Original Article
Mol Imaging Radionucl Ther 2023;32:35-41 DOI:10.4274/mirt.galenos.2022.93823

The Impact of Metabolic ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Parameters on the Prognosis of Resectable Pancreatic Adenocarcinoma

^{18}F-Florodeoksiglukoz Pozitron Emisyon Tomografisi/Bilgisayarlı Tomografi Metabolik Parametrelerinin Rezektabl Pankreas Adenokarsinomunun Prognozu Üzerine Etkisi

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Abstract

Objectives: ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) is a useful staging method in pancreatic cancer. The prognosis of pancreatic adenocarcinoma is affected by the tumor stage and resectable state. Maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of primary tumors are related to prognostic parameters in pancreatic cancer. This study compared ^{18}F-FDG PET/CT findings with prognostic factors and overall survival of patients with pancreatic cancer.

Methods: Patients with pancreatic adenocarcinoma, referred to our department between 2015 and 2022 for staging, were retrospectively evaluated. Head-to mid-thigh PET/CT images were obtained 1 h after ^{18}F-FDG injection. Demographic data, survival, and clinical and pathological findings of 39 patients, who underwent surgery after PET/CT imaging, were collected. All primary tumor MTV, SUV_{max}, background SUV_{max}, and TLG data have were measured.

Results: The images of 39 patients (24 women and 15 men) with a mean age of 66.62±9.60 years were evaluated. The mean SUV_{max}, MTV 40%, and TLG of the primary tumors in the pancreatic tissue were 6.28±2.33, 19.33±9.77, and 66.56±45.99, respectively. The average survival after disease diagnosis was 18.97±11.47 (2-55) months. MTV and TLG were significantly higher in patients who died during our study. SUV_{max} has a significant effect on mortality.

Conclusion: ^{18}F-FDG PET/CT metabolic parameters of SUV_{max}, MTV, and TLG could help predicting the prognosis of pancreatic cancer preoperatively and follow-up in patients with resectable tumors. Additionally, in our study group tumor grade and perineural invasion significantly affected overall survival.

Keywords: Positron emission tomography/computed tomography, pancreatic cancer, metabolic tumor volume, total lesion glycolysis, maximum-standardized uptake value

Öz

Amaç: ^{18}F-florodeoksiglukoz (FDG)-pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT), pankreas kanserinde yararlı bir evreleme yöntemidir. Pankreas adenokarsinomunun prognozunu, tümör evresi ve rezektabl olması etkilemektedir. Primer tümörün maksimum standartlaştırılmış alım değeri (SUV_{maks}), metabolik tümör hacmi (MTV) ve toplam lezyon glikolizisi (TLG), pankreas kanserinde prognostik parametrelerle ilişkili olduğu gösterilmiştir. Bu çalışma, pankreas kanserli hastaların ^{18}F-FDG PET/BT bulgularınının prognostik faktörler ve sağkalım ile arasındaki ilişkiyi araştırmayı amaçlamıştır.

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Received: 02.04.2022 **Accepted:** 26.06.2022

Yöntem: 2015-2022 yılları arasında bölümümüze evreleme için sevk edilen pankreas adenokarsinomu tanılı hastalar retrospektif olarak değerlendirildi. ^{18}F-FDG enjeksiyonundan 1 saat sonra baş-uyluk ortası PET/BT görüntüleri elde edildi. PET/BT görüntüleme sonrası opere edilen 39 hastanın demografik bilgileri, sağkalım süreleri, klinik ve patolojik bulguları toplandı. Primer tümöre ait MTV, SUV_{maks}, arka plan SUV_{maks} ve TLG verileri ölçülerek hesaplamalar yapıldı.

Bulgular: Yaş ortalaması 66.62±9.60 yıl olan 39 hastanın (24 kadın ve 15 erkek) görüntüleri değerlendirildi. Pankreas dokusunda primer tümörün ortalama SUV_{maks}, MTV %40 ve TLG'si sırasıyla 6.28±2.33, 19.33±9.77 ve 66.56±45.99 idi. Hastalık teşhisi sonrası ortalama sağkalım 18.97±11.47 (2-55) ay olarak bulundu. Çalışmamız sırasında ölen hastalarda MTV ve TLG anlamlı olarak daha yüksekti. SUV_{maks}'ın mortalite üzerinde önemli bir etkisi olduğu saptandı.

Sonuç: Preoperatif olarak elde edilen metabolik ^{18}F-FDG PET/BT parametreleri olan SUV_{maks}, MTV ve TLG rezektabl pankreas kanserinin prognozunu öngörmede ve takipte yardımcı olabilir. Ek olarak, tümör derecesi ve perinöral invazyon da genel sağkalımı önemli ölçüde etkilediği çalışmamızda anlaşılmıştır.

Anahtar kelimeler: Pozitron emisyon tomografisi/bilgisayarlı tomografi, pankreas kanseri, metabolik tümör hacmi, toplam lezyon glikolizis, maksimum standartlaştırılmış alım değeri

Introduction

Pancreatic cancer is one of the deadliest cancer types with high mortality rates, since it is usually detected with distant metastases. Due to the location of the tumor, it might not present symptoms in the initial stage. Even though the resection of the tumor has a curative effect, not every patient can gain the advantage of surgery. Mortality rates are almost 15% in a patient with an early stage (1,2,3).

The prognostic factors in pancreatic cancer are already been defined and mostly related to pathological findings such as tumor size, grade, lymph node metastases, tumor differentiation, perineural invasion, and lymphovascular invasion. These prognostic factors are proved to affect recurrence and survival (1,4).

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is widely used in patients with pancreatic cancer. The contribution of PET/CT in clinical management is already known, particularly in staging. Detecting distant metastases could change the treatment decision, which also affects survival. A prospective multicenter study emphasized a 40% effect on management after ^{18}F-FDG PET/CT imaging on initial staging (5). Furthermore, ^{18}F-FDG PET/CT imaging could provide beneficial information about recurrence (6). The most commonly used parameter for metabolic activity is the maximum standardized uptake value (SUV_{max}) for defining the aggressiveness of the tumor and disease. Higher SUV_{max} is well known for low differentiation and poor prognosis (7). PET/CT also allows volume measurement with the combination of metabolic parameters. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are shown to be helpful in understanding the prognosis of the disease in many cancer types. MTV and TLG are the best volumetric data that provide information about the tumor mass burden on the whole body. These data provide valuable information about survival, which could even be a prognostic indicator of worse clinical behavior (8,9).

This study correlated the volumetric analyses and ^{18}F-FDG parameters with prognostic factors of patients, increasing the knowledge of the relationship between survival after the disease diagnosis and PET data.

Materials and Methods

Patients with biopsy-proven pancreatic adenocarcinoma that were referred to our department for staging with ^{18}F-FDG PET/CT between 2015 and 2022 were retrospectively evaluated. All patients underwent surgery after PET/CT. Patients who received treatment or underwent surgery before PET/CT were excluded from the study. The histopathology reports of patients had been received after surgery. All demographic data and pathological prognostic findings after surgery were obtained. Grade and size of the tumor, positivity for lymphovascular invasion, perineural invasion, and lymph node metastases were the data included in our study for the correlation. The tumor grade was classified as well or poor differentiated. Other the data besides tumor size were classified as positive or negative.

For the ^{18}F-FDG PET/CT protocol, all patients received approximately 111-370 Mbq (3-10 mci) of ^{18}F-FDG. After 45-60 min with an empty bladder, head to mid-thigh whole body CT (130kV, 50-80 mAs; slice thickness, 3 mm) and PET images were obtained (GE Healthcare, Wisconsin, USA). Oral contrast was used in all patients; in the meantime, intravenous contrast could not be performed in all patients. All PET/CT was were obtained using the same protocol; 1 h after injection of ^{18}F-FDG, head to mid-thigh images were obtained. All images were retrospectively evaluated again, and findings were noted. Patients with distant metastases were excluded from the study to understand the effect of

the measurements of only primary tumor burden. ^{18}F-FDG uptake >2.5 than background activity was accepted as pathological. The region of interest was drawn from the primary tumor location in the pancreatic tissue. SUV_{max}, MTV (cm^3), and TLG (g/mL) of the primary tumor were measured using a GE Healthcare PET workstation (Figure 1). For MTV and TLG data, 40% cut-off value was defined as suggested in routine measurements. This threshold is most commonly used for measurements of metabolic volume parameters (10). Background SUV_{max} was also measured from the gluteal region where there was no pathological activity. The background SUV_{max} ratio was used in calculating the ratio with primary tumor SUV_{max} when necessary.

The survival data of the patients were obtained from the hospital system during the collection of the data of this study. The survival data were calculated as months after initial diagnosis and followed by ^{18}F-FDG PET/CT. The mortality rates were also collected from the patients who died during the data collection of the study. Ethical approval was obtained from the University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee no: 3105, date: 02.02.2021, and all patients provided written informed consent.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences software for Windows (version 17.0; IBM, Armonk, NY, USA). Individual and aggregate data were summarized using descriptive statistics, including mean, standard deviations, medians (min-max), frequency distributions, and percentages. The Normality of the data distribution was verified by histogram graphs and the Kolmogorov-Smirnov test. For the variables that were not normally distributed, the Mann-Whitney U test was conducted to compare groups. The presence of correlation was analyzed with Spearman's rho test. For survival analyses, Kaplan-Meier analyses were used in the univariate analyses, and Cox regression was used in the multivariate analyses. Receiver operating characteristic (ROC) analysis was used to define cut-off values. P values <0.05 were considered statistically significant.

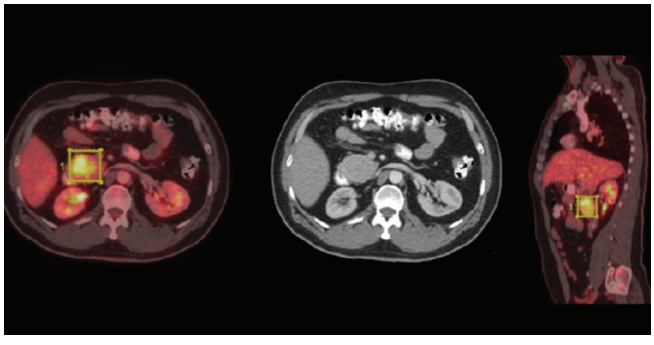

Figure 1. Volumetric measurement of the primary lesion on the head of the pancreas with a 23.59 cm^3 metabolic tumor volume and 112.1 g/mL of total lesion glycolysis

Results

Thirty-nine patients with histologically proven resectable pancreatic adenocarcinoma were included in this study. Of 39 patients, 24 were male, with a mean age of 66.62±9.60 (min-max: 41-80) years. The mean SUV_{max} of the primary tumor was 6.28±2.33, and the background to primary tumor SUV_{max} ratio was 8.09±3.50. The mean MTV and TLG values of the primary tumor were 19.33±9.77 cm^3 and 66.56± 45.99 g/mL, respectively.

The mean tumor size of the primary tumor was 3.31±1.78 cm. Patients were divided into the well (n=32) or poorly (n=7) differentiated groups. Twenty-eight patients from the group had pathologically proven local lymph node metastases. Based on the pathology reports after surgery, 36 patients were positive for lymphovascular invasion, whereas 30 patients were positive for perineural invasion (Table 1).

The mean overall survival rate after diagnosis was 18.97±11.47 (2-55) months. Twenty-two patients were

Table 1. Demographics of the patients enrolled to study

Clinical characteristics	Values
Sex (n) Male Female	 24 15
Age mean ± SD (min-max)	66.62±9.60 (41-80)
Primary tumor size (cm)	3.31±1.78 (0.6-9)
Grade of the tumor (n) Well-differentiated Less-differentiated	 32 7
Lymph node metastases (n) Positive Negative	 28 11
Primary tumor SUV_{max} (min-max)	6.28±2.33 (2.8-13.9)
Metabolic tumor volume (cm^3)	19.33±9.77
Total lesion glycolysis (g/mL)	66.56±45.99
Lymphovascular invasion (n) Positive Negative	 36 3
Perineural invasion (n) Positive Negative	 30 9
Overall survival after diagnosis (months)	18.97±11.47

SD: Standard deviation, min: Minimum, max: Maximum, SUV_{max}: Maximum standardized uptake value

reported dead during the data collection of our study. In the Kaplan-Meier analyses, overall survival had a significant relationship with primary tumor grade and perineural invasion (p=0.026; p=0.005 respectively, Figure 2). Multivariate Cox regression analysis has shown that SUV_{max} has a significant effect as an independent factor on mortality (p=0.045, hazard ratio: 1.56, 95% confidence interval: 1.01-2.4, Figure 3). The TLG and MTV data of the patients who have died during the study were significantly higher than patients who were alive in the univariate analyses (p<0.001 and p<0.001, Figure 4).

Poorly differentiated tumor grade had a significant relationship with higher primary tumor SUV_{max} (p=0.031). Patients positive for lymph node metastases had significantly higher primary tumor SUV_{max} than the negative group. TLG of the primary tumor was significantly higher in patients with perineural invasion (p=0.049).

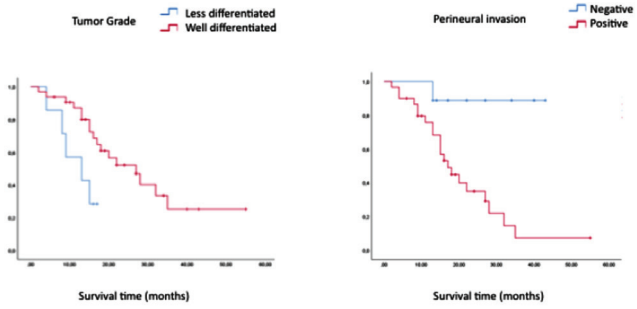

Figure 2. Kaplan-Meier curves of tumor grade and perineural invasion

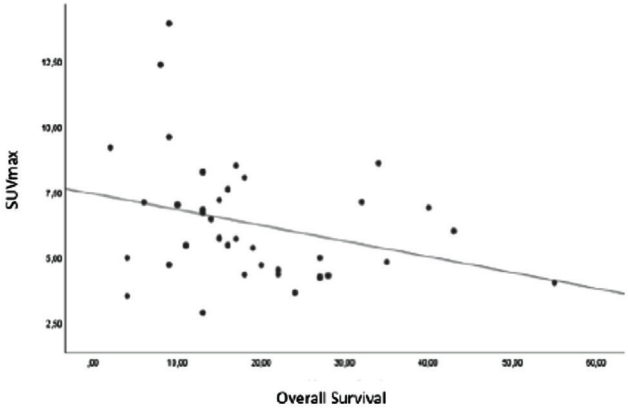

Figure 3. Effect of SUV_{max} as an independent factor on survival
SUV_{max}: Maximum standardized uptake value

ROC analysis was conducted for the cut-off values that were defined for the PET data that are statistically significant (Table 2). Primary tumor size with a cut-off value of 3.15 cm, sensitivity, specificity, positive predictive value, and negative predictive values were 59.09%, 88.24%, 86.67%, and 62.50%, respectively. The cut-off value for MTV was 13.80 cm^3 and sensitivity, specificity, positive predictive value, and negative predictive values were 95.45%, 70.59%, 80.77%, and 92.31%, respectively. The TLG cut-off value was 56.85 g/mL with sensitivity, specificity, positive predictive value, and negative predictive value of 77.27%, 94.12%, 94.44%, and 76.19% (Figure 5). Nonetheless, ROC analyses for SUV_{max} values did not show a significant result (p=0.854).

Discussion

SUV_{max} measurements have been successfully used and provided valuable information about the tumor's behaviour (11,12). Furthermore, SUV_{max} has been described as an independent prognostic factor in pancreatic cancer (13). Metabolic parameters of the tumor are shown to be as important as the anatomical information for the patient's prognosis. Nevertheless, as a drawback, the heterogeneous distribution of the ^{18}F-FDG inside the tumor could be deceptive. Other than in our routine daily practice, metabolic volume measurements are also available for evaluating tumor characteristics. In particular, studies have emphasized that metabolic volumetric data is helpful for understanding prognosis, tumor aggressiveness, and therapy assessment (9,14,15). The most useful volumetric parameters of MTV and TLG define additional and more detailed knowledge about tumor and metabolic function. Some studies have emphasized the effect of volumetric parameters on survival in pancreatic adenocarcinoma, more than SUV_{max} (16,17).

Patients who died had significantly higher MTV and TLG values than patients who were alive during the study. Another study similar to this study concept with 63 patients with resectable pancreatic adenocarcinoma reported a significant relationship between metabolic parameters and survival. The cut-off levels of MTV of 7.38 cm^3 and TLG

Table 2. ROC analysis and the cut-off values

	Cut-off	Sensitivity	Specificity	PPV	NPV	CI (95%)	p
Tumor size	3.15	59.09%	88.24%	86.67%	62.50%	0.58-0.9	**0.010**
MTV cm^3	13.80	95.45%	70.59%	80.77%	92.31%	0.79-0.9	**<0.001**
TLG g/mL	56.85	77.27%	94.12%	94.44%	76.19%	0.74-0.9	**<0.001**

ROC: Receiver operating characteristic, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, PPV: Positive predictive values, NPV: Negative predictive values, CI: Confidence interval

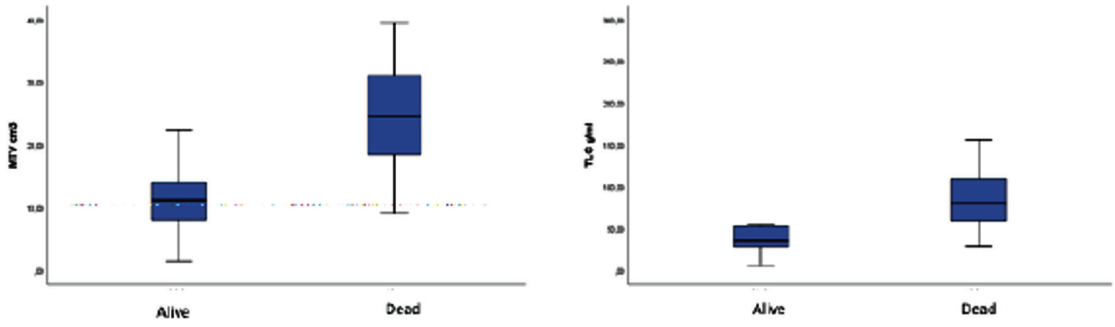

Figure 4. TLG and MTV data of the patients were significantly higher in patients who died during the study in univariate analyses
MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

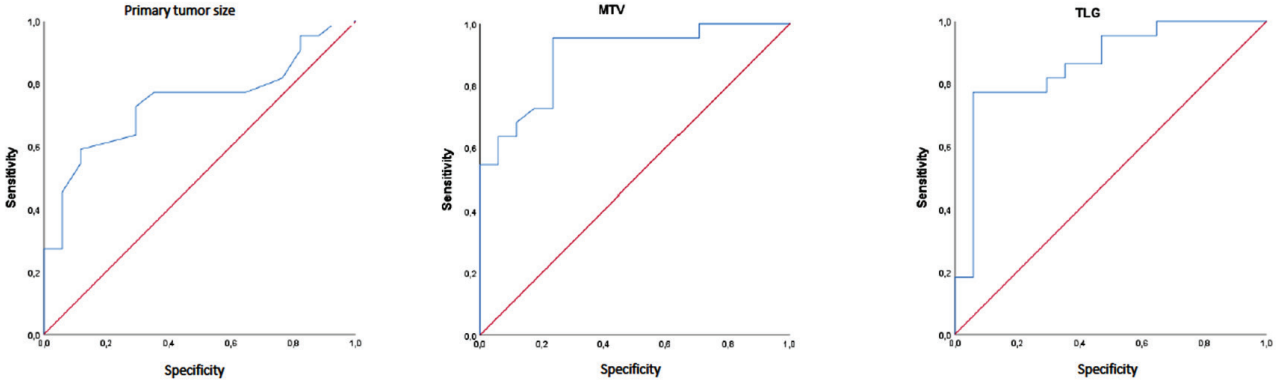

Figure 5. ROC curves for the cut-off values of primary tumor size, MTV and TLG
ROC: Receiver operating characteristic, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

of 18.6 g/mL of this study were lower than our results found in the ROC analysis (18). Furthermore, one of the latest studies found a significant effect of MTV and TLG on survival. The median levels of MTV: 10 cm^3 and TLG: 55 were compatible with our cut-off levels (19). Likelihood, there is still no consensus on the volume thresholds of the measurements, and the results slightly differ also with other studies.

Compatible with other studies, we have found that higher primary tumor SUV_{max} had a significant effect on mortality. Furthermore, tumor grade and perineural invasion were found to have a significant effect on overall survival in our patient group (7,20). Additionally perineural invasion was significantly correlated with TLG of the primary tumor in our study. Some other studies have reported no relationship between metabolic parameters and survival to either the lymphatic or perineural invasion (21,22). Another study emphasized a significant relationship between metabolic parameters and lymphovascular invasion (18). ^{18}F-FDG PET/CT findings are indicated for predicting tumor biology in pancreatic cancer. Perineural invasion is as a negative prognostic factor and is related to tumor aggressiveness (22,23). The difference in our results from other studies could be caused by patients with metastases, who were excluded from our study, which could affect a more perineural positivity in the initial stage of these patients. Furthermore, we also believe that the results might be affected by the heterogeneous distribution or a small number of patients.

Daily practice of the ^{18}F-FDG PET/CT reports do not always include volumetric analyses. However, with the results of our study, we emphasized that the volumetric measurements and correlations should be considered for reporting. This would lead the clinician to decide on the next step after or even before surgery for operable patients, especially guiding for patient-specific treatment and follow-up of curative disease with being aware of early recurrence.

Study Limitations

This retrospective study has limitations. First of all this was a retrospective study. Since referral patients from other hospitals, not all patients were followed-up in our hospital.

Hence, we could not reach the detailed time to progression data. Furthermore, interobserver or intraobserver agreement of the ^{18}F-FDG PET/CT data analyses was not considered. Prospective trials with more patients should be conducted to evaluate predicting mortality with volumetric analyses and change rates of either overall survival or quality of life of the patient.

Conclusion

Metabolic volumetric parameters of ^{18}F-FDG PET/CT can provide beneficial prognostic information that could direct the treatment and follow-up strategy in staging resectable pancreatic adenocarcinoma. Additionally, SUV_{max} has a significant effect on mortality, whereas tumor grade and perineural invasion has been shown to have a significant effect on overall survival.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Sisli Etfal Training and Research Hospital Ethics Committee no: 3105, date: 02.02.2021.

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B., Ö.B., Ö.E., B.Y.Ö., Concept: Ö.E., Design: Ö.E., M.B., Data Collection or Processing: Ö.E., B.Y.Ö., Analysis or Interpretation: Ö.E., Literature Search: Ö.E., Ö.B., Writing: Ö.E., Ö.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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