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Value of a ^{18}F-FDG PET/CT Semi-quantitative Parameter (SUV_{max}) in Predicting the Survival of Patients with Esophageal Cancer Subtypes

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Abstract

Background: Flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan is employed for initial staging and restaging of esophageal cancer patients.
Objectives: The present study aimed to assess the value of a semi-quantitative parameter of ^{18}F-FDG PET/CT scan, that is, maximum standardized uptake value (SUV_{max}), to determine its correlation with patient survival in two subtypes of esophageal cancer, including squamous cell carcinoma (SCC) and adenocarcinoma.
Patients and Methods: This cross-sectional study was performed on patients with esophageal SCC and adenocarcinoma, undergoing ^{18}F-FDG PET/CT scan for initial staging before any treatment. The ^{18}F-FDG PET/CT semi-quantitative parameter (SUV_{max}) was determined by reviewing the PET/CT images. The patients were reevaluated using ^{18}F-FDG PET/CT scan for restaging within 12 - 24 months.
Results: No significant difference was observed in the SUV_{max} values of the primary tumor, metastatic lymph nodes, or distant metastasis between the adenocarcinoma and SCC groups, regardless of response to treatment. Similarly, no significant association was found between the short-term survival of patients with adenocarcinoma and the SUV_{max} values of the primary tumor, metastatic lymph nodes, or distant metastasis. Based on the survival curve, one- and two-year survival rates were estimated at 75% and 63.9% in patients with SCC and at 80% and 60% in patients with adenocarcinoma, respectively. In the SCC group, a significantly higher SUV_{max} was detected in deceased patients with distant metastatic lesions compared to cancer survivors. According to the area under the ROC curve, the SUV_{max} of metastatic lesions showed high potential for predicting the mortality of SCC patients.
Conclusion: The assessment of SUV_{max} in distant metastatic lesions by ^{18}F-FDG-PET/CT may help predict the survival of patients with esophageal SCC. However, ^{18}F-FDG-PET/CT findings were not associated with the survival of esophageal adenocarcinoma; therefore, further evaluations on a larger sample size and a longer follow-up are required.

Keywords: Esophageal Cancer, FDG PET/CT Scan, Survival

1. Background

Esophageal cancer subtypes, including squamous cell carcinoma (SCC) and adenocarcinoma, have dominant characteristics, such as lymphatic spread due to the absence of a serosa layer in the esophagus and risk of systemic metastasis. It is generally essential to determine both local and distant metastatic spread of esophageal cancer for precise treatment planning (1). Metabolic imaging using flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) scan has received special attention in detecting the local spread of disease and its distant metastasis for initial staging and treatment planning. This technique has been particularly effective in detecting distant metastatic lesions (2, 3) and also in the assessment of response to neoadjuvant therapies, which is fundamental to treatment for many esophageal cancer patients (4, 5). However, modalities, such as computed tomography (CT) scan and endoscopic ultrasound (EUS), are mainly employed for the diagnosis of locally advanced tumors and commonly fail to detect distant metastatic lesions (6).

The predictive potential of ^{18}F-FDG PET/CT scan for the survival of esophageal cancer patients remains unknown following routine treatments (7). To date, ^{18}F-FDG PET/CT scan has been recommended for the initial staging of esophageal cancer patients. It has been demonstrated that

^{18}F-FDG PET/CT findings might be correlated with the tumor grade and aggressiveness (8). According to our literature review, only few studies have evaluated the association of ^{18}F-FDG PET/CT semi-quantitative parameters with local and distant extension of esophageal cancer and patient survival (9, 10).

2. Objectives

This study aimed to evaluate a semi-quantitative parameter of ^{18}F-FDG PET/CT, that is, maximum standardized uptake value (SUV_{max}), in patients with SCC and adenocarcinoma subtypes and to investigate its ability to differentiate between these two categories. Moreover, this study aimed to evaluate the potential of ^{18}F-FDG PET/CT scan in the assessment of tumor characteristics, such as local and distant metastatic extensions, and to determine the association of tumor SUV_{max} with patient survival.

3. Patients and Methods

This cross-sectional study was performed on newly diagnosed patients with one of the major subtypes of esophageal carcinoma, that is, SCC or adenocarcinoma, who were referred for initial staging during 2013 - 2019. To the best of our knowledge, there was no confounding risk factor (unrelated to underlying esophageal cancer) in this study affecting the number of patients with either SCC or adenocarcinoma. The patients' background information, including the demographic data, medical and pharmacological records, clinical symptoms, final diagnostic pathology findings, and follow-up records were collected by reviewing their medical records.

The ^{18}F-FDG-PET/CT images were analyzed on an Advantage Workstation version 4.5 (ADW 4.5), and all images of the patient were reviewed for primary tumor (T), metastatic regional lymph nodes (N), and distant metastatic lesions (M). The semi-quantitative parameter, SUV_{max}, was calculated automatically for each primary tumor, regional lymph node, and distant metastatic lesion for each patient in a designated region of interest (ROI) for each lesion. The images were reviewed by two readers simultaneously. One experienced nuclear medicine physician and one experienced radiologist with specific PET training reviewed all the images, and the final decision was made based on their consensus. Information regarding the treatment protocol (i.e., surgery, chemotherapy, and radiotherapy) was also extracted by reviewing the patients' medical records.

The patients were followed-up for 12-24 months after the initial treatment and were reevaluated for restaging with ^{18}F-FDG PET/CT scan. Response to treatment (complete or partial) was defined as a complete or partial reduction of the size or metabolic activity of all TNM staging components on follow-up imaging. Non-response to treatment (stable or progressive disease) was defined as a stable disease or an increase in the size or metabolic activity of one of the TNM components on follow-up imaging. Any new lesion or any increase in the size or metabolic activity of any TNM components represented a progressive disease.

For statistical analysis, data are presented as mean ± standard deviation (SD) for quantitative variables and summarized by frequency (percentage) for categorical variables. Continuous variables were compared using *t*-test or Mann-Whitney U test if the data did not have a normal distribution or if the assumption of equal variance was violated across the study groups. The categorical variables were also compared using chi-square test. P-values $\leq$ 0.05 were considered statistically significant. For statistical analysis, SPSS version 23.0 for Windows (IBM SPSS Statistics for Windows, released in 2015, IBM Corp., Armonk, NY, USA) was used.

4. Results

A total of 36 patients with esophageal SCC and 15 patients with esophageal adenocarcinoma were included in this study. Comparison of the two groups regarding the baseline characteristics (i.e., mean age and sex) indicated no significant difference between these groups (Table 1). Regarding the tumor location, SCC was more commonly located in the mid portion of the esophagus, while adenocarcinoma was located prominently in the distal part. Based on the ^{18}F-FDG-PET/CT findings (Table 1), no significant difference was observed between the SCC and adenocarcinoma subtypes in terms of the mean primary tumor SUV_{max} (12.97 ± 7.74 vs. 10.41 ± 5.48, P = 0.283), lymph node involvement (50.0% vs. 46.7%, P = 0.122), and presence of distant metastasis (25.0% vs. 40.0%, P = 0.325).

With respect to treatment outcomes, 69.4% of patients with SCC and 53.3% of patients with adenocarcinoma were responsive to neoadjuvant chemoradiotherapy. Surgery was subsequently required for 27.8% of SCC patients and 26.7% of adenocarcinoma patients. Death was reported in 36.1% of SCC patients and 40.0% of adenocarcinoma patients, with no significant difference between the groups (P = 0.103). Overall, one- and two-year survival rates were 75.0% and 63.9% in the SCC group and 80.0% and 60.0% in the adenocarcinoma group, indicating no significant inter-group difference (Table 1).

According to Table 2, comparison of responder and non-responder subgroups showed no significant difference in the mean SUV_{max} values of the primary tumor,

Table 1. The Baseline Information of Patients with Squamous Cell Carcinoma (SCC) or Adenocarcinoma [a, b]

Variables	SCC group	Adenocarcinoma group	P-value
Demographic information			
Male	21 (58.3)	8 (53.3)	0.743
Female	15 (41.7)	7 (46.7)	0.436
Mean age (y)	64.53 ± 12.47	60.67 ± 13.16	0.326
Tumor location			0.014
Distal	18 (50.0)	14 (93.3)	
Mid-portion	15 (41.7)	0 (0.0)	
Proximal	2 (5.6)	0 (0.0)	
Diffuse	1 (2.8)	1 (6.7)	
PET/CT findings			
Mean SUV_{max} of the primary tumor	12.97 ± 7.74	10.41 ± 5.48	0.283
Mean SUV_{max} of metastatic lymph nodes	5.58 ± 3.51	8.47 ± 5.34	0.130
Mean SUV_{max} of distant metastatic lesions	5.65 ± 3.16	5.00 ± 4.82	0.789
Lymph node involvement present	18 (50.0)	7 (46.7)	0.122
Distant metastasis present	9 (25.0)	6 (40.0)	0.325
Treatment outcome			
Responder to treatment	25 (67.5)	8 (53.3)	0.273
Non-responder to treatment	12 (32.5)	7(46.7)	0.079
Surgery required following neoadjuvant therapy	10 (27.8)	4 (26.7)	0.935
Death during follow-up	13 (36.1)	6 (40.0)	0.794
Mean interval between diagnosis and death (months)	9.85 ± 7.19	17.00 ± 10.75	0.124
One-year survival	75.0%	80.0%	0.562
Two-year survival	63.9%	60.0%	0.437

Abbreviations: SCC, squamous cell carcinoma; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value.
[a] Values are expressed as mean ± SD or No. (%).
[b] There is no statistically significant finding.

lymph nodes, or distant metastasis between these subgroups of SCC and adenocarcinoma groups.

As demonstrated in Table 3, the SUV_{max} of distant metastasis was significantly higher in deceased patients compared to survivors, with no significant difference in the SUV_{max} of primary tumor or lymph nodes in the SCC group (Table 3). In patients with adenocarcinoma, the SUV_{max} values of the primary tumor, lymph nodes, and distant metastasis were not significantly different between the deceased and surviving patients and were not predictive of patient survival.

Figures 1 and 2 demonstrate the Kaplan-Meier curves for the two-year survival of patients with esophageal SCC and adenocarcinoma, respectively. Also, Figures 3 and 4 demonstrate patients with esophageal SCC and adenocarcinoma, respectively.

5. Discussion

The role of ^{18}F-FDG PET/CT scan in the initial staging of esophageal carcinoma has been extensively studied (11). Although according to the National Comprehensive Cancer Network (NCCN) guidelines (12), there is not enough evidence to justify the routine application of this imaging modality for the initial staging of all esophageal carcinoma patients, it has been recommended by several associations, including the American Association for Thoracic Surgery (AATS) (13). The AATS emphasized the importance of ^{18}F-FDG PET/CT scan in detecting distant metastatic sites, which is essential in treatment planning. Besides, few other studies have evaluated the prognostic value of ^{18}F-FDG PET/CT scan in esophageal cancer patients and reported contradictory results (14).

The present study evaluated the potential of ^{18}F-FDG PET/CT scan in predicting response to treatment and prog-

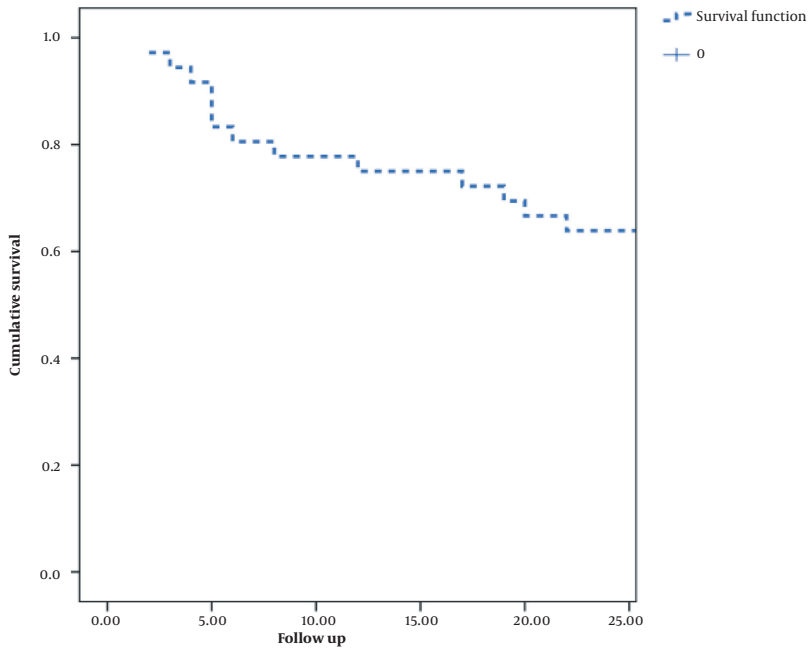

Figure 1. The Kaplan-Meier curve for the two-year survival of patients with esophageal squamous cell carcinoma (SCC).

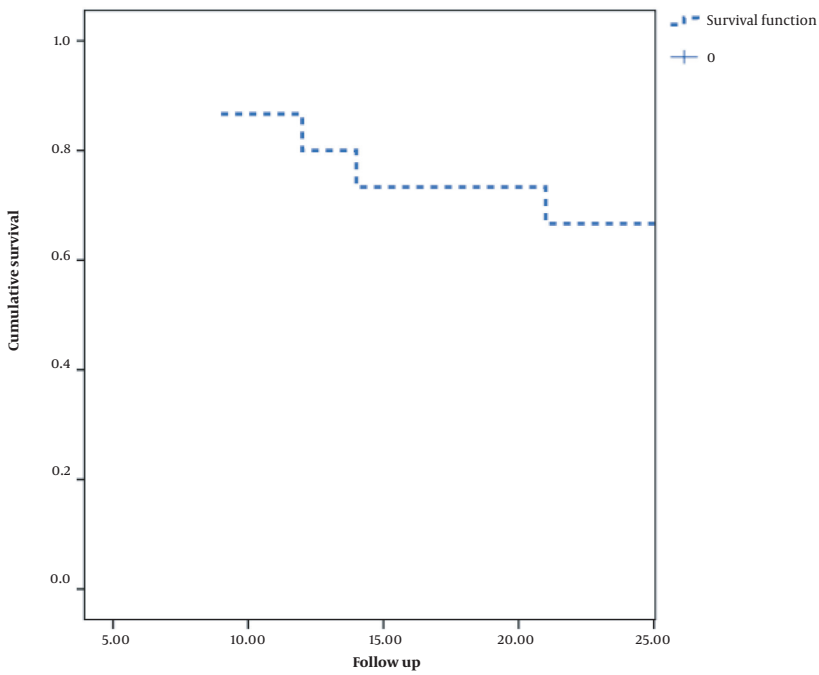

Figure 2. The Kaplan-Meier curve for the two-year survival of patients with esophageal adenocarcinoma

Table 2. Association of ^{18}F-FDG PET/CT Findings with Response to Chemotherapy [a]

Variables	Response (+)	Response (-)	P-value
SCC type			
Mean SUV_{max} of primary tumor	12.78 ± 7.93	13.34 ± 7.73	0.852
Mean SUV_{max} of metastatic lymph nodes	4.49 ± 2.10	7.14 ± 4.62	0.129
Mean SUV_{max} of distant metastasis	3.46 ± 2.82	7.30 ± 2.51	0.127
Adenocarcinoma type			
Mean SUV_{max} of primary tumor	10.06 ± 6.32	10.82 ± 4.88	0.816
Mean SUV_{max} of metastatic lymph nodes	10.66 ± 8.10	6.82 ± 2.22	0.395
Mean SUV_{max} of distant metastasis	2.70 ± 1.22	5.76 ± 5.60	0.683

Abbreviations: SCC, squamous cell carcinoma; SUV, standardized uptake value; 18F-FDG PET/CT, Flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography.
[a] There is no statistically significant finding.

Table 3. Association of PET/CT Findings with Death

Index	Death (+)	Death (-)	P-value
SCC type			
Mean SUV_{max} of primary tumor	12.39 ± 6.52	13.37 ± 8.63	0.731
Mean SUV_{max} metastatic lymph node	6.38 ± 4.59	4.86 ± 2.21	0.390
Mean SUV_{max} of distant metastasis	7.18 ± 2.18	1.85 ± 0.49	0.023 [a]
Adenocarcinoma type			
Mean SUV_{max} of primary tumor	10.81 ± 4.88	10.06 ± 6.32	0.816
Mean SUV_{max} of metastatic lymph nodes	6.82 ± 2.22	10.66 ± 8.09	0.395
Mean SUV_{max} of distant metastasis	5.76 ± 5.60	2.70 ± 1.68	0.683

Abbreviations: SCC, squamous cell carcinoma; SUV, standardized uptake value; PET/CT, positron emission tomography/computed tomography.
[a] Statistically significant finding.

nosis of patients with esophageal SCC and adenocarcinoma. One significant finding of this study was that measurement of SUV_{max} in distant metastatic lesions was significantly associated with mortality in the SCC group, whereas no such association was observed in patients with adenocarcinoma. Nevertheless, the results of previous studies regarding the prognosis of patients with esophageal cancer based on ^{18}F-FDG PET/CT findings are contradictory.

In a study by Mantziari et al. on patients with SCC, high values of SUV_{max} had a significant relationship with higher tumor stages and could predict tumor recurrence and long-term survival (15). In another study by Kim et al., the SUV_{max} of primary esophageal tumor lesion could predict distant metastasis with 67% sensitivity, 83% specificity, and 76% diagnostic accuracy (16). In a study by Bosch et al. on patients with esophageal adenocarcinoma, the tumor SUV_{max} predicted local tumor progression with 40% sensitivity and 73% specificity (17), which contradicted the findings of the current study. However, in a study by Fatima et al., similar to the present research, there was no significant difference in the SUV_{max} values of the primary tumor and metastatic regional lymph nodes between the SCC and adenocarcinoma groups (18).

Additionally, in a study by Lindner et al., the value of SUV_{max} was significantly related to tumor stage and tumor size. If patients had SUV_{max} values < 6 at the primary tumor site, surgery resulted in a higher long-term survival compared to cases with SUV_{max} values > 6; nevertheless, no such relationship was detected in response to neoadjuvant therapy (19). In another study by Wang et al. to determine the stage of esophageal tumor, the diagnostic accuracy of ^{18}F-FDG PET/CT scan was 85.7%. There was also a significant difference in the value of SUV_{max} between the T2 and T3 groups (20). Overall, ^{18}F-FDG PET/CT scan showed high potential in predicting the outcomes and short-term survival

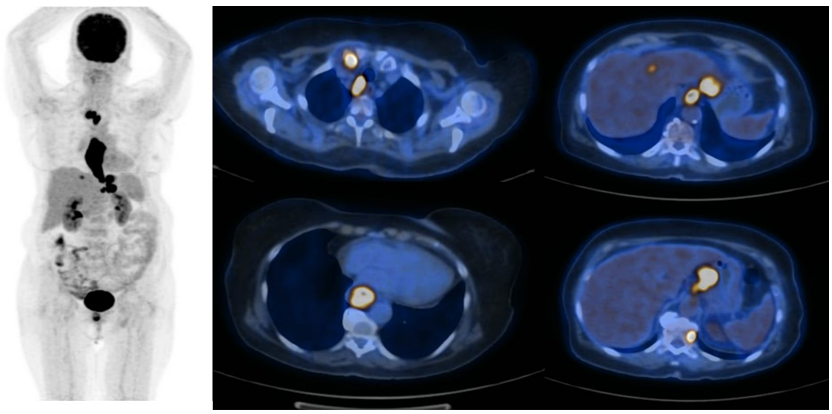

Figure 3. The maximum intensity projection (MIP) and axial PET/CT images of a patient with esophageal squamous cell carcinoma (SCC). There is a primary esophageal elongated tumor, regional mediastinal hypermetabolic lymph nodes, and distant hypermetabolic metastases of the liver and bone.

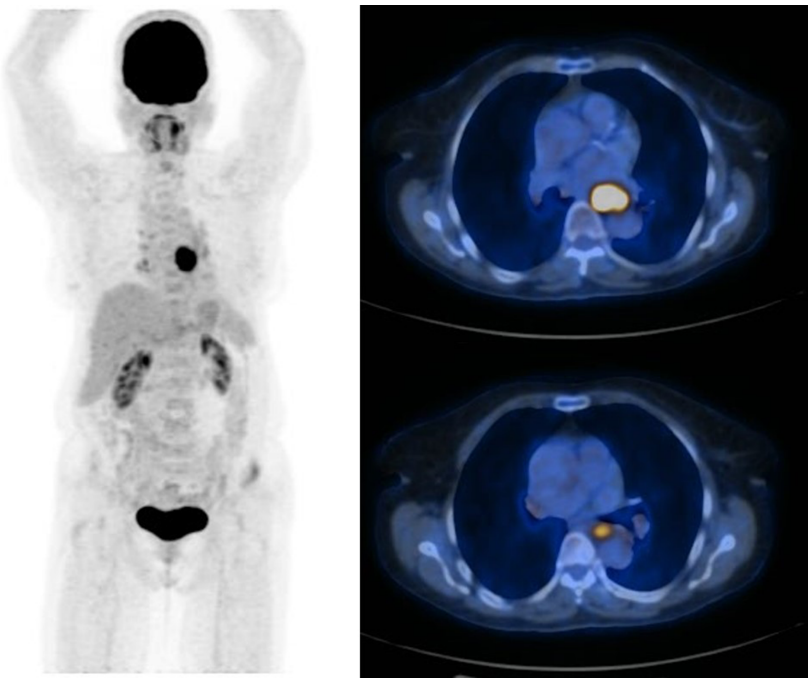

Figure 4. The maximum intensity projection (MIP) and axial PET/CT images of a patient with esophageal adenocarcinoma. There is a focal mid-esophageal primary tumor and no definite evidence of hypermetabolic distant metastasis. Mildly hypermetabolic lymph nodes were reactive in the final pathology report.

of patients with esophageal SCC compared to esophageal adenocarcinoma.

It should be noted that the results of the present study might be potentially affected by the small sample size; therefore, further studies with a larger sample size and a longer follow-up are recommended.

In conclusion, the SUV_{max} value according to ^{18}F-FDG PET/CT scan for distant metastatic lesions could predict the short-term survival of patients with SCC. However, in patients with esophageal adenocarcinoma, the value of SUV_{max} on ^{18}F-FDG PET/CT scan was not predictive of patient survival.

Footnotes

Authors' Contribution: Study concept and supervision, Dr. Abtin Doroudinia; Data collection and writing the manuscript, Hemmat Ebrat; Editing of the manuscript, Dr.

Mehrdad Bakhshyesh Karam; and Methodology and statistics, Dr. Habib Emami.

Clinical Trial Registration Code: This is not a clinical trial study.

Conflict of Interests: Dr. Abtin Doroudinia is reviewer for Iranian Journal of Radiology.

Data Reproducibility: No new data were created or analyzed in this study. Data sharing does not apply to this article.

Ethical Approval: This study was approved by the Institutional Review Board (IRB) (IR.SBMU.NRITLD.REC.1400.004; link: ethics.research.ac.ir/ProposalCertificateEn.php?id=194545).

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