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ORIGINAL ARTICLE

Evaluation of Overall Survival Predictions In Inoperable Pancreas Ductal Adenocarcinoma

İnoperabl Pankreas Duktal Adenokarsinomunda Genel Sağ Kalım Öngörücülerinin Değerlendirilmesi

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ABSTRACT

Objective: In this study, we aimed to determine the independent predictive parameters of overall survival (OS) of patients with inoperable pancreatic ductal adenocarcinoma (PDAC) and to investigate whether these parameters can be used as potential biomarkers to shape precision medicine practices for PDAC patients.
Materials and Methods: The clinical and pathological data of patients who were diagnosed with inoperable pancreatic ductal adenocarcinoma between January 2016 and December 2019 and who underwent 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in our department were retrospectively analyzed. Tumor diameter, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated from FDG PET/CT images. Univariate and multivariate Cox regression analyzes were performed to investigate the variable affecting overall survival. Overall survival data were analyzed using the Kaplan–Meier method, using the log-rank test.
Results: A total of 48 patients, 31 male and 17 female, with a mean age of 65.85 ± 1.64 were included in the study. In univariate Cox regression analyzes were performed to examine the factor affecting OS. Clinicopathological factors (tumor localization, tumor diameter, stage) and FDG PET/CT parameters (SUVmax, MTV and TLG) with a p-value of < 0.2 were compared to multivariate Cox regression analysis. TLG was found to be the only independent predictor of OS. In the Kaplan-Meier analysis, the median OS duration of the patients with a median value of TLG below 298.34 was 13.87 months, while the median OS duration was found to be 4.97 months in patients with a TLG value above this value.
Conclusion: In our study, TLG value, which is an FDG PET/CT parameter that reflects both the metabolic activity and the volume of the tumor, was found to be the only independent predictor of the OS of inoperable PDAC patients. TLG can be used as a potential biomarker for survival in patients with inoperable PDAC and may assist precision medicine applications.

Keywords: Pancreatic ductal adenocarcinoma; fluorodeoxyglucose; Positron emission tomography / computed tomography; total lesion glycolysis

ÖZ

Amaç: Bu çalışmada, inoperabl pankreas duktal adenokarsinom (PDAK) tanılı hastaların genel sağ kalımının (GSK) bağımsız öngörücü parametrelerini saptamayı ve bu parametrelerin PDAK hastaları için hassas tıp uygulamalarını şekillendirmede potansiyel biyobelirteç olarak kullanılıp kullanılamayacağını araştırmayı amaçladık.
Gereç ve Yöntem: Ocak 2016 - Aralık 2019 tarihleri arasında inoperabl pankreas duktal adenokarsinom tanısı alan ve bölümümüzde Flor-18 florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (FDG PET/BT) tetkiki yapılan hastaların klinik ve patolojik verileri retrospektif olarak incelendi. FDG PET/BT görüntülerinden tümörün çapı, maksimum standardize tutulum değeri (SUDmaks), metabolik tümör volümü (MTV) ve toplam lezyon glikolizisi (TLG) hesaplandı. GSK üzerine etki eden değişkenlerin araştırılması için tek değişkenli ve çok değişkenli Cox regresyon analizleri yapıldı. GSK verileri Kaplan–Meier yöntemiyle, log-rank testi kullanılarak incelendi.
Bulgular: Çalışmaya ortalama yaşı 65.85 ± 1.64 olan 31'i erkek 17'si kadın toplam 48 hasta dahil edildi. GSK üzerine etki eden faktörleri incelemek için yapılan tek değişkenli Cox regresyon analizlerinde p değeri:< 0.2 olan klinikopatolojik faktörler (tümör lokalizasyonu, tümör çapı, evre) ve FDG PET/BT parametrelerinin (SUDmaks, MTV ve TLG) çok değişkenli Cox regresyon analizine dahil edilmesi sonucu TLG'nin, GSK'ın tek bağımsız öngürücüsü olduğu bulundu. Yapılan Kaplan-Meier analizinde, TLG'nin median değerinin 298.34'ün altında olan hastaların ortanca GSK süresi 13.87 ay iken, TLG değeri bu değerin üstünde olan hastalarda ortanca GSK süresi 4.97 ay olarak bulundu.
Sonuç: Çalışmamızda, tümörün hem metabolik aktivitesini hem de hacmini birlikte yansıtan, FDG PET/BT parametresi olan TLG değeri, inoperabl PDAK hastalarının GSK'nın tek bağımsız öngörücüsü olarak bulundu. TLG, inoperabl PDAK'lı hastalarda sağ kalım için potansiyel bir biyobelirteç olarak kullanılabilir ve hassas tıp uygulamalarına yardımcı olabilir.

Anahtar kelimeler: Pankreas duktal adenokarsinom; Florodeoksiglukoz; Pozitron emisyon tomografisi/bilgisayarlı tomografi; toplam lezyon glikolizi

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent exocrine malignancy of the pancreas with high mortality risk and is the 7th leading cause of cancer deaths worldwide (1) The five-year survival is reported to be 9% and this decreases to 2% in advanced stage PDAC (2). At the time of initial diagnosis, approximately 80% of the patients have locally spread or distant metastatic disease. The poor prognosis of PDAC may be related to the propensity for early metastatic spread (3). Surgery is the only curative treatment modality for PDAC (4). However, only 15-20% of patients are candidates for surgery (4). Effective imaging methods are needed to avoid unnecessary surgeries and to estimate the prognosis.

Fluorine-18-fluorodeoxyglucose positron emission tomography /computed tomography (FDG PET/CT) is a non-invasive imaging technique to evaluate the glucose metabolism of malignant cells (5). FDG PET/CT is used to diagnose and stage many malignancies, including pancreatic carcinoma. Prognostic dates achieved by F-18 FDG PET/CT in pancreas cancers have been reported in many studies (6-8). information obtained with FDG PET/CT in pancreatic cancer. However, most of these studies examined resected early-stage PDAC or both early and advanced-stage PDAC together indiscriminately.

In our study, we aimed to investigate the prognostic predictive values of clinicopathological factors (tumor localization, tumor diameter and stage), maximum standard uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of primary tumor obtained by FDG PET/CT, in patients with inoperable PDAC, and also independent predictive parameters for overall survival in patients with inoperable PDAC.

Materials-Methods

The clinical and pathological data of patients diagnosed as PDAC and followed up with FDG PET/CT in our department between January 2016 and December 2019 were investigated retrospectively. Resectable PDAC, intraductal papillary mucinous neoplasms, endocrine tumors, cystic neoplasms, pancreatic metastases, and duodenal, ampullary and biliary tract cancers were excluded from the study. According to these criteria, 48 patients were enrolled. The diagnosis of PDAC was confirmed histopathologically in all cases. The patients were staged according to the TNM classification of the International Union for Cancer Control (UICC) (9). Age, gender, lymph node metastasis status and overall survival of the patients were evaluated. Overall survival was recorded as the time passed from the date of FDG PET/CT to the date of death. The death dates of the patients were obtained from the hospital records.

Regular follow-ups that include physical examination, abdominal CT or ultrasonography and tumor markers were applied for all patients. The majority of patients were given gemcitabine-based chemotherapy, while some patients were given adjuvant palliative treatments.

Ethics Committee

The Approval with number 2021/023 from the medical faculty of KTO Karatay University was obtained for this study. Our studies are compatible with all procedures applied for studies with human participation, institutional and/or national research committee ethical standards and the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

FDG PET/CT Imaging Protocol

Intravenous FDG (3.7 MBq/Kg) was given to patients for PET/CT imaging, after 6 hours of fasting. Blood glucose levels were lower than 200 mg/dl before the imaging in all patients. Sixty minutes after injection, PET/CT imaging was performed from the skull base to the upper thigh with Siemens 16 Truepoint PET/CT scanner (Siemens AG Medical Solutions, Erlangen, Germany). Images were evaluated in transaxial, coronal and sagittal plane sections with different colours and contrast slices. FDG PET/CT findings of the patients were interpreted together by two nuclear medicine specialists. SyngoTrueD VD20A software was used for image processing.

Calculation of FDG PET/CT Parameters

The region of interest was drawn from the FDG PET/CT images, including the regions showing pathological FDG uptake in the pancreas. The SUVmax and SUVmean were calculated from within the plotted area of interest. The MTV value, which shows the metabolic tumor volume in the selected area of interest, was calculated by an automatic software (SyngoTrueD VD20A) selecting the threshold of 42% of SUVmax in the area of interest recommended in the literature (10) for soft tissue tumors. The total lesion glycolysis (TLG) value was obtained by multiplying the MTV by the SUVmean values.

Statistical Analysis

Data were analyzed by SPSS 26.0 (SPSS Inc, Chicago, IL, USA). The normality of the distributions of the study variables was checked with the Kolmogorov-Smirnov test. Since all numerical variables did not show a normal distribution, their median values were used. Categorical variables were presented as n (%). Comparisons between groups were made using the Mann-Whitney-U or Kruskal-Wallis tests. Spearman's correlation test was used for the correlation of quantitative parameters. Univariate and multivariate regression analyzes were applied for the variables that affect overall survival. For overall survival, variables that were found to be at $p<0.2$ on univariate analysis were included in multivariate analysis. Overall survival data were analyzed by Kaplan–Meier method, using the log-rank test. A p-value of <0.05 was considered statistically significant.

Results

Forty-eight patients, (31 male and 17 female), with a mean age of 65.85 ± 1.64 years were enrolled in our study. Mean pancreatic tumor diameter: 38.50 mm, median SUVmax for pancreatic tumor: 10.30, median MTV value for pancreatic tumor 69.83, and median TLG value for pancreatic tumor: 298.34. The demographic and the clinical data of the patients are presented in Table 1.

Table 1. Patient Characteristics

	n (%)
Age	
≤65 years	23 (% 47.92)
>65 years	25 (% 52.08)
Gender	
Male	31 (% 64.58)
Female	17 (% 35.42)
Tumor localization	
Head	25 (% 52.08)
Corpus	23 (% 47.92)
Tail	0
Median tumor diameter (mm)	38.50
Stage	
Stage III	21 (% 43.75)
Stage IV	27 (% 56.25)
Median SUVmax	10.30
Median MTV	69.83
Median TLG	298.34

SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis;

Table 2. Univariate and multivariate Cox regression analyzes for overall survival in patients with inoperable pancreatic ductal adenocarcinoma

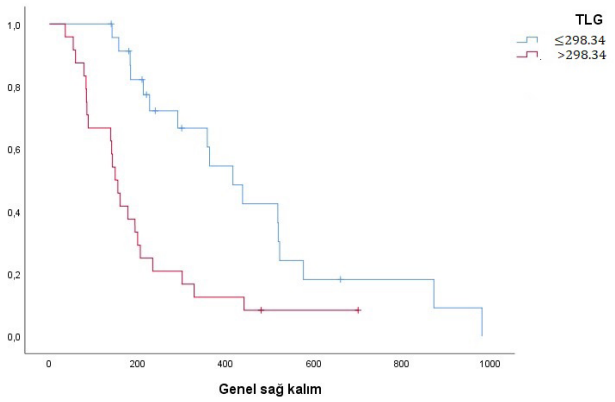
	Univariate analysis			Multivariate analysis		
	HR	**%95 CI**	**p**	**HR**	**%95 CI**	**p**
Age(≤65->65)		0.387-1.445				
Gender (Male-Female)		0.389-1.457				
Tumor localization (Head-Corpus)		0.930-3.352			0.756-3.419	
Tumor diameter (mm) (≤38.50->38.50)		0.565-1.077			0.294-1.737	
Stage (III-IV)		0.979-3.709			0.939-4.510	
SUVmax (≤10.30->10.30)		1.199-4.575			0.564-3.008	
MTV (≤69.83->69.83)		1.228-4.615			0.225-2.373	
TLG (≤298.34-298.34)		1.621-6.228			1.061-15.228	

CI, confidence interval; HR, hazard ratio; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis;

The tumor was located in the head of the pancreas in 25 patients (52.08%) and the corpus in 23 patients (47.92%). None of the patients has a tumor located in the tail of the pancreas in the study. Median MTV and TLG values of tumors located in the corpus of the pancreas were significantly higher than those located in the head part (p=0.06 and 0.013, respectively). No significant difference was found for SUVmax. Twenty-one (43.75%) and 27 (56.25%) of the patients were at stage III and stage IV respectively. No significant relation was found between FDG PET/CT parameters in stage groups of pancreas tumors. While significant moderate correlation was found between tumor diameter and MTV (r= 0.670, p: <0.001) and TLG (r= 0.668, p: <0.001) values, no significant correlation was found between tumor diameter and SUVmax values.

The median follow-up time was 6.93 months for the patients. Thirty-nine patients died during follow-up. Tumor localization, tumor diameter, stage, SUVmax, MTV and TLG were included in the multivariate analysis to investigate the factors that affect overall survival (Table 2). TLG was found to be the only independent predictive factor that affects overall survival [Hazard ratio (HR)= 4.019, 95% confidence interval (CI) 1.061-15.228, p= 0.041]. The median overall survival time was 13.87 months for patients with a median TLG value lower than 298.34 but was 4.97 months for those with higher values (p: <0.001). Overall survival curves of patients with TLG values higher and lower than 298.34 are shown in figure 1.

Figure 1. Overall survival curves of patients grouped by TLG values (≤298.34 - >298.34)



Discussion

Pancreatic ductal adenocarcinoma is an aggressive and lethal disease with a 5-year survival rate of only 2-9%. It has an increasing incidence trend all over the world and constitutes 1-2% of all cancers (2). Predicting prognosis in PDAC may aid to choose sensitive medicine practices. In our study, an FDG PET/CT parameter TLG, which shows both tumor volume and metabolism, was found as an independent predictor of overall survival in inoperable PDAC patients.

In patients with PDCA, a relationship between tumor size and overall survival was reported (11), however contrary publications have been published in the literature (12, 13). In our study, a significant and moderate correlation was found with tumor size and MTV and TLG values. In univariate regression analysis, Tumor diameter was found a significantly effective variable on overall survival, but on the contrary, it was not found as an independent predictive factor on overall survival in multivariate regression analysis. Stroma-dense desmoplastic reaction in the tumor, non-viable tumor cells due to the hypoxic environment around the tumor and intra-tumoral heterogeneity may be the factors that may cause tumor diameter has not a prognostic value.

SUVmax is a commonly used parameter in FDG PET/CT and shows the highest FDG uptake density in the area of interest but does not reflect the metabolic activity of the entire tumor. TLG was found a better prognostic predictor than SUVmax in many studies that involved both PDAC and different cancers (14, 15). In line with previous studies (6, 17), we found that SUVmax was not an independent predictive factor of overall survival in our study.

TLG, which defines the metabolic activity of the tumor and the tumor volume, may show total tumor burden excluding the non-neoplastic parts of the tumor (18, 19). Among the clinicopathological factors and FDG PET/CT parameters evaluated in our study, only TLG was the independent predictor of overall survival. Furthermore, we found that patients with a TLG value higher than 298.34 have approximately 9 months less survival than patients below this value.

The limitations of our study were its retrospective character, low patient number, and one-centre experience. In addition, TLG is affected by many factors such as partial volume effect, image resolution, reconstruction method, and the time elapsed between FDG injection and imaging. Therefore, prospective multicenter studies using standardized protocols on different FDG PET/CT scanners are needed to validate our results.

Conclusion

In our study, the TLG value obtained from FDG PET/CT, which shows both metabolic activity and volume of the tumor was found as an independent predictive parameter for the overall survival of patients in inoperable PDAC. TLG may be used as a potential biomarker in patients with inoperable PDAC and may aid to detect patients that need intense therapy.

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