



Volumetric Evaluation of Staging ¹⁸F-FDG PET/CT Images in Patients with Esophageal Cancer

Özofagus Kanserli Hastalarda Evreleme ¹⁸F-FDG PET/CT Görüntülerinin Hacimsel Değerlendirilmesi

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Abstract

Objectives: The aim of this study was to evaluate the metastatic potential of primary tumor and survival in esophageal cancer (EC) patients by using metabolic tumor volume (MTV) and total lesion glycolysis (TLG) from the staging ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) images. Another aim is to determine a tumor volume-based cut-off value to predict long-term survival.

Methods: Medical records of EC patients were retrospectively evaluated. Sixty-two patients with staging ¹⁸F-FDG PET/CT and at least five years of follow-up were included in the study. The region of interest to the primary tumor and all metastatic sites was created and MTV and TLG values of the primary tumor (MTVp, TLGp) and total tumor volume (MTVt and TLGt) values were obtained. The relationship between the obtained MTV and TLG values and short-time (one-year) and long time (five-year) survival was investigated.

Results: Significant factors on survival were determined as lymph node or distant metastasis (p=0.024, 0.008, respectively) at the staging PET/CT. A significant relationship between volumetric parameters of the primary tumor and total tumor burden (MTVp, TLGp, MTVwb and TLGwb) between survivors and non-survivors for one-year and five-year was detected. In receiver operating characteristics analysis, the most significant volumetric parameter was MTVwb, with area under curve 0.771 in estimated five-year survival. The best cut-off value was detected as 36.1 mL with 78% sensitivity and 75% specificity for MTVwb in determining long-term survivors.

Conclusion: Tumor burden in ¹⁸F-FDG PET/CT images at the time of staging of patients with EC will contribute to the prediction of long-term survivors.

Keywords: ¹⁸F-FDG PET/CT, metabolic tumor volume, esophageal cancer

Öz

Amaç: Bu çalışmanın amacı evreleme ¹⁸F-florodeoksiglukoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/CT) görüntülerinden metabolik tümör hacmi (MTV) ve toplam lezyon glikolizini (TLG) kullanarak özofagus kanseri (ÖK) hastalarında primer tümörün metastatik potansiyelini ve sağkalımı değerlendirmektir. Diğer bir amaç, uzun süreli sağkalımı tahmin etmek için tümör hacmine dayalı bir eşik değeri belirlemektir.

Yöntem: ÖK tanılı hastaların tıbbi kayıtları geriye dönük olarak değerlendirildi. Evreleme anında ¹⁸F-FDG PET/CT yapılan ve en az beş yıllık takip süresi olan 62 hasta çalışmaya dahil edildi. Primer tümörün ve tüm metastatik bölgelerin ilgi alanı oluşturuldu ve primer tümörün MTV ve TLG değerleri (MTVp, TLGp) ve toplam tümör hacmi (MTVt ve TLGt) değerleri elde edildi. Elde edilen MTV ve TLG değerleri ile kısa süreli (bir yıllık) ve uzun süreli (beş yıllık) sağkalım arasındaki ilişki araştırıldı.

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Bulgular: Sağkalım üzerinde önemli faktörler evreleme PET/BT'de lenf nodu veya uzak metastaz bulunması (sırasıyla; $p=0,024$, $0,008$) olarak belirlendi. Primer tümörün volumetrik parametreleri ile toplam tümör yükü (MTVp, TLGp, MTVwb ve TLGwb) arasında, bir yıl ve beş yılda sağ kalanlar ve ölenler arasında anlamlı bir ilişki tespit edildi. Alıcı işlem karakteristikleri analizinde, beş yıllık sağkalımı tahmin etmede en önemli hacimsel parametre eğrinin altındaki alan $0,771$ ile MTVwb idi. Uzun süreli sağ kalanların belirlenmesinde MTVwb için en iyi kesim değeri %78 duyarlılık ve %75 özgüllük ile $36,1$ mL olarak tespit edildi.

Sonuç: ÖK'li hastaların evreleme anındaki ^{18}F -FDG PET/BT görüntülerindeki tümör yükü, uzun dönemde sağ kalanların tahminine katkıda bulunacaktır.

Anahtar kelimeler: ^{18}F -FDG PET/BT, metabolik tümör hacmi, özofagus kanseri

Introduction

Esophageal cancer (EC) ranks seventh cause in terms of incidence and the sixth most common cause of mortality across the world (1). Five-year survival rate is 19.9% (2). In distant metastatic (DM) disease, worse prognosis and lower five-year survival rates are declared (5.2%) (2).

^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a standard diagnostic workup in EC. PET/CT provides essential information about the distribution of the lesions, size, and presence of metastases at the time of staging. As a quantitative parameter standard uptake value (SUV) provides information about the intensity of the uptake in the lesion and most commonly maximum standard uptake value (SUV_{max}) is used to determine the tumor metabolic activity (3). However, SUV do not represent the whole tumor (4). Metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG) are the parameters that are increasingly being studied to define the combined volumetric and metabolic characteristics of the tumors (5,6).

This study evaluates the relationship between the volumetric characteristics of the primary tumor obtained from the staging ^{18}F -FDG PET/CT images and the metastatic potential of the primary tumor at the time of diagnosis in EC patients. Another aim is, use volumetric parameters, to determine a volume-based cut-off value to predict long-term survival in EC patients.

Materials and Methods

Patients' medical records, who had undergone ^{18}F -FDG PET/CT at the time of initial staging with EC, between January 2008 and September 2019 at our department, were retrospectively analyzed. Patients whose follow-up was insufficient (less than five-years) were excluded. In total, 62 patients were included in this study. This study was approved by the Local Ethical Committee at Dokuz Eylul University Institution (decision no: 2019/23-09, date: 16.09.2019).

^{18}F -FDG PET/CT

Patients with appropriate patient preparation (fasting for at least 4 h and adequate blood glucose levels) were enrolled in PET/CT. Approximately 1 h after the average injection of 4.1 MBq/kg ^{18}F -FDG all scan was performed using a Philips Gemini TOF PET/CT (Eindhoven, Netherlands). The emission scans were 10-12 beds per patient and for 1.5 minutes/bed position and the transmission scans were obtained from low-dose CT with 50 mAs and 120 kVp, 5 mm re-structured section thickness.

Determination of Region of Interest (ROI)

Conventional and volumetric data of the primary tumor and all metastatic sites were obtained by drawing the ROI of the primary tumors from PET/CT images via LIFEX software (<http://www.lifexsoft.org>) by a nuclear medicine physician (12 years of experience) (7,8). To prevent manual error, the area of interest was drawn in the tumor area with a minimum SUV of 2 and above (Figure 1). SUV (maximum and mean), MTV and TLG of the primary tumor (MTVp, TLGp) and total tumor volume in the whole body (MTVwb and TLGwb) values were obtained.

Statistical Analysis

Statistical Package for the Social Sciences software version 22.0 for Windows was used for statistical analysis. A statistically significant difference between the obtained SUV, MTV and TLG values and short-time (one-year), long time (five-year) survival; lymph node (LN) and DM in subgroups according to the localization and histopathology were investigated. Non-parametric tests (The Mann-Whitney U test and Kruskal-Wallis test) were used because of the heterogeneity of our data. A p value of <0.05 was set as significant. The receiver operating characteristics (ROC) analysis was performed for significant parameters ($p<0.05$) to determine a cut-off value to predict long and short-time survival. Median overall survival (OS) and cumulative survival were calculated using Kaplan-Meier analysis.

Patient Group and Treatment Procedure

Thirty-one patients were administered neoadjuvant chemotherapy (NCRT) but only 13 of them had surgery

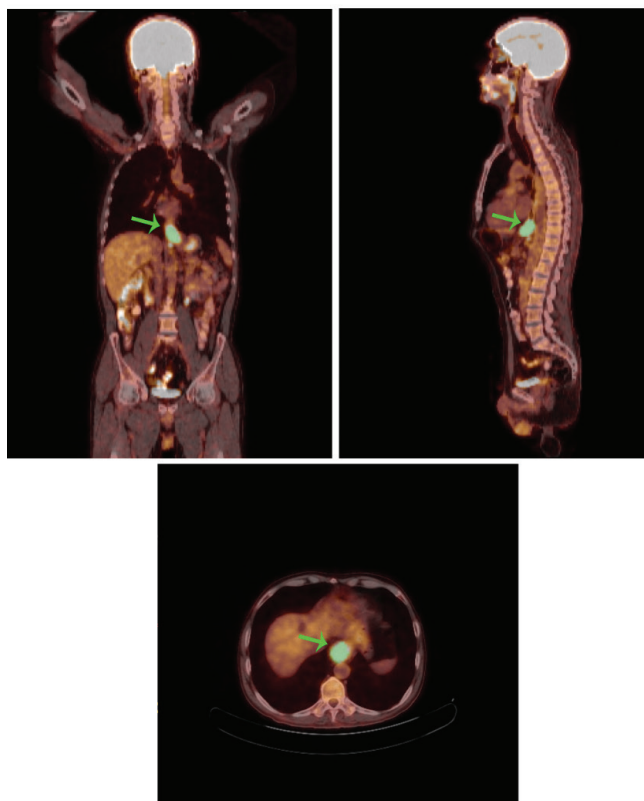


Figure 1. Arrows depicts an example of region of interest in a patient after NCRT. One patient underwent surgery after only neoadjuvant chemotherapy. Four patients underwent surgery as first-line treatment. Thirteen patients with no chance of surgery or local treatment were administered only chemotherapy. After diagnosis, twelve patients had no chance to start a treatment procedure. One patient with only local disease had no chance to administer chemotherapy, only radiotherapy applied, resulted with progression.

Results

Seventeen (27.4%) of 62 patients had DM and 42 (67.7%) had local lymph node metastasis (LNM). Twenty patients (32.3%) had only a local tumor with no metastasis (NM) (no LNM or DM). Twenty-five patients (40.3%) had primary tumor and local only lymph node metastasis (OLNM), and seventeen patients (27.4%) had both local LN and DM (lung, bone, liver or distant lymph node). Fifty patients (80.6%) had squamous cell cancer (SCC) and 12 patients (19.4%) had adeno cancer (AC). Primary tumors were located in the upper, middle and lower esophagus, in 10 (16.1%), 26 (41.9%), and 26 (41.9%) patients, respectively (Table 1).

LNM was detected in 62% of the SCC and 91.7% of the AC groups, and DM rates were 24% and 41.7%, respectively.

	Total (all patients)
Patient number	62 (100%)
Mean age	60±12 (26-85)
AC	12 (19.4%)
SCC	50 (80.69%)
Upper	10 (16.1%)
Middle	26 (41.9%)
Lower	26 (41.9%)
1-year survivors	30 (48.4%)
1-year non-survivors	32 (51.6%)
5-year survivors	12 (19.4%)
5-year non-survivors	50 (80.6%)
Female	22 (35.5%)
Male	40 (64.5%)
NM	20 (32.3%)
LNM	42 (67.7%)
OLNM	25 (40.3%)
DM	17 (27.4%)

AC: Adeno cancer, SCC: Squamose cell cancer, NM: No metastasis, LNM: Lymph node metastasis positive, OLNM: Only lymph node metastasis, DM: Distant metastasis

According to metastasis rates, no significant difference was detected between pathological subgroups ($p>0.05$). It was observed that primary tumor volumetric parameters (MTVp, TLGp, SUV_{max} and SUV_{mean}) were not significant indicators in predicting LN or DM at the time of staging.

Median OS was detected 13.3 ± 2.0 months [95% confidence interval (CI): 9.35-17.26]. Median OS for NM, OLNM and DM was detected 20.9 ± 16.4 months, 12.6 ± 2.2 and 8.3 ± 3.2 , respectively ($p=0.004$) (Figure 2). LNM and DM at the staging PET/CT were detected as significant factors ($p=0.024$, 0.008 , respectively) on OS in the Kaplan-Meier analysis. However, location of the tumor, gender, or histopathological subtype were not significant factors ($p>0.05$). One-year and five-year cumulative OS were determined as $56.5\pm 0.63\%$ and $19.4\pm 0.50\%$, respectively.

When evaluated according to histopathological subtypes, MTVp, TLGp, and SUV_{max} and SUV_{mean} of the primary tumor had no significant difference between SCC and AC patients ($p>0.05$). Similarly, MTVp, TLGp, and SUV_{max} and SUV_{mean} of the primary tumor were not related to the tumor's localization ($p>0.05$). According to the localization of the primary tumor, a significant difference was detected between SCCs and AC ($p<0.005$). SCCs were detected mainly located in the middle esophagus, unlike AC located mainly in the lower esophagus.

A significant relationship between volumetric parameters of the primary tumor and total tumor burden (MTVp, TLGp, MTVwb and TLGwb) between survivors and non-survivors for one-year and five-year was detected. In ROC analysis, the most significant volumetric parameter was MTVwb, with area under curve (AUC) 0.771 in estimated five-year survival. The results are given in Table 2. According to the

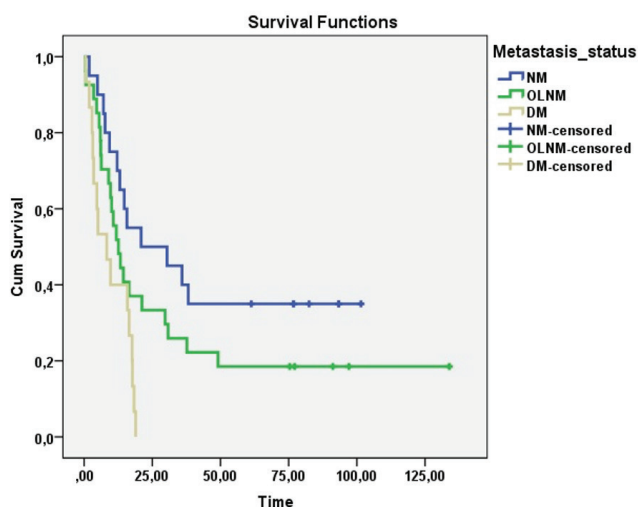


Figure 2. Kaplan-Meier curves demonstrate 5-year survival in patient groups according to metastasis (no metastasis, only lymph node metastasis, and distant metastasis)

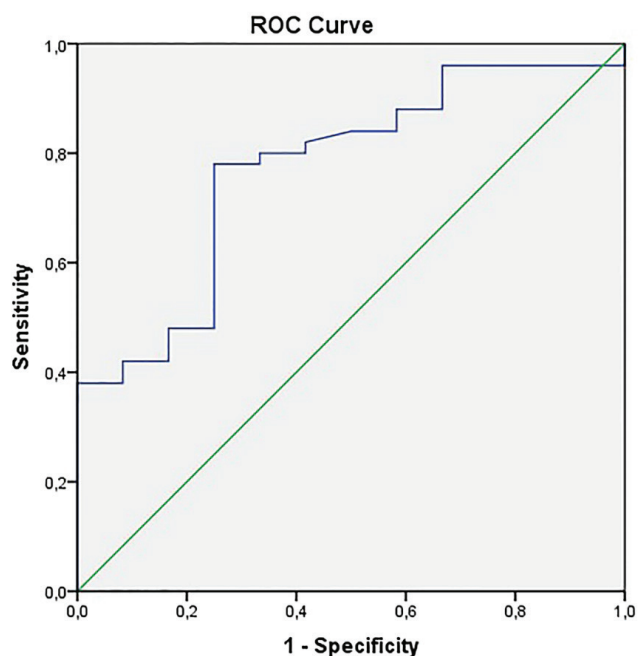


Figure 3. Receiver operating characteristics curve of MTVwb for 5-year survival is given in the figure
MTVwb: Metabolic tumor volume of whole body

Youden index, the best cut-off value was detected as 36.1 mL with 78% sensitivity and 75% specificity for MTVwb in determining long-term survivors (Figure 3). When patients were divided into groups according to the cut-off value as low (<36.1 mL) and high (≥36.1 mL) MTVwb, Kaplan-Meier analysis demonstrated high and low MTVwb as a significant factor on OS (p<0.001). In the low MTVwb and high MTVwb groups, OS was detected as 10.1±1.94 and 35.9±19.34 months, respectively (Figure 4).

Discussion

In this study, we investigated the metastatic potential of the primary tumor at the time of diagnosis and the role of metabolic parameters (MTV and TLG) in OS for both the primary tumor and metastasis obtained from ¹⁸F-FDG PET/CT images. We determined a cut-off value for tumor volume to predict long-time survivors. Among the volumetric parameters, MTVwb, which depicts whole-body tumor volume (tumor burden) in a patient, was determined to be the most significant parameter in detecting five-year survival in patients with EC.

An endpoint of our study was whether the primary tumor’s metabolic features obtained from staging PET/CT was associated with LN or DM. Studies investigate the relation between the metabolic parameters in EC patients and LN or DM or response to treatment. A study, which investigated LNM status at baseline PET/CT, determined in multivariate analysis that MTV of primary tumor with 40% threshold method [Odds ratio (OR): 1.127, p=0.04] and SUR_{max} (maximum tumor-to-blood SUV ratio) (OR:

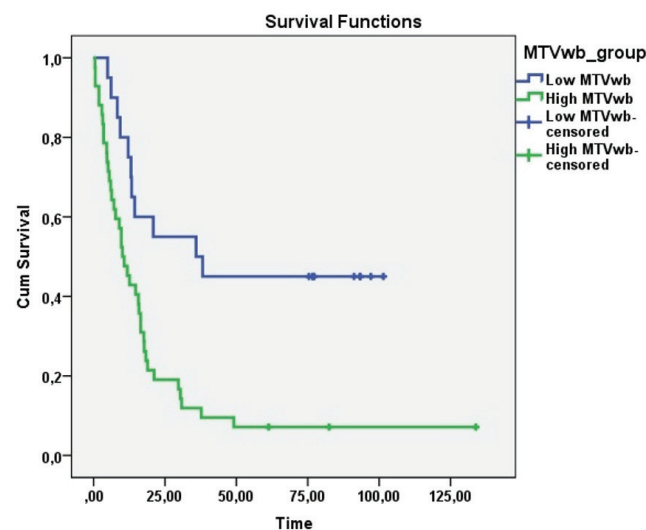


Figure 4. Kaplan-Meier curves demonstrate 5-year survival in patient groups according to low (<36.1 mL) and high (≥36.1 mL) MTVwb groups
MTVwb: Metabolic tumor volume of whole body

Table 2. Receiver operating characteristics analysis results of survival

	1-year survival			5-year survival		
	p value	AUC	(95% CI)	p value	AUC	(95% CI)
MTVp	0.048	0.646	(0.508-0.785)	0.041	0.691	(0.525-0.857)
TLGp	0.053	0.643	(0.505-0.782)	0.089	0.659	(0.500-0.819)
MTVwb	0.012	0.686	(0.553-0.820)	0.004	0.771	(0.631-0.911)
TLGwb	0.009	0.694	(0.562-0.826)	0.011	0.739	(0.597-0.882)

AUC: Area under curve, CI: Confidence interval, MTVp: Metabolic tumor volume of primary tumor, TLGp: Total lesion glycolysis of primary tumor, MTVwb: Metabolic tumor volume of whole body, TLGwb: Total lesion glycolysis of whole body

1.446, $p=0.004$) were independent predictors of LNM, with sensitivity and specificity were 51.2%, 83.7% vs. 53.7%, 79.1% respectively. In the detection of occult LNM, only MTV was detected significantly ($p=0.024$) (9). However, our study revealed that primary tumor metabolic parameters (MTVp, TLGp, SUV_{max} and SUV_{mean}) were not significant indicators in predicting LN or DM at the time of staging. Also, the discrimination of histopathological subtypes of EC is impossible with current imaging modalities. One study suggested that SUV_{max} was not related to histopathological subtypes of EC but, MTV values of AC patients were significantly higher than those of SCC patients (10). However, there are also studies, which could not determine histopathological subtypes with SUV_{max} or MTV (11). Similarly, in our study, primary tumor's volumetric parameters have no significant difference in discriminating histopathological subtypes or localization of the primary tumor ($p>0.05$). Two main histological subtypes, SCC and AC, account for 95% of all EC cases (12). SCC is the most commonly seen subtype and mainly located in the mid to upper part of the esophagus (13). However, AC is mainly located in the distal esophagus. In accordance with literature, according to the localization of primary tumors, a significant difference was detected between the two histopathological subtypes ($p=0.005$) in our study.

Comparison of primary tumor MTV and TLG calculated from initial PET/CT images in patients with EC and treatment response, OS and progression-free survival have been investigated in various studies (14,15,16,17,18,19). A study reported that MTV and TLG of the primary tumor were associated with survival after surgery ($p\leq 0.05$) (16). Another study, which included 151 EC patients, while MTV of the primary tumor was detected as an independent prognostic factor on OS ($p=0.021$), the SUV_{max} of the primary tumor was not significant (17). Similarly, in our study, among the metabolic features of the primary tumor (SUV_{max} , SUV_{mean} , MTVp and TLGp) only MTVp was significantly related to one-year and five-year OS ($p=0.048$, 0.041, respectively).

There are studies have investigated the role of whole-body TLG and MTV on survival in EC patients. Kitajima et al. (20) stated that MTVwb and TLGwb are predictors of OS in univariate analysis ($p<0.0001$), but multivariate analysis pointed to a reduction rate of TLG [Hazard ratios (HR): 2.21, 95% CI, 1.04-4.68; $p=0.040$] as an independent predictor of OS. In a study in which pretreatment whole-body TLG, MTV and SUV_{max} were investigated in patients with EC, while SUV_{max} was not significant, whole-body TLG and MTV were determined as independent predictors of OS, local control, and progression-free survival. HR of TLG and MTV for OS were determined as HR: 2.15 and HR: 2.36, respectively (21). Similarly, our results demonstrate that MTVwb and TLGwb are significant predictors of OS. Apart from our study, Takahashi et al. (21) studied in a limited group and included in their study only patients with stage 2 and 3 thoracic esophageal SCC patients and created the groups for low and high MTV and TLG based on median values (15.57 mL for MTV and 103.68 for TLG). Additionally, in their study, they underline that whole-body TLG has a higher HR than MTV. However, our results determined MTVwb has a higher predictive value than TLGwb. In another study, the five-year survival rate was detected as 49.8%, and MTVp, TLGp and TLGwb were associated with OS. The only significant parameter was TLGwb in multivariate analysis. However, that study included only stage 1-3 SCC EC patients and did not calculate MTVwb values (22). Similar to our results, Zhang et al. (11) reported in their study, in which 36 patients evaluated for short (less than one-year) and long (higher than one-year) survival, higher MTV values were related to short OS in EC. In our study, LNM and DM at the staging PET/CT were detected as significant factors ($p=0.024$, 0.008, respectively) on OS in EC patients. Additionally, metastasis groups (NM, OLN and DM) were significant factors in long-term survival ($p=0.004$). However, the determined MTVwb cut-off value was demonstrated as the most significant factor on OS ($p<0.001$).

Study Limitations

Limited sample size, heterogeneity in the number of patients in the pathological subgroups and the retrospective design of the study are the main limitations.

Our patient group is a heterogeneous group consisting of patients with a diagnosis of EC who underwent PET/CT at the time of staging, but in clinically different stages, with different treatment and management processes. In the treatment management, patients with EC are primarily evaluated in terms of operability, and even in locally advanced stages, the lesion size is reduced with neoadjuvant treatment methods. The surgery option is considered first because surgery is accepted as the most effective treatment strategy (23). In metastatic patients, chemotherapy regimens are the first choice. However, some patients may die before starting or completing treatment regimens, with complications such as bleeding due to the disease, fistula, aspiration, decreased oral intake due to mass effect, while still at the time of staging. Although heterogeneity may seem like a disadvantage in our study group, in general practice, we already encounter a heterogeneous patient group.

In our data, in predicting long-term survivors, AUC was calculated 0.771 for MTVwb. This value is acceptable for determine a cut-off value. The ROC curve is a plot of sensitivity versus 1-specificity at all possible cut-off values. Different cut-off values could be calculated from ROC plot. However, we determined our best cut-off value as 36.1 mL using Youden index. In it is also possible to determine different cut-off values for different patient groups. Including only local/or only metastatic patients could give different cut-off values. Heterogeneity of our data could be seen as an advantage in this regard. Conducting similar studies in different clinics will be beneficial for consolidating the results of our study.

Conclusion

This study suggests that, in addition to the role of metabolic volume of the primary tumor in initial ¹⁸F-FDG PET/CT, tumor burden (MTVwb) in ¹⁸F-FDG PET/CT images at the time of staging of patients with EC will contribute to the prediction of the long-term survivors. Patients with MTVwb <36.1 mL at the staging ¹⁸F-FDG PET/CT could demonstrate better OS results and this value could predict long-term survivors.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethical Committee at Dokuz Eylul University Institution (decision no: 2019/23-09, date: 16.09.2019).

Informed Consent: Retrospective cross sectional study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.P.K.Ş., A.A., G.Ç.K., Concept: N.P.K.Ş., G.Ç.K., Design: N.P.K.Ş., G.Ç.K., Data Collection or Processing: N.P.K.Ş., Analysis or Interpretation: N.P.K.Ş., A.A., Literature Search: N.P.K.Ş., Writing: N.P.K.Ş.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-249.
2. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda. Available from: https://seer.cancer.gov/csr/1975_2018/ based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
3. Makino T, Yamasaki M, Tanaka K, Tatsumi M, Takiguchi S, Hatazawa J, Mori M, Doki Y. Importance of positron emission tomography for assessing the response of primary and metastatic lesions to induction treatments in T4 esophageal cancer. *Surgery* 2017;162:836-845.
4. Meacham CE, Morrison SJ. Tumour heterogeneity and cancer cell plasticity. *Nature* 2013;501:328-337.
5. Hanamoto A, Tatsumi M, Takenaka Y, Hamasaki T, Yasui T, Nakahara S, Yamamoto Y, Seo Y, Isohashi F, Ogawa K, Hatazawa J, Inohara H. Volumetric PET/CT parameters predict local response of head and neck squamous cell carcinoma to chemoradiotherapy. *Cancer Med* 2014;3:1368-1376.
6. Hofheinz F, Li Y, Steffen IG, Lin Q, Lili C, Hua W, van den Hoff J, Zschaek S. Confirmation of the prognostic value of pretherapeutic tumor SUR and MTV in patients with esophageal squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* 2019;46:1485-1494.
7. Wheeler JM, Warren BF, Mortensen NJ, Ekanyaka N, Kulacoglu H, Jones AC, George BD, Kettlewell MG. Quantification of histologic regression of rectal cancer after irradiation: a proposal for a modified staging system. *Dis Colon Rectum* 2002;45:1051-1056.
8. Nioche C, Orlhac F, Boughdad S, Reuzé S, Goya-Outi J, Robert C, Pellet-Barakat C, Soussan M, Frouin F, Buvat I. LIFEX: A freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity. *Cancer Res* 2018;78:4786-4789.
9. Xu M, Wang L, Ouyang M, Lin J, Wang L, Zheng X, Miao S, Tang K. Prediction of lymph node metastasis by PET/CT metabolic parameters in patients with esophageal squamous cell carcinoma. *Nucl Med Commun* 2019;40:933-939.
10. Korkmaz U, Hacıoğlu MB, Kostek O, Sut N, Kodaz H, Erdoğan B, Ustun F, Saynak M, Tastekin E, Cicin I, Durmus-Altun G. The relationship between FDG PET/CT-defined metabolic parameters and the histopathological subtype of oesophageal carcinomas. *Pol J Radiol* 2020;85:e254-e260.
11. Zhang YH, Herlin G, Rouvelas I, Nilsson M, Lundell L, Brismar TB. Texture analysis of computed tomography data using morphologic and

- metabolic delineation of esophageal cancer-relation to tumor type and neoadjuvant therapy response. *Dis Esophagus* 2019;32:doy096.
12. Thrumurthy SG, Chaudry MA, Thrumurthy SSD, Mughal M. Oesophageal cancer: risks, prevention, and diagnosis. *BMJ* 2019;366:l4373. Erratum in: *BMJ* 2019;366:l5391.
 13. Martin-Richard M, Díaz Beveridge R, Arrazubi V, Alsina M, Galan Guzmán M, Custodio AB, Gómez C, Muñoz FL, Pazo R, Rivera F. SEOM Clinical Guideline for the diagnosis and treatment of esophageal cancer (2016). *Clin Transl Oncol* 2016;18:1179-1186.
 14. I H, Kim K, Kim SJ, Kim IJ, Pak K, Kim H. Prognostic value of metabolic volume measured by F-18 FDG PET-CT in patients with esophageal cancer. *Thorac Cancer* 2012;3:255-261.
 15. Martínez A, Infante JR, Quirós J, Rayo JI, Serrano J, Moreno M, Jiménez P, Cobo A, Baena A. Baseline 18F-FDG PET/CT quantitative parameters as prognostic factors in esophageal squamous cell cancer. *Rev Esp Med Nucl Imagen Mol (Engl Ed)* 2021:S2253-654X(21)00107-4.
 16. Tustumi F, Duarte PS, Albenda DG, Takeda FR, Sallum RAA, Junior UR, Buchpiguel CA, Ceconello I. Prognostic value of 18F-fluorodeoxyglucose PET/computed tomography metabolic parameters measured in the primary tumor and suspicious lymph nodes before neoadjuvant therapy in patients with esophageal carcinoma. *Nucl Med Commun* 2021;42:437-443.
 17. Hyun SH, Choi JY, Shim YM, Kim K, Lee SJ, Cho YS, Lee JY, Lee KH, Kim BT. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. *Ann Surg Oncol* 2010;17:115-122.
 18. Jayachandran P, Pai RK, Quon A, Graves E, Krakow TE, La T, Loo BW Jr, Koong AC, Chang DT. Postchemoradiotherapy positron emission tomography predicts pathologic response and survival in patients with esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;84:471-477.
 19. Domachevsky L, Kashtan H, Brenner B, Nidam M, Morgenstern S, Kundel Y, Groshar D, Bernstine H. Baseline 18F-FDG PET/CT as predictor of the pathological response to neoadjuvant therapy in esophageal cancer: a retrospective study. *Medicine (Baltimore)* 2018;97:e13412.
 20. Kitajima K, Kaida H, Nakatani K, Ishibashi M, Morita T, Nakajo M, Tamaki Y, Minamimoto R. Assessment of tumor response to definitive chemoradiotherapy and prognosis prediction in patients with esophageal cancer judged by PET response criteria in solid tumors: multicenter study in Japan. *Nucl Med Commun* 2020;41:443-451.
 21. Takahashi N, Umezawa R, Takanami K, Yamamoto T, Ishikawa Y, Kozumi M, Takeda K, Kadoya N, Jingu K. Whole-body total lesion glycolysis is an independent predictor in patients with esophageal cancer treated with definitive chemoradiotherapy. *Radiother Oncol* 2018;129:161-165.
 22. Park SY, Lee SJ, Yoon JK. The prognostic value of total lesion glycolysis via 18F-fluorodeoxyglucose PET-CT in surgically treated esophageal squamous cell carcinoma. *Ann Nucl Med* 2016;30:81-88.
 23. Harada K, Rogers JE, Iwatsuki M, Yamashita K, Baba H, Ajani JA. Recent advances in treating oesophageal cancer. *F1000Res* 2020;9:F1000 Faculty Rev-1189.