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Original Article *Özgün Araştırma*

INVESTIGATION OF 18F-FDG PET / CT AND CLINICOPATHOLOGICAL DATA OF DIFFUSE TYPE GASTRIC CANCERS

Difüz Tip Gastrik Kanserlerin 18F-FDG PET/CT ve Klinikopatolojik Verilerinin İncelenmesi

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ABSTRACT

Objective: One of the subtypes of stomach cancer, which is one of the leading causes of cancer-related deaths, is diffuse-type stomach cancer. In our study, it was aimed to retrospectively investigate the results of F-18-labeled fluorodeoxyglucose positron emission tomography, which is an imaging method frequently used in the diagnosis and follow-up of gastric cancer, in diffuse type gastric cancer subtypes and to review patient data in the light of the literatüre

Material and Methods: Forty-four patients diagnosed with diffuse-type gastric cancer in a single center were included in the study. Clinical, pathological and positron emission tomography data of the patients were analyzed.

Results: The mean age of the patients was 61.93. Sixteen (36.4%) of the patients were female, 28 (63.5%) were male. When the histopathological results of specimens obtained by endoscopic and surgical methods are examined, diffuse-type stomach cancer patients; 36 (81.8%) were Signet-Ring Cell, 8 (18.2%) were weak poorly cohesive type gastric cancer. Low F-18-labeled fluorodeoxyglucose involvement was observed in 8 (18.2%) patients, while high involvement was observed in 36 (81.8%). Nineteen of the patients had metastases. When SUV_{max}, $SUV_{mean,}$ metabolic tumor volume and total lesion glycolysis values were compared, a significant correlation was found between signet ring cell gastric cancers and weak cohesive type gastric cancers, and between presence and absence of metastasis ($p < 0.05$).

Conclusion: Although SUV_{max} values were lower in our diffuse type gastric cancer patient series compared to other gastric cancer patients, it was observed that it was higher in advanced diffuse type gastric cancers than in early stage patients. In addition, when the diffuse type gastric cancer subtypes signet-ring cell and weak poorly cohesive type gastric cancers were compared in terms of positron emission tomography results, it was observed that there was no significant difference, and this is an information that is not available in the literature.

***Keywords**: Diffuse type, gastric cancer, poorly cohesive, signet-ring cell, ^{18}F-FDG PET/CT*

ÖZ

Amaç: Kansere bağlı ölümlerin önde gelen nedenlerinden biri olan mide kanserinin alt tiplerinden biri de diffüz tip mide kanseridir. Çalışmamızda mide kanseri tanı ve takibinde sıklıkla kullanılan bir görüntüleme yöntemi olan F-18 ile işaretli florodeoksiglukoz Pozitron emisyon tomografisinin, diffüz tip mide kanseri alt tiplerinde sonuçlarının retrospektif olarak araştırılması ve literatür ışığında gözden geçirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya tek merkezde diffüz tip mide kanseri tanısı konulan 44 hasta dahil edildi. Hastaların klinik, patolojik ve Pozitron emisyon tomografi verileri analiz edildi.

Bulgular: Çalışmaya alınan hastaların yaş ortalaması 61.93 idi. Hastaların 16'sı (%36.4) kadın, 28'i (%63.5) erkekti. Endoskopik ve cerrahi olarak alınan spesimenlerin histopatolojik sonuçları incelendiğinde, diffüz tip mide kanserli hastalar; 36'sı (%81.8) taşlı yüzük hücreli mide kanseri, 8'i (%18.2) zayıf kohezif tip mide kanseriydi. Hastaların 8'inde (%18.2) düşük florodeoksiglukoz tutulumu görülürken, 36 hastada (%81.8) yüksek tutulumu mevcuttu. Hastaların 19'unda metastaz vardı. SUV_{max}, SUV_{mean}, metabolik tümör hacmi ve toplam lezyon glikoliz değerleri açısından karşılaştırıldığında, taşlı yüzük hücreli mide kanserleri ile zayıf kohezif tip mide kanserleri arasında ve metastaz varlığı ile yokluğu arasında anlamlı ilişki bulundu ($p<0.05$).

Sonuç: Diffüz tip mide kanseri hasta serimizde SUV_{max} değerleri diğer mide kanserli hastalara göre daha düşük olmasına rağmen ileri evre diffüz tip mide kanserlerinde erken evre olgulara göre daha yüksek olduğu gözlendi. Ayrıca diffüz tip mide kanseri alt tipleri olan taşlı yüzük hücreli mide kanserleri ile zayıf kohezif tipi mide kanserleri SUV_{max}, SUV_{mean}, metabolik tümör hacmi ve toplam lezyon glikoliz değerleri açısından karşılaştırıldığında anlamlı fark saptanmadı ve bu literatürde bulamadığımız bir bilgidir.

***Anahtar Kelimeler**: Diffüz tip, mide kanseri, taşlı yüzük hücresi, zayıf kohezif, ^{18}F-FDG PET/CT*

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INTRODUCTION

Gastric cancer is one of the most common causes of cancer-related deaths (1). According to Lauren classification, gastric cancers are divided into intestinal and diffuse-types. Poorly cohesive (PC) and Signet-Ring Cell (SRC) are diffuse-type gastric cancers (2). Gastric cancers have different clinical, epidemiological and molecular features. SRC gastric cancer, which is a diffuse-type gastric cancer, is generally considered to have a worse prognosis (3). The majority of diffuse-type gastric cancers consist of SRC containing globoid mucin droplets in the center of the cell and where the nucleus is pushed aside (4).

Positron emission tomography/computed tomography (^{18}F-FDG PET/CT) imaging method using fluoro-2-deoxy-D-glucose is an imaging technique based on increased glucose uptake in malignant cells. It can be used in the detection of many tumors, preoperative staging and follow-up of postoperative tumor recurrence. In addition, ^{18}F-FDG PET/CT can be used to predict the responsiveness of preoperative chemotherapy (5, 6). PET/CT has an important role in the evaluation of lymph node involvement and distant metastases in gastric cancer (7). The SUV_{max} value calculated by PET/CT, showing the uptake value of the FDG uptake at the relevant localization, is a numerical parameter that is calculated semi-quantitatively and shows the tumor metabolism. However, the SUV_{max} value (Maksimum standardized uptake value) may not accurately reflect the metabolic activity of the tumor. FDG uptake is high in gastric tumors, especially in the intestinal type and advanced-stage tumors (8). However, it is known that FDG affinity may be lower than intestinal types in SRC gastric tumors (9). Recently, there are publications reporting that the use of volume-based parameters such as MTV (metabolic tumor volume) and TLG (total lesion glycolysis) has higher specificity and sensitivity than SUV_{max} in terms of survival (10). However, according to the study of Na et al., Unlike SUV_{max}, MTV and TLG were not found as prognostic factors in gastric cancers (11). In our study, visual and quantitative data and clinicopathological data obtained by ^{18}F-FDG PET/CT imaging of patients diagnosed with diffuse-type gastric cancer in a single center were examined, and it was aimed to investigate the relationship of the data with the subtype and stage of the disease.

MATERIALS AND METHODS

Ethics Committe Aproval: Sivas Cumhuriyet University Ethics Committee of Clinical Research, date: 14.04.2021, number: 2021-04/19.

Study Group

According to Lauren's classification in 2016-2020, 44 patients who were diagnosed with SRC gastric cancer and weak PC gastric cancer, which are subtypes of diffuse-type gastric cancer, and who were followed-up and treated in our University Hospital with screening ^{18}F-FDG PET/CT images were included in the study. Retrospective data were obtained with the approval of the local ethics committee and institutional permission for the study. In addition to data such as age, gender, presence of metastases, localization of metastases, PET images and histopathological data were obtained. ^{18}F-FDG PET/CT images of 44 patients included in the study were re-evaluated and clinicopathological data were analyzed.

^{18}F-FDG PET/CT Imaging Procedure, Acquisitions and Analysis

PET/CT imaging was performed with a combined PET/CT scanner (Discovery 600 PET/CT GE Medical Systems, USA). Each patient fasted for at least 6 h before imaging. After ensuring that blood glucose was <180 mg/dL, approximately 0.14 mCi/kg ^{18}F-FDG was administered intravenously 1 h before image acquisition. Attenuation correction of PET images was performed with the CT data. The CT scan was performed firstly and right after the CT acquisition. A standard PET imaging protocol was taken from the cranium to the mid-thigh with an acquisition time of 3

min/bed in 3-dimensional mode. All PET studies were acquired in 3-D mode. CT images were acquired with 70 mA, 120 kV, axial slice thickness of 2.5 mm. CT and PET images were matched and fused into transaxial, coronal, and sagittal images. The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing Workstation (AW Volume Share5 GE Medical Systems S.C.S, France). Then the visual and semi-quantitative analyses were performed respectively. For PET images, an adaptive threshold setting of 42 % of the maximum lesional metabolic activity was used and the ROI was placed within the tumor while avoiding the peripheral area.

SUV_{max}, SUV_{mean} and MTV were calculated from attenuation-corrected ^{18}F-FDG PET images for tumor mass. The SUV_{max} was computed by standard methods from the activity in the most intense voxel in the three-dimensional tumor region from the transaxial whole-body images. The standardized uptake value (SUV) was calculated by the following formula:[Activity of ROI (mCi/ml) × Bodyweight (gram)] ÷ Injected dose (mCi). SUV_{mean} was determined from the average voxel counts within the tumor region. TLG was then calculated as: "TLG=SUV_{mean} X MTV".

If there was no increased FDG uptake in PET images compared to other normal non-tumor areas of the stomach in the primary tumor localization, the SUV_{max} value was accepted as 1.

Statistical Analysis

The obtained data were evaluated with the SPSS 23.0 program (Statistical Package for the Social Sciences, SPSS Inc., Chicago). The normality of the data was examined by the Kolmogorov-Smirnov test. If the data provided the parametric conditions, they were analyzed with the independent sample t-test for two independent groups and the F test (ANOVA) for more than two groups. While using ANOVA for comparisons with more than two groups, Tukey tests were used for those who provided the homogeneity assumption and Tamhane's T2 tests were used for those who did not provide the assumption of homogeneity to determine which group was different from the others. If any or all of the assumptions were not met, the Mann-Whitney U test was used for two independent groups and the Kruskal Wallis test was used for more than two independent groups. A Chi-square test was used to evaluate the data obtained by counting. The level of error was taken as 0.05.

RESULTS

Age, gender, histopathological subtype, tumor localization, presence of diabetes and body mass index data of 44 patients diagnosed with diffuse-type gastric cancer were analyzed. The average age of the patients was 61.93. Sixteen (36.4%) of the patients were female, 28 (63.6%) were male. While 23 (52.3%) of the patients were under 65 years old, 21 (47.7%) were over 65 years old. When 44 patients diagnosed with diffuse-type gastric cancer were examined histopathologically; 36 (81.8%) had SRC gastric cancer, and 8 (18.2%) had weak PC gastric cancer. In 10 of the patients (22.7%), the tumor was associated with the cardia region of the stomach. Seven (15.9%) of the patients were isolated cardia tumors, while 3 (6.8%) were cardia + corpus tumors. While 8.3% (3 patients) of SRC gastric cancers had diabetes, 37.5% (3 patients) of weak PC gastric cancers had diabetes, and the difference between them was significant (p=0,03). When evaluated according to the body mass index, 3 of our patients (6.8%) were thin, 15 (34.1%) were normal weight, 14 (31.8%) were overweight and 12 (27.3%) were obese (Table 1).

While low FDG uptake was observed in the primary tumor localization in 8 of the patients (18.2%), high FDG uptake was detected in 36 patients (81.8%). While low FDG uptake was observed in 1 (12.5%) of the 8 patients with the weak PC type at the primary tumor location, 7 (87.5%) had high FDG uptake. While low FDG uptake was observed in the primary tumor localization in 7 (19.4%) of the gastric cancer patients

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with SRC, high FDG uptake was detected in 29 patients (80.6%) (Table 2).

Table 1: Data of patients diagnosed with diffuse type gastric cancer.

		Patients	%
Age	<65	23	52.3
	>65	21	47.7
Gender	Female	16	36.4
	Male	28	63.6
Subtype	SCR	36	81.8
	PC	8	18.2
Localization	Cardia	10	22.7
	Noncardia	34	77.3

SRC: Signet-Ring Cell, PC: Poorly Cohesive

When evaluated in terms of metastasis, 19 (43.2%) of the patients had metastasis and 90.9% of metastases were associated with abdominal lymphadenopathies (Table 3).

There was a significant relationship between the SUV_{max} value of the tumor localization in the stomach and metastasis. The probability of metastasis was higher in patients with a high median SUVmax value (p=0.047). Median SUV_{max} value was 4.95 in metastatic patients, while median SUV_{max} value was found to be 3.05 in patients without metastasis. While the median SUV_{mean} value was 2.95 in metastatic patients, it was 2.75 in patients without metastasis. When evaluated in terms of Median SUV_{mean}, there was no significant relationship between presence/absence of metastasis. (p=0.574). While the median MTV value was 32.23 in metastatic patients, it was 36.12 in patients without metastasis. When evaluated in terms of median MTV, there was no significant relationship between presence/absence of metastasis (p= 0.693). While the median TLG value was 121.49 in metastatic patients, it was found to be 140.41 in patients without metastasis. When evaluated in terms of median TLG, there was no significant relationship between presence/absence of metastasis (p = 0.901) (Table 4).

There was no statistically significant difference in Median SUV_{max} values measured in malignant tumor localization between gastric cancer with SRC and weak PC type gastric cancer (p= 0.357). Median SUV_{max} value was 4.2 in gastric cancers with SRC, while it was 4.8 in weak PC gastric cancers. While the median SUV_{mean} value was 2.75 in patients with SRC gastric cancer, it was found as 3.25 in patients with weak PC gastric cancer. There was no difference between the groups in terms of median SUV_{mean} values (p= 0.604). While the median MTV value was 32.24 in patients with SRC gastric cancer, it was found as 36.13 in patients with weak PC gastric cancer. There was no difference between the groups in terms of median MTV values (p= 0.678). While the median TLG value was 140.4 in patients with SRC gastric cancer, it was found as 131.97 in patients with weak PC gastric cancer. There was no difference between the groups in terms of median TLG values (p= 0.678) (Tablo 5).

Table 2: FDG uptake level

FDG uptake	Diffuse-Type Gastric Cancer		SRC		PC	
	Patients	Percent	Patients	Percent	Patients	Percent
High	36	81.8	29	80.6	7	87.5
Low	8	18.2	7	19.4	1	12.5
Total	44	100.0	36	100	8	100

FDG: Florodeoksiglukoz, SRC: Signet-Ring Cell, PC: Poorly Cohesive

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Table 3: Metastasis locations

	Number of patients	%
Abdominal LAP	11	57.9
Peritoneum	2	10.5
Abdominal LAP + Bone	1	5.3
Abdominal LAP + Peritoneum + Acid	1	5.3
Abdominal LAP + Supraclavicular LAP	2	10.5
Abdominal LAP + Lung + Bone	1	5.3
Abdominal LAP + Acid	1	5.3
Total	19	100

LAP: Lymphadenopathy

Table 4: Change in SUV_{max}, SUV_{mean}, MTV and TLG data with presence or absence of metastasis

Metastasis	Patients	Median SUV_{max}	Median SUV_{mean}	Median MTV	Median TLG
Yes	25	4.95	2.95	32.23	121.49
No	19	3.05	2.75	36.12	140.41
Total	44	4.35	2.80	34.86	131.97
P		p= 0.047*	p=0.574	p= 0.693	p=0.901

SUV_{max}: Maximum standardized uptake value, SUVmean: Mean standardized uptake value, MTV: Metabolic tumor volüme, TLG: Total lesion glycolysis. *: $p<0.05$

Table 5: Change in SUV_{max}, SUV_{mean}, MTV and TLG results according to diffuse type gastric cancers types

Types	Patients	Median SUV_{max}	Median SUV_{mean}	Median MTV	Median TLG
SRC	36	4.2	2.75	32.24	121.5
PC	8	4.8	3.25	36.13	140.4
Total	44	4.35	2.80	34.86	131.97
P		p= 0.357	p= 0.604	p= 0.678	p=0.678

SRC: Signet-Ring Cell, PC: Poorly cohesive, SUV_{max}: Maximum standardized uptake value, SUVmean: Mean standardized uptake value, MTV: Metabolic tumor volüme, TLG: Total lesion glycolysis.

DISCUSSION

SRC carcinoma of the stomach is a histological type based on microscopic features, and its clinicopathological features and prognosis are still controversial. Although the incidence of gastric cancer has decreased in recent years, the incidence of SRC cancer subtypes, which constitute 11-37% of all gastric cancers, are relatively increasing (12). The World Health Organization defines SRC carcinoma as a PC carcinoma that consists of tumor cells containing prominent cytoplasmic mucin and an eccentrically located crescent-shaped core (13). Surgery is the preferred treatment method, especially in middle and advanced-stage gastric cancer. Early diagnosis, accurate clinical staging and appropriate surgical intervention are known to contribute significantly to prognosis (14). ^{18}F-

FDG PET/CT is a frequently used imaging method that provides both anatomical and functional information in gastric cancer patients in preoperative staging and postoperative follow-up. Studies have been conducted to correlate SUV_{max}, SUV_{mean}, MTV and TLG values obtained from ^{18}F-FDG PET/CT scans with tumor differentiation, liver metastasis, distant metastases and biochemical tumor markers (15, 16).

It has been reported that high FDG uptake may be associated with higher tumor aggressiveness and worse prognosis (15). It has been reported in the literature that the FDG uptake of diffuse-type stomach cancers is lower than other gastric tumors (9, 17-19). In our study, significant FDG uptake was not observed in the tumor localization in ^{18}F-FDG PET/CT in 19.4% of the patients, while high FDG uptake was detected in 80.6% of the patients. Alakuş et al. reported the mean SUVmax in intestinal-type gastric cancer as 7.85 (range, 2.3-14.4), the average SUV_{max} in diffuse-type gastric cancer as 3.1 (range, 1.0-11.5) (19). In addition, some studies have shown that SUV_{max} value in gastric cancer can be associated with prognosis by showing a positive correlation with metastasis (18). In our study, results consistent with the literature were obtained, and a significant relationship was found between the increase in SUV_{max} value and the presence of metastasis, especially for diffuse-type gastric cancer. While SUV_{max} value was 3.05 in non-metastatic diffuse gastric cancers, SUV_{max} value was found as 4.95 in patients with metastatic disease. In our study, although the SUV_{max} value of diffuse-type gastric cancer is lower than the intestinal type, it has been shown that the metastatic diffuse-type increases SUV_{max} relatively. Although it has been shown in a study that high MTV level is associated with poor prognosis (15) in our study, no significant difference was observed between metastatic patients and non-metastatic patients in terms of MTV levels. In addition, when SUV_{mean} was examined in terms of TLG, no significant relationship was observed between the presence of metastases.

Our study observed that SRC gastric cancer, which is a subtype of diffuse-type gastric cancer according to Lauren classification (2) and weak PC gastric cancer, did not have a significant difference in terms of SUV_{max}, SUV_{mean}, MTV and TLG values. These results are information that we do not encounter in the literature.

The literature has reported that gastric cancer is associated with obesity (especially in diffuse-type gastric cancer) and diabetes mellitus (20, 21). When examined in terms of the place of diabetes in etiology in our case series; We have seen that diabetes is detected at a higher rate especially in weak PC type gastric cancer. In addition, the majority of our patients (59.1%) were overweight or obese. However, there is a need for larger patient series in this regard.

The biggest limitation of our study was that it was retrospective and other clinical and radiological findings could not be evaluated.

In conclusion, although studies have reported that FDG uptake may be low in diffuse-type gastric cancer, in our study, the rate of diffuse-type gastric cancer with low FDG up was low. In addition, it was found that SUV_{max} value was higher in patients with metastasis. When SUV_{max}, SUV_{mean}, MTV and TLG values were compared, there was no significant difference between SRC and PC, which are diffuse-type gastric cancer subtypes, and this was an information we could not find in the literature.

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