates hypermetabolism (SUV_{max} = 10.1) in the region of the right maxillary sinus (B). FDG uptake extends posteriorly to involve the pterygoid plate and medially into the right posterior nasal cavity. Fused ^{18}F-FDG PET/CT images demonstrate the ^{18}F-FDG avidity of the maxillary sinus mass (C).

may have implications not only for the clinical management and also for their prognostic stratification of salivary gland ACCs. Thus, we think that quantitative ^{18}F-FDG PET/CT values including maximum, mean, peak, tumor-to-mediastinal blood pool and tumor-to-liver standardized uptake value (SUV_{max}, SUV_{mean}, SUV_{peak}, $SUV_{ratio[med]}$ and $SUV_{ratio[liver]}$), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) could have implications for the prognosis of patients with salivary gland ACC. In consideration of this information, we performed this retrospective study to determine the yield of pretreatment quantitative ^{18}F-FDG PET/CT parameters for the prediction of progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) in patients with salivary gland ACC following definitive treatment.

2. Materials and methods

2.1. Study design and patients

This retrospective study was approved by the institutional review board of our hospital, and the requirement for informed consent was waived. Utilizing the electronic hospital medical record system, patients who were diagnosed with histopathologically proven ACC between January 2009 and October 2017 were reviewed at the University of Minnesota Medical Center (U-Health). Data regarding patient characteristics, clinical and pathologic tumor features were acquired from an analysis of electronic medical records. The inclusion criteria were patients who had undergone ^{18}F-FDG PET/CT with subsequent successful conclusive treatment for previously untreated ACC of the salivary glands. Conclusive treatment was described as surgery, and then radiotherapy and/or chemotherapy in the most of cases, after which no residual tumor was found in the immediate postoperative period by surgical margins, endoscopy, or imaging. The exclusion criteria were a recurrent disease at presentation, subtotal resection with unsuccessful adjuvant treatment with persistent residual tumor existing posttreatment setting and the absence of available ^{18}F-FDG PET/CT imaging information.

2.2. Treatments

All patients underwent complete excision of tumors with or without radiotherapy and/or chemotheraphy. The histological grade, surgical margin and the presence of PNI of the tumor tissues were comprehensively analyzed by a skilled pathologist. ACC was grouped based on its morphological pattern as two types: low and high grade. The surgical margin was regarded as positive if residual tumor tissue was identified at the margin of the surgical specimens.

Patients with unfavorable pathological features, such as the positive surgical margin, regional lymph node involvement, PNI, and lymphovascular invasion underwent adjuvant radiotherapy. Chemotherapy was not a component of the standard therapeutic regimen and was exclusively applied on adjuvant setting or for palliation to the patients with advanced tumor stages (stage III–IV).

2.3. ^{18}F-FDG PET/CT technique and image analysis

A combined ^{18}F-FDG PET/CT system (Biograph Sensation 16; Siemens Medical Solutions, Knoxville, TN, USA) was used with a continuous spiral technique utilizing an eight-slice helical CT after intravenous administration of 3 MBq/kg of ^{18}FDG. Standard patient preparation involved a fasting period of a minimum 6 h and a serum glucose level lower than 180 mg/dL prior to ^{18}F-FDG injection. Throughout imaging acquisition, patients were scanned with a whole-body ^{18}F-FDG PET from the vertex extending down to the patient's feet with the arms raised. The 3-mm cut thickness triplanar reconstructions of the enhanced diagnostic CT were used for image analysis. Automated coregistration of the CT and ^{18}F-FDG PET scans was conducted with commercially available software-Syngo.Via® (Siemens Healthcare Forchheim, Germany).

A double-board-certified radiologist and nuclear medicine physician with 10 years experience (Z.C) in reading combined ^{18}F-FDG PET/CT in patients with head and neck cancer drew a volumetric region of interest (VOI) on the primary tumor on ^{18}F-FDG PET/CT axial images (Fig. 1). The VOIs were drawn on the most representative section of the images, in which the tumor size was the largest or the conspicuity of the lesion was highest. Any necrotic portion was avoided to the fullest extent possible. The SUV_{max} of the mediastinal blood pool and liver parenchyma was measured and used as reference SUV for background activity. The ratio of the SUV_{max} of the primary tumor to the SUV_{max} of mediastinal blood pool and liver parenchyma defined the $SUV_{ratio[med]}$ and $SUV_{ratio[liver]}$, respectively. These parameters were utilized to minimize the variability in SUV measurement.

The total tumor volume was segmented via the threshold of the mediastinal blood pool activity SUV to determine MTV, which was calculated using a semiautomated contouring software on Syngo.Via® (Siemens Healthcare Forchheim, Germany). TLG was established as a product of the average SUV (SUV_{mean}) multiplied by the number of voxels in the MTV (i.e., $SUV_{mean} \times MTV$).

2.4. Clinical endpoints and statistical analysis

For a continuous variable, descriptive statistics are presented, and for a categorical variable, count and percent are reported. *P*-values are calculated from two-sample *t*-test for continuous variables and Fisher's exact test for categorical variables. < 0.05 is considered as statistical significance. Each calculation was carried out using SPSS 23.0 for Windows (IBM, Armonk, NY, USA).

OS was defined as the time between the initial treatment and time of death from any cause or the last clinical follow-up (at which time data were censored). Patient follow-up was documented to the date last seen in the clinic or to the date of expiration. PFS was defined as the time between the initial treatment and the first evidence of disease progression. DMFS was defined as the absence of any distant metastasis at

the last follow-up.

The receiver-operating-characteristic (ROC) curve was plotted to identify the most discriminating cut-off points for each parameter to maximize the sensitivity and specificity in predicting the PFS, DMFS, and OS. Survival curves were represented with the Kaplan-Meier method and were compared utilizing the Log-rank test. Cox proportional hazards regression model was performed to determine any significant correlations of the clinicopathological factors or ^{18}F-FDG PET/CT parameters with PFS, DMFS, and OS. The results of the Cox proportional regression analysis were expressed as adjusted hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs). All patients were dichotomized into two groups using the most accurate value of all ^{18}F-FDG PET/CT parameters and clinicopathological factors gathered from ROC analysis. Variables utilized to stratify survival consist of the age, sex, primary tumor site, tumor size, T stage, N stage, M stage, overall stage, pathological grade, lymphovascular invasion, perineural invasion, surgical margin status, and treatment group (surgery with or without adjuvant radiotherapy or chemotheraphy). Overall tumor stage 1 and 2 were classified as early stage, and stage 3 and 4 were classified as an advanced stage.

3. Results

3.1. Patient characteristics

The twenty-three patients constitute the final cohort. The median age at diagnosis was 58 years, (range 21–91) and 15/23 patients (65.2%) were male. According to the acquired information, salivary gland tumors were staged based on the American Joint Committee for Cancer's (AJCC) staging protocols [16]. T3 and T4 disease composed 15/23 (65.2%) of the study population, while only 2/25 (8.7%) of patients had the N1-N3 disease and TNM stage 3–4 in 14 (60.8%) patients. The high-grade tumor was identified in 8/23 (34.8%) patients. Eleven patients had ACCs arising from the major salivary glands and 12 from the minor salivary glands. Pathological examination of the primary tumor tissue demonstrated that PNI (73.9%) was common, accompanied by lymphovascular invasion (34.8%). Total of 21/23 patients had postoperative adjuvant radiotherapy, and five had adjuvant chemotherapy. Table 1 summarizes the study population. The tumor progression was identified in 12 (52%) patients: in a local site in 2 (8.7%) patients and distant sites in 10 (43.4%) patients in the follow-up period. Nine (39%) patients were alive without disease, 3 (13%) had died because of the disease-specific cause, and 11 (47.8%) were alive with locoregional and distant recurrences at the last follow-up.

Twelve (52.2%) patients had recurrences with a median time of 21.4 months (95% CI, 9.3–64.5). The median time to locoregional and distant recurrences was 24.3 months (95% CI, 7.2–87.1) and 20.8 months (95% CI, 9.6–57.4), respectively.

3.2. ROC curve analyses for ^{18}F-FDG PET/CT measurements

The median values (interquartile range) of the ^{18}F-FDG PET/CT parameters were SUV_{max}, 8.9 (7.6–10.2); SUV_{mean}, 4.7 (3.7–5.7); SUV_{peak}, 6.4 (4.9–7.6); $SUV_{ratio[med]}$, 3.6 (2.9–4.2); $SUV_{ratio[liver]}$, 2.7 (1.9–3.0); MTV, 19 (4.5–31.7) mL, and TLG, 75 (26–154) g. To compare the performance of ^{18}F-FDG PET/CT parameters for predicting survival, ROC curve analysis was performed. The AUCs of ^{18}F-FDG PET/CT measurements for DMFS, PFS and OS were as follows: SUV_{max} (0.588, 0.655 and 0.533, respectively), SUV_{mean} (0.530, 0.575 and 0.450); SUV_{peak} (0.576, 0.492 and 0.500); $SUV_{ratio[med]}$ (0.623, 0.572 and 0.791); $SUV_{ratio[liver]}$ (0.676, 0.553 and 0.850); MTV (0.715, 0.613 and 0.883), and TLG (0.738, 0.621 and 0.875) (Figs. 2,3 and Supplementary Figs. 1–4S). The best accuracy of survival prediction was acquired from TLG (AUC = 0.745), followed by MTV (AUC = 0.737), $SUV_{ratio[liver]}$ (AUC = 0.693) and $SUV_{ratio[med]}$ (AUC = 0.662). Volume-based ^{18}F-FDG PET/CT parameters of MTV and TLG revealed significantly better performance than SUV_{max}, SUV_{mean} and SUV_{peak} ($p < 0.001$) in predicting OS, DMFS and PFS. Standardized ^{18}F-FDG PET/CT parameters of $SUV_{ratio[liver]}$ and $SUV_{ratio[med]}$ showed slightly better predictive performance than SUV_{max}, SUV_{mean} and SUV_{peak} ($p < 0.05$). The AUCs gathered from ROC curve analysis for OS, PFS and DMFS are revealed in Table 2. The optimal cutoff values for OS were 8.49 for SUV_{max}, 4.74 for SUV_{mean}, 5.99 for SUV_{peak}, 4.14 for $SUV_{ratio[med]}$, 2.69 for $SUV_{ratio[liver]}$, 5.3 mL for MTV, and 27.7 g for TLG; whereas optimal cutoff values for DMFS and PFS were 9.68 and 8.84 for SUV_{max}, respectively, 4.39 and 4.55 for SUV_{mean}, 4.83 and 5.67 for SUV_{peak}, 4.14 and 3.53 for $SUV_{ratio[med]}$, 2.78 and 2.41 for $SUV_{ratio[liver]}$, 8.3 and 4.35 mL for MTV, and 31.6 and 19.5 g for TLG, respectively (Table 3 and Supplementary Table 1S). Figs. 4, 5 and Supplementary Fig. 5S demonstrates the Kaplan-Meier curves for OS, PFS, and DMFS (all $p < 0.05$). In the Kaplan-Meier curves, every curve represented censored and uncensored data, and “vertical lines” represented censored data.

Table 1
Patient and tumor characteristics.

Variables	No. of patients	%
Sex		
Female	*8*	*34,8*
Male	*15*	*65,2*
Median age, y	58 (range = 21–91)	
Longest diameter		
> 3 cm	*7*	*30,4*
< 3 cm	*16*	*69,6*
Primary sites		
Major salivary gland	*11*	*47,8*
Minor salivary gland	*12*	*52,2*
Histological grade		
High	*8*	*34,8*
Low	*15*	*65,2*
T stage		
T1–2	*8*	*34,8*
T3–4	*15*	*65,2*
N stage		
N0	*21*	*91,3*
N1–2-3	*2*	*8,7*
M stage		
M0	*19*	*82,6*
M1	*4*	*17,4*
Perineural invasion		
Yes	*17*	*73,9*
No	*6*	*26,1*
Lymphovascular invasion		
Yes	*8*	*34,8*
No	*15*	*65,2*
Resection margin		
Positive	*12*	*52,2*
Negative	*11*	*47,8*
Adjuvant radiotherapy		
Yes	*21*	*91,3*
No	*2*	*8,7*
Adjuvant chemotheraphy		
Yes	*5*	*21,7*
No	*18*	*78,2*

Abbreviations: No, number; cm, centrimeter.

3.3. Overall survival (OS)

The overall survival rate was found to be 90.9% at 3 years and 55.3% at 5 years, with 3 deaths occurred during the follow-up period of 35.5 months (range, 9–100.6) (Fig. 4).

Log-rank tests showed that $SUV_{ratio[med]} > 4.14$, $SUV_{ratio[liver]} > 2.69$, MTV > 5.3 mL, and TLG > 27.7 g were significantly associated with decreased OS (all $p < 0.05$).

The cox regression analysis revealed that $SUV_{ratio[med]} > 4.14$ (HR = 2.78, 95% CI = 0.91–8.50; $p = 0.018$), $SUV_{ratio[liver]} > 2.69$ (HR = 1.83, 95% CI = 0.73–4.57; $p = 0.041$), MTV > 5.3 mL

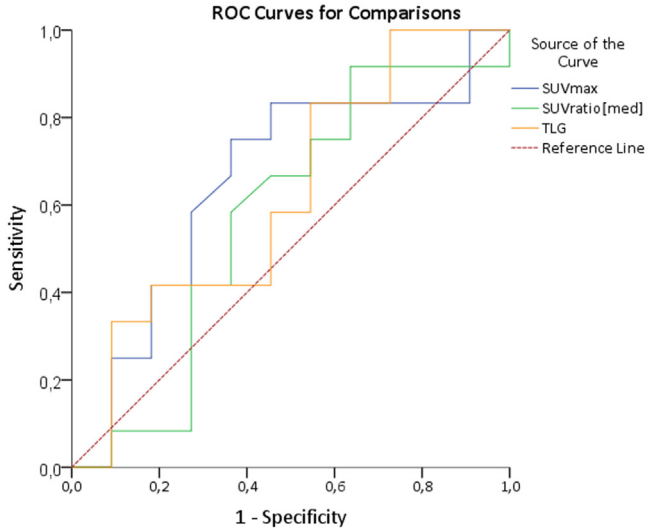

Fig. 2. Receiver operating characteristic (ROC) curves of progression free survival (PFS) according to best performing quantitative ^{18}F-FDG PET/CT variables grouped as SUV parameters (SUV_{max}, SUV_{mean}, SUV_{peak}), standardized SUV parameters ($SUV_{ratio[med]}$, $SUV_{ratio[liver]}$) and volumetric ^{18}F-FDG PET/CT parameters (MTV, TLG).

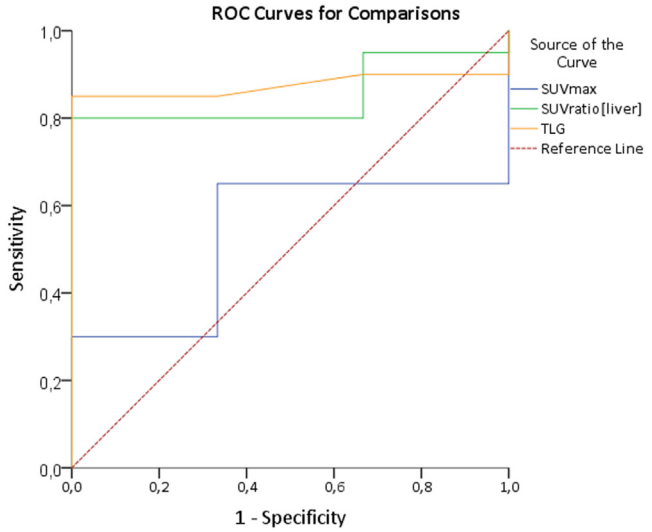

Fig. 3. Receiver operating characteristic (ROC) curves of overall survival (OS) according to best performing quantitative ^{18}F-FDG PET/CT variables grouped as SUV parameters (SUV_{max}, SUV_{mean}, SUV_{peak}), standardized SUV parameters ($SUV_{ratio[med]}$, $SUV_{ratio[liver]}$) and volumetric ^{18}F-FDG PET/CT parameters (MTV, TLG).

(HR = 30.3, 95% CI = 2.82–100.7; $p = 0.035$) and TLG > 27.7 g (HR = 30.3, 95% CI = 2.82–100.7; $p = 0.035$) remained independent variables predictive of OS (Fig. 6).

3.4. Distant metastasis-free survival (DMFS)

The distant metastases were identified in 10 (43.4%) patients during post-treatment follow-up. The 3-year and 5-year distant metastasis-free survival for all the patients were 59.8%, and 19.9%, respectively. Time to developing distant metastasis was negatively influenced by overall advanced stage and M1 stage at initial diagnosis, $SUV_{ratio[med]} > 4.14$, $SUV_{ratio[liver]} > 2.78$, MTV > 8.3 mL, and TLG > 31.6 g on univariate analyses (Supplementary Fig. 5S) (all $p < 0.05$).

However, in the multivariate analysis, M1 stage (HR = 4.98, 95% CI = 1.29–19.22; $p = 0.019$), $SUV_{ratio[med]} > 4.14$ (HR = 7.63, 95%

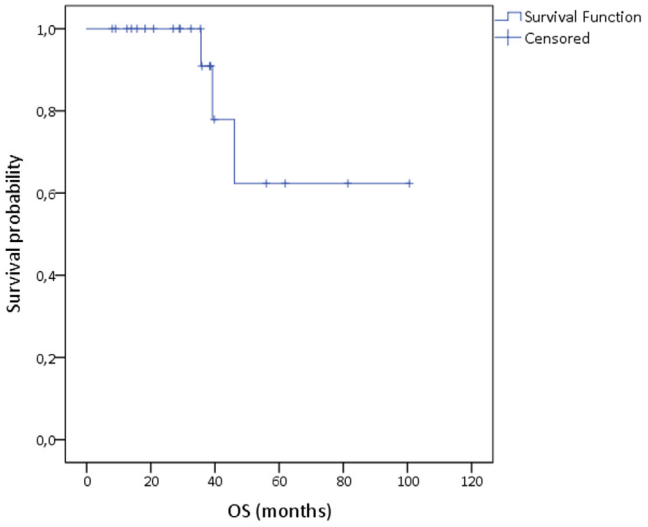

Fig. 4. Kaplan-Meier curve demonstrates the overall survival (OS). Vertical ticks are censored observations.

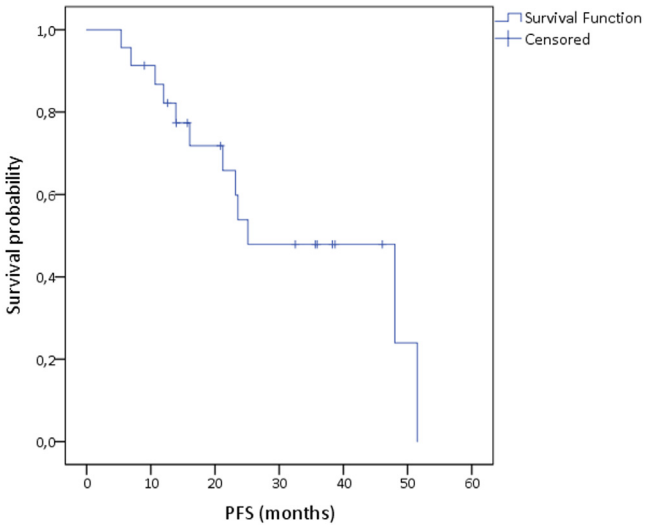

Fig. 5. Kaplan-Meier curve demonstrates the progression free-survival (PFS). Vertical ticks are censored observations.

Table 2
The Area under curves (AUCs) of quantitative ^{18}F-FDG PET/CT parameters obtained from ROC curve analysis for OS,PFS and DMFS were demonstrated.

	AUC (95% Cl)		
Variable	Metastasis	Progression	Death
SUV_{max}	0.5885 (0.3369, 0.8401)	0.6553 (0.4121, 0.8985)	0.5333 (0.2386, 0.8281)
SUV_{mean}	0.5308 (0.2672, 0.7944)	0.5758 (0.3215, 0.8300)	0.4500 (0.1385, 0.7615)
SUV_{peak}	0.5769 (0.3309, 0.8229)	0.4924 (0.2360, 0.7488)	0.5000 (0.1583, 0.8417)
$SUV_{ratio[med]}$	0.6231 (0.3739, 0.8722)	0.5720 (0.3153, 0.8286)	0.7917 (0.5396, 1.0000)
$SUV_{ratio[liver]}$	0.6769 (0.4432, 0.9106)	0.5530 (0.2988, 0.8073)	0.8500 (0.6808, 1.0000)
MTV	0.7154 (0.4979, 0.9329)	0.6136 (0.3658, 0.8614)	0.8833 (0.7431, 1.0000)
TLG	0.7385 (0.5263, 0.9506)	0.6212 (0.3771, 0.8653)	0.8750 (0.7322, 1.0000)

Abbreviations: CI, confidence interval; MTV, metabolic tumor volume; SUV, standardized uptake value; TLG, total lesion glycolysis.

Table 3
Cox proportional regression analysis is used. Clinicopathological and ^{18}F-FDG PET/CT parameters associated with tumor progression and survival are examined individually. A p-value < 0.05 is highlighted in yellow.

	Overall survival		Progression-free survival	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex: male vs. female	*1.077 (0.096, 12.01)*	*0.9521*	*0.533 (0.161, 1.769)*	*0.3039*
Age: one unit increase	*1.668 (0.141, 19.80)*	*0.6850*	*0.521 (0.138, 1.972)*	*0.3369*
Location: minor vs. major	*0.988 (0.085, 11.48)*	*0.9922*	*0.261 (0.066, 1.032)*	*0.0554*
Longest diameter: > 3 vs. < 3 cm	*NA*[*]	*0.9982*	*1.093 (0.306, 3.902)*	*0.8909*
T stage: T3–4 vs. T1–2	*NA*[*]	*0.9973*	*0.921 (0.257, 3.302)*	*0.8994*
N stage: N1–3 vs. N0	*1.760 (0.157, 19.77)*	*0.6467*	*3.119 (0.654, 14.87)*	*0.1535*
M stage: M1 vs. M0	*NA*[*]	*0.9976*	*3.496 (0.967, 12.64)*	*0.0563*
Overall type: Stage 3–4 vs. 1–2	*0.331 (0.028, 3.841)*	*0.3764*	*3.581 (0.751, 17.06)*	*0.1093*
Pathology grade: high vs. low	*2.568 (0.225, 29.27)*	*0.4475*	*1.806 (0.548, 5.950)*	*0.3312*
Lymphovascular invasion: yes vs. no	*NA*[*]	*0.9976*	*1.034 (0.301, 3.554)*	*0.9582*
Perineural invasion: yes vs. no	*1.986 (0.175, 22.48)*	*0.5795*	*1.006 (0.258, 3.923)*	*0.9937*
Surgical margin: yes vs. no	*1.414 (0.122, 16.45)*	*0.7820*	*0.748 (0.216, 2.598)*	*0.6479*
Radiotherapy: yes vs. no	*NA*[*]	*0.9980*	*0.953 (0.120, 7.538)*	*0.9636*
Chemotherapy: yes vs. no	*0.545 (0.048, 6.153)*	*0.6238*	*1.438 (0.410, 5.045)*	*0.5704*
SUVmax > 8.49[a]/8.84[b]	*1.704 (0.152, 19.13)*	*0.666*	*3.323 (0.855, 12.91)*	*0.023*
SUVmean > 4.74[a]/4.55[b]	*0.192 (0.012, 3.099)*	*0.245*	*1.293 (0.363, 4.603)*	*0.692*
SUVpeak > 5.99[a]/5.67[b]	*0.587 (0.052, 6.589)*	*0.666*	*0.464 (0.133, 1.617)*	*0.228*
SUVratio[med] > 4.14[a]/3.53[b]	*2.781 (0.910, 8.500)*	*0.018*	*2.45 (0.723, 8.331)*	*0.045*
SUVratio[liver] > 2.69[a]/2.41[b]	*1.838 (0.739, 4.573)*	*0.041*	*3.62 (0.987, 13.33)*	*0.032*
MTV > 5.3[a]/4.35[b]	*30.3 (2.82, 100.7)*	*0.035*	*11.2 (0.57, 67.15)*	*0.028*
TLG > 27.7[a]/19.5[b]	*30.3 (2.82, 100.7)*	*0.035*	*9.6 (1.781, 40.85)*	*0.021*

Abbreviations: CI, confidence interval; HR, hazard ratio; MTV, metabolic tumor volume; SUV, standardized uptake value; TLG, total lesion glycolysis.

[*] *Due to small sample size.*

[a] *Cut-off value for overall survival.*

[b] *Cut-off value for progression free survival.*

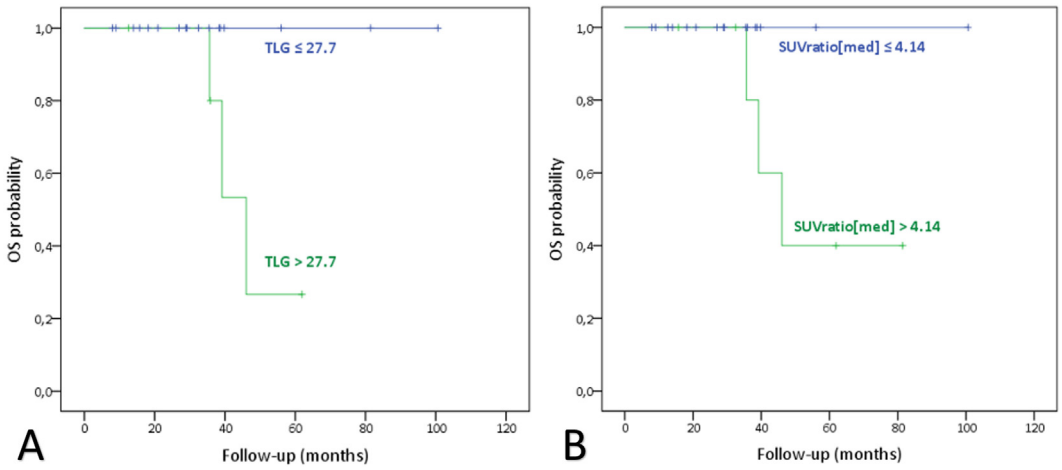

Fig. 6. Kaplan-Meier curves reveal the comparisons of overall survival (OS) based on the cutoff value of TLG (A) and $SUV_{ratio[med]}$ (B) measured on pretreatment ^{18}F-FDG PET/CT scans. Cox regression analysis, $p = 0.035$ (A) and $p = 0.018$ (B). Vertical ticks are censored observations.

CI = 1.94–22.51; $p = 0.031$), $SUV_{ratio[liver]} > 2.78$ (HR = 2.66, 95% CI = 0.67–10.41; $p = 0.026$), MTV > 8.3 mL (HR = 5.58, 95% CI = 0.70–44.34; $p = 0.040$) and TLG > 31.6 g (HR = 14.09, 95% CI = 1.92–96.86; $p = 0.017$) were independent variables predictive of DMFS but overall advanced stage at initial diagnosis was of no significant influence on distant metastasis-free survival outcomes (Supplementary Fig. 6S).

3.5. Progression-free survival (PFS)

Locoregional and distant recurrences were found in 2 (8.7%) and 10 (43.4%) patients, respectively, during post-treatment follow-up. The 3-year progression-free survival for all the patients was 47.9% (Fig. 5). Log-rank tests showed that minor salivary gland tumors, M1 stage at initial diagnosis, $SUV_{max} > 8.84$, $SUV_{ratio[med]} > 3.53$, $SUV_{ratio[liver]} > 2.41$, MTV > 4.35 mL, and TLG > 19.5 g were significantly associated with PFS in the univariate analysis (all $p < 0.05$).

For tumor progression, the multivariate cox regression analysis revealed that patients with a $SUV_{max} > 8.84$ (HR = 3.32, 95% CI = 0.85–12.91; $p = 0.023$), $SUV_{ratio[med]} > 3.53$ (HR = 2.45, 95% CI = 0.72–8.33; $p = 0.045$), $SUV_{ratio[liver]} > 2.41$ (HR = 3.62, 95% CI = 0.98–13.33; $p = 0.032$), MTV > 4.35 mL (HR = 11.2, 95% CI = 0.57–67.15; $p = 0.028$) and TLG > 19.5 g (HR = 9.6, 95% CI = 1.78–40.85; $p = 0.021$) were significantly correlated with PFS (Figs. 7 and 8).

4. Discussion

The current study analyzed the prognostic values of SUV_{max}, SUV_{mean}, SUV_{peak}, $SUV_{ratio[med]}$, $SUV_{ratio[liver]}$ and volumetric measurements of MTV and TLG from pretreatment ^{18}F-FDG PET/CT images

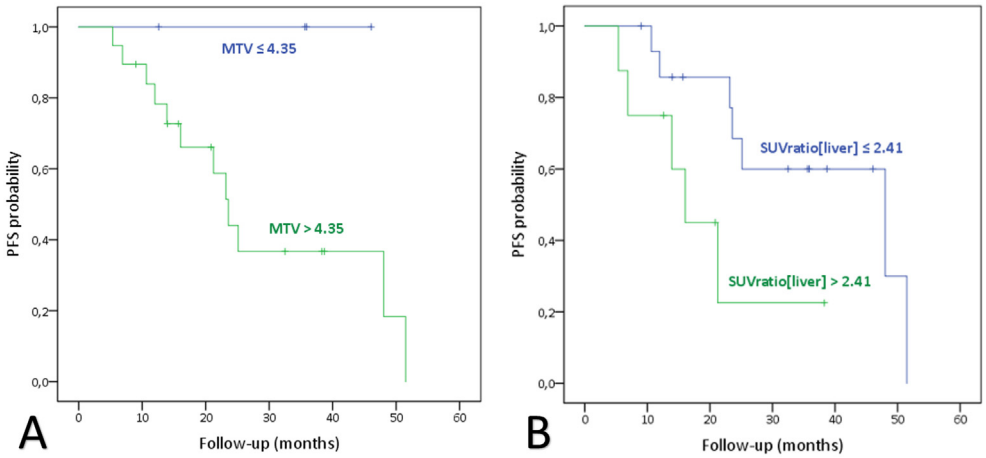

Fig. 7. Kaplan-Meier curves reveal the comparisons of progression free survival (PFS) based on the cutoff value of MTV (A) and $SUV_{ratio[liver]}$ (B) measured on pretreatment ^{18}F-FDG PET/CT scans. Cox regression analysis, $p = 0.028$ (A) and $p = 0.032$ (B). Vertical ticks are censored observations.

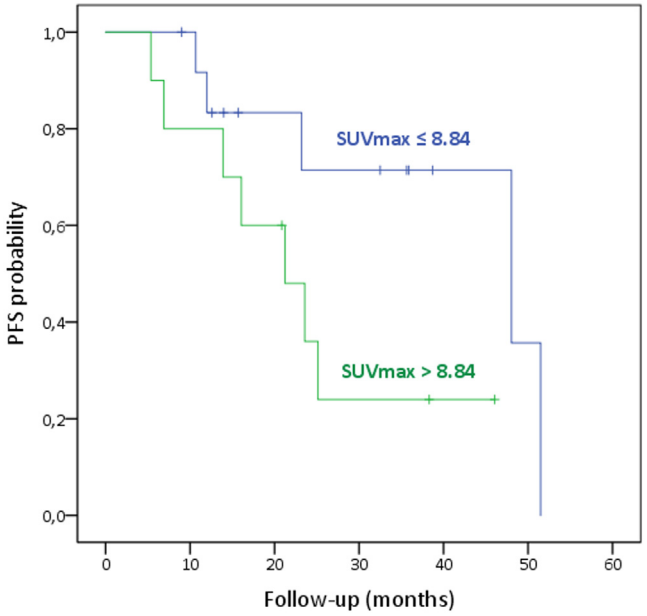

Fig. 8. Kaplan-Meier curves reveal the comparisons of progression free survival (PFS) based on the cutoff value of SUV_{max} measured on pretreatment ^{18}F-FDG PET/CT scans. Cox regression analysis, $p = 0.023$. Vertical ticks are censored observations.

of 23 ACC patients. The $SUV_{ratio[med]}$, $SUV_{ratio[liver]}$, MTV and TLG were predictive factors of DMFS, PFS, and OS. Additionally, SUV_{max}, minor salivary gland location and distant metastasis at initial diagnosis were predictors of PFS; M1 stage and overall stage 3–4 predicted DMFS. Cox regression analysis confirmed that the higher $SUV_{ratio(med)}$, $SUV_{ratio(liver)}$, MTV, and TLG values predicted DMFS, PFS, and OS independently, while SUV_{max} was an independent predictor of only PFS. The SUV_{max} value was not predictive of OS and DMFS. An MTV > 4.3 mL or TLG > 27.7 g was correlated with a > 30-fold higher risk of overall mortality. Furthermore, a $SUV_{ratio[med]}$ of 4.14 or higher was significantly associated with a decreased DMFS (HR = 7.63) in our Cox regression analysis. The quantitative values of ^{18}F-FDG PET/CT, especially the volumetric and standardized parameters, improved the capability to predict the PFS, DMFS, and OS in patients with salivary gland ACC. These results support the hypothesis that low ^{18}F-FDG uptake in tumor tissue may indicate more indolent tumor behavior, whereas the high ^{18}F-FDG uptake may represent more aggressive tumor behavior [17].

Regardless of the predictive value of SUV_{max} for PFS, the current study was unable to determine any significant association between SUV_{max} and DMFS or OS in the Cox regression analysis. Additional volumetric and standardized measurements of ^{18}F-FDG PET/CT, such as MTV, TLG, and SUV_{ratio}, are required because increasing ^{18}F-FDG uptake in the tumor tissue may not be necessarily related to tumor aggressiveness. Volume-based parameters of MTV and TLG, may reflect the metabolic burden of the tumor tissue more precisely and offer a potentially more accurate method compared to the single-pixel-based SUV parameters. Furthermore, SUV is intrinsically variable and may fluctuate among individual PET scanners and between centers unless these are cross-calibrated [18]. In order to minimize this variability, we applied a standardized ratio of ^{18}F-FDG uptake (tumor SUV/mediastinal blood pool or liver parenchyma SUV), named as tumor-to-background SUV ratio.

Recently, SUV_{max} of ^{18}F-FDG PET/CT was found to be an independent predictor of DMFS in 34 patients with head and neck ACC following definitive treatment [8]. The SUV_{max} > 4.15 and high-grade histology were predictor variables of DMFS and disease specific-free survival. Nevertheless, volumetric or standardized parameters of ^{18}F-FDG PET/CT were not evaluated in this study. In a study by Jung et al. [19], forty patients with head and neck ACCs were examined. Lower PFS rates were found to be correlated with advanced T stage, advanced overall stage, SUV_{max} > 5.1, and TLG > 40.1 g of the primary tumor. In the study of Lim et al. [20], SUV_{max} was a predictive factor of PFS, while volumetric ^{18}F-FDG PET/CT parameters were independent predictor variables of DMFS and disease specific-free survival once controlling the clinicopathological variables. Patients with MTV > 14.8 mL or TLG > 45.5 g revealed a 5.9-fold increased risk of distant metastasis and a 4.2-fold increased risk of disease specific mortality. Ryu et al. [21] demonstrated that the volumetric ^{18}F-FDG PET/CT parameters were independent predictors of PFS in patients with salivary gland ACC. In consequence of these studies, it is proposed that metabolic ^{18}F-FDG PET parameters could assist as predictor variables of survival in salivary gland ACC.

Several studies have pointed out an unfavorable impact of PNI on local control and survival for salivary gland ACC [4,22]. However, in our study, PNI did not have any considerable impact on survival and the occurrence of distant metastases. We suppose that the proximity of minor salivary glands to the vital anatomical structures may limit the prognostic impact of PNI on survival. The TNM stage is a well-known prognostic factor for clinical outcome [23–25]. Nevertheless, the overall stage was not a significant prognostic factor for disease progression in this study, which indicates that besides the morphology of the tumor, the metabolic parameters should be considered for

prognostic analysis. Adjuvant radiotheraphy and chemotheraphy at the primary tumor site have been reported as a prognostic factor [26–28]. In the current study, we could not recognize any correlation between these factors and survival outcomes. The presence of a positive surgical margin appears to be a substantial prognostic factor as well, while some studies have been unable to determine this observation [29–31]. Furthermore, we were unable to identify any significant correlation between a positive surgical margin and survival. This could be resulting from the effect of adjuvant radiotherapy for local tumor control [32]. The lack of prognostic power for these factors in the current study highlights the value of pretreatment standardized and volumetric ^{18}F-FDG PET/CT parameters.

DMFS which is not typically accepted by the Food and Drug Administration (FDA) as a valid proxy in drug development trials is nevertheless medically meaningful in this context. We believe that prediction of DMFS is substantial because currently many new drugs for salivary gland ACCs have been tested in the setting of metastatic diseases as a whole, and usually survival gain is the main end point. Our results may help refine clinical trials by identifying the factors associated with distant metastasis and the possible confounders of survival.

This study has some drawbacks, such as the small patient number, heterogeneous treatments, and the inherent selection bias due to retrospective design. The small patient number along with the infrequent occurrence of the ACCs could lead to decreased statistical power to examine any relation between ^{18}F-FDG PET/CT parameters and the prediction of prognosis. Since late recurrence is a typical feature of ACC, the follow-up period was relatively short to evaluate long-term prognosis. Moreover, the measurement of SUV parameters is affected by numerous technical factors, such as a region of interest definition, image resolution, the time between tracer injection and imaging, plasma glucose level, and attenuation correction. The SUV parameter cutoffs may vary among patient populations as per ^{18}F-FDG PET/CT scanners and imaging acquisition techniques. In the present study, all patients were scanned utilizing the identical ^{18}F-FDG PET/CT scanner based on a standard protocol to sustain reproducibility.

Our study proposes that volumetric and standardized parameters on pretreatment ^{18}F-FDG PET/CT may be beneficial to predict DMFS, PFS, and OS in salivary gland ACC patients. The enhanced prediction of prognosis may improve proper post-treatment surveillance planning in patients with high $SUV_{ratio[med]}$, $SUV_{ratio[liver]}$, MTV and TLG. Largescale prospective studies are required to confirm our results as well as the prognostic significance of quantitatively measured volumetric and standardized ^{18}F-FDG PET/CT parameters in this setting.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical standards

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 2013 revised Helsinki declaration or comparable ethical standards.

Informed consent was not required.

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