Original Article
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The Relationship Between HER-2 Expression Levels and ^{18}F-FDG PET/CT Parameters in Gastric Cancer

Mide Kanseri Hastalarında HER-2 Ekspresyon Düzeyleri ve ^{18}F-FDG PET/BT Parametreleri Arasındaki İlişki

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Abstract

Objectives: Human epidermal growth factor receptor-2 (HER-2) is a protooncogene encoded by ERBB2 on chromosome 17. ^{18}Fluoride-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) examination is frequently used to detect distant metastasis in gastric cancer imaging. This study aimed to investigate the relationship between the data obtained in the ^{18}F-FDG PET/CT examination and HER-2 expression status in patients with gastric cancer.

Methods: A total of 115 patients diagnosed with gastric cancer between 2016 and 2020, with HER-2 immunohistochemical followed by ^{18}F-FDG PET/CT examination for staging purposes were included.

Results: HER-2 immunohistochemical examination revealed 71 patients (61.7%) with negative and 44 (38.3%) with positive results. The median maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) values of patients positive with HER-2 were 9.95, 5, 30.44, and 139.16, respectively, whereas patients negative with HER-2 were 9.3,5.4,36.62, and 190.424, respectively (p>0.05). The median cancer antigen 19-9 (CA 19-9) levels of patients positive with HER-2 was 33.52, whereas 11.79 in those who were negative (p=0.016). The mean age was 69.3±9.35 years in patients with distant metastases, whereas 65.2±10.9 in those without distant metastases (p=0.042). Median SUV_{max} and SUV_{mean} values in patients with distant metastases were 11.1 and 6.3, respectively, and 8.2 and 4.5 in those without distant metastases (p=0.002 and p=0.001, respectively). The median CA 19-9 and carcinoembryonic antigen (CEA) levels in patients with distant metastases were 31.34 and 9.20, respectively, whereas those without distant metastases were 11.55 and 2.26, respectively (p=0.011 and p=0.001, respectively).

Conclusion: In our study, no statistically significant difference was found in terms of HER-2 status, SUV_{max}, SUV_{mean}, MTV, TLG, distant metastasis, presence of lymph node metastasis, age, gender, tumor diameter, grade, and localization, and CEA levels in patients with gastric cancer. A statistically significant difference was found between HER-2 status and CA 19-9 levels. A statistically significant relationship was found between distant metastases in the ^{18}F-FDG PET/CT examination and SUV_{max}, SUV_{mean}, age, CEA levels, and histopathologic diagnosis; however, the relationship between distant metastasis in the ^{18}F-FDG PET/CT scan and MTV, TLG, tumor diameter, localization, and grade was not statistically significant.

Keywords: Gastric cancer, PET/CT, HER-2, ^{18}F-FDG

Öz

Amaç: İnsan epidermal büyüme faktörü reseptörü-2 (HER-2) kromozom 17 üzerinde ERBB2 tarafından kodlanan bir protoonkogendir. Mide kanseri görüntülemesinde ^{18}fluoride-florodeoksiglikoz pozitron emisyon tomografi/bilgisayarlı tomografi (^{18}F-FDG PET/BT) tetkiki uzak metastaz taraması için sıklıkla kullanılmaktadır. Bizim bu çalışmadaki amacımız patolojik olarak mide kanseri tanısı konmuş hastalarda ^{18}F-FDG PET/BT tetkikinde elde edilen veriler ile HER-2 ekspresyonu arasındaki ilişkinin araştırılmasıdır.

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Yöntem: Çalışmamıza 2016 ve 2020 yılları arasında mide kanseri tanısı konulmuş, evreleme amacıyla ^{18}F-FDG PET/BT tetkiki yapılmış ve patolojik olarak HER-2 incelemesi yapılmış 115 mide kanseri hastası dahil edilmiştir.

Bulgular: Çalışmamızdaki hastaların HER-2 immünohistokimyasal incelemesine göre 71'i (%61,7) negatif, 44'ü (%38,3) pozitif olarak değerlendirilmiştir. HER-2 pozitif olan hastaların medyan maksimum standartlaştırılmış alım değeri (SUV_{maks}), ortalama standartlaştırılmış alım değeri ($SUV_{ortalama}$), metabolik tümör hacmi (MTV), toplam lezyon glikoliz (TLG) değeri sırasıyla 9,95, 5, 30,44, 139,16 iken, HER-2 negatif olan hastaların ise sırasıyla 9,3, 5,4, 36,62 ve 190,424 idi (p>0,05). HER-2 pozitif olan hastaların medyan CA 19-9 değeri 33,52 iken, negatif olan hastaların 11,79 idi (p=0,016). ^{18}F-FDG PET/BT tetkikinde uzak metastaz bulunan hastalarda ortalama yaş 69,3±9,35 iken, uzak metastaz olmayanlarda ortalama yaş 65,2±10,9 idi (p=0,042). ^{18}F-FDG PET/BT tetkikinde uzak metastaz bulunan hastalarda medyan SUV_{maks} ve $SUV_{ortalama}$ değerleri sırasıyla 11,1 ve 6,3 iken, uzak metastaz olmayanlarda sırasıyla 8,2 ve 4,5 idi (p=0,002, p=0,001 sırasıyla). Uzak metastaz bulunan hastalarda medyan CA 19-9 ve CEA düzeyleri sırasıyla 31,34 ve 9,20 iken, uzak metastaz olmayanlarda sırasıyla 11,55 ve 2,26 idi (p=0,011 ve p=0,001 sırasıyla).

Sonuç: Çalışmamızda mide kanseri hastalarında HER-2 durumu ile SUV_{maks}, $SUV_{ortalama}$, MTV, TLG, uzak metastaz varlığı, lenf nodu metastazı varlığı, yaş, cinsiyet, tümör çapı, tümör derecesi, tümör lokalizasyonu ve CEA düzeyleri açısından istatistiksel olarak anlamlı bir farklılık yoktu ancak HER-2 durumu ile CA 19-9 değerleri arasında istatistiksel olarak anlamlı bir fark bulundu. ^{18}F-FDG PET/BT tetkikinde uzak metastaz bulunması ile SUV_{maks}, $SUV_{ortalama}$, yaş, CEA düzeyleri ve histopatolojik tanı arasında istatistiksel olarak anlamlı bir ilişki saptanırken, MTV, TLG, tümör çapı, tümör lokalizasyonu ve tümör derecesi arasındaki ilişki istatistiksel olarak anlamlı değildi.

Anahtar kelimeler: Mide kanseri, PET/BT, HER-2, ^{18}F-FDG

Introduction

Gastric cancer is one of the most common cancers worldwide (1). Gastric cancer was the most important part of cancer-related deaths until the 1980s but was replaced by lung cancer after these years (2,3). However, most patients with gastric cancer in western society are currently diagnosed as advanced, and despite advances in understanding the biology of gastric cancer, median survival is still under 12 months. Therefore, personalized treatment development is important (4).

Human epidermal growth factor receptor-2 (HER-2) is a protooncogene encoded by ERBB2 on chromosome 17. The main role of HER-2 protein in these tissues is to support cell proliferation and prevent apoptosis. Therefore, it facilitates excessive uncontrolled cell growth and tumorigenesis processes (5). The importance of this protein is understood in patients with breast cancer, and the developed antagonists gave positive results in the treatment, thus, other types of cancer have been investigated. Patients with gastric cancer constitute a significant part of the research carried out in this regard (5,6). The National Comprehensive Cancer Network (NCCN) guidelines recommended tumor HER-2 overexpression assessment using immunohistochemistry and in situ hybridization method in patients with inoperable locally advanced, recurrent, or metastatic gastric adenocarcinoma for whom HER-2 receptor antagonist therapy are considered (6).

^{18}Fluoride-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) examination is frequently used for the detection of distant metastasis in gastric cancer imaging. The role of ^{18}F-FDG PET/CT in the initial diagnosis of gastric cancer is not established. However, ^{18}F-FDG PET/CT examination is recommended in all patients who are clinically indicated according to the NCCN guidelines, without metastases detected by other radiological imaging methods (7).

The determination of HER-2 status became standard in patients with gastric cancer; however, its evaluation requires an invasive procedure. Therefore, the development of noninvasive techniques to predict the HER-2 status is important. Limited publications investigated the relationship between HER-2 status and tumor markers in patients with gastric cancer. Thus, evaluation of PET/CT as a technique for this purpose is important. However, study findings are conflicting on this subject.

This study aimed to investigate the relationship between the data obtained in the ^{18}F-FDG PET/CT examination, HER-2 expression status and histopathological features, the usage of ^{18}F-FDG PET/CT, and level of tumor markers in predicting the HER-2 status in patients with gastric cancer.

Materials and Methods

A total of 115 patients diagnosed with gastric cancer between 2016 March and 2020 January, with HER-2 immunohistochemical examination followed by ^{18}F-FDG PET/CT examination for staging purposes were included in this study. Operable patients diagnosed with endoscopic biopsy were included in the study using ^{18}F-FDG PET/CT examination for staging before surgery, whereas inoperable patients diagnosed with endoscopic biopsy were included in the study with ^{18}F-FDG PET/CT examination before chemotherapy or radiotherapy. A total of 63 patients had a history of operation after diagnosis, wherein 52 were not operated on. Out of 63 patients who were operated on, 11 had distant metastasis on FDG PET/CT examination and 52 had none. This study was conducted following the principles of the Declaration of Helsinki. This study was approved by Cumhuriyet University Non-interventional

Clinical Research Ethics Committee with decision number: 2019-09/05. Verbal and written consent forms were obtained from all study participants.

Imaging Protocol with ^{18}F-FDG PET/CT: Patients were asked for at least 4-6 hours of fasting, and blood glucose measurements of all patients were done before the imaging. Radiopharmaceutical injection was given to patients with fasting blood glucose <200 mg/dL. An average of 10 mCi of ^{18}F-FDG was administered to the patients during the ^{18}F-FDG PET/CT examination.

All patients were kept in the restroom for 45-60 min after the injection. The imaging of patients was performed with a General Electric Discovery PET/CT 600 device (GE Medical Systems, LLC, 3000 N. GRANDVIEW BLVD., WAUKESHA, WI., U.S.A.). CT imaging was performed at 120 kV, 172 mAs with a spiral 16 slice scanner for attenuation correction and anatomical correlation. PET imaging was performed in 3 dimensions to cover the body part from the vertex to the middle of the thigh, including the cranium with 3 dimensions, and PET imaging was performed for approximately 2 min in each bed position. Axial, coronal, and sagittal fusion images were created using the iterative reconstruction method. Maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) values were calculated from the PET images. An adaptive threshold setting of 42% of the maximum lesional metabolic activity was used for PET images and the region of interest (ROI) was placed within the primary tumor in the stomach while avoiding the peripheral area. SUV_{max} measurement of metastatic lymph nodes and distant metastatic lesions was not evaluated.

The SUV was calculated with the following formula:

[Activity in ROI (mCi/mL) × Bodyweight (gram)] ÷ Injected Dose (mCi)

TLG reflects the metabolic activity of the entire tumor and was calculated by multiplying the MTV by the SUV_{mean} value. An adaptive threshold setting of 42% of the maximum lesional metabolic activity was used for PET images and the ROI was placed within the tumor while avoiding the peripheral area (8).

Immunohistochemical Staining: Hematoxylin-eosin stained sections prepared from formalin-fixed paraffin blocks were examined, and from the paraffin blocks of these preparations, 3 micron thick sections were taken into the positively charged slide. Immunohistochemical staining of tissues with completed deparaffinization was performed in ROCHE VENTANA BENCHMARK XT (Ventana Medical Systems, Tucson, Arizona, USA) automated staining device using a c-erbB-2 antibody (PATHWAY anti-HER-2/neu clone 4B5, Rabbit Monoclonal Primary Antibody, Ventana Medical Systems, Tucson, Arizona, USA, 2017) in a ready-to-use form. HER-2 positivity was determined using a light microscope.

Immunohistochemical Assessment: Only the membranous staining was considered significant in the immunohistochemical c-erbB-2 staining evaluation, whereas the cytoplasmic granular and nuclear staining were not evaluated. The modified form of the HercepTest scoring system was used for gastric cancers (9,10). All cases were divided into four groups as score 0, score 1+, score 2+, and score 3+. Patients with immunohistochemical staining scores of 0 and 1+ were considered negative, whereas scores 2+ and 3+ were accepted as positive (11).

Statistical Analysis

The data obtained were evaluated with Statistical Package for the Social Sciences 23.0 program (SPSS Inc., Chicago). The Kolmogorov-Smirnov test was used to check the normality of the data. An independent sample t-test for two independent groups and the F-test [analysis of variance (ANOVA)] test for more than two groups were used for data with parametric conditions. ANOVA was used to compare more than two groups, whereas the Tukey tests were used in those with homogeneity assumption and Tamhane's T2 tests in those without homogeneity assumption to determine which group is different from the others. The Mann-Whitney U test was used for two independent groups and the Kruskal-Wallis test for more than two independent groups if any or all assumptions are not provided. Chi-square test was used to evaluate the data obtained by counting. The margin of error was taken as 0.05. The tests performed for sample volume calculation revealed a standard deviation related to the A event as 6, with the margin of error as 1.2, whereas the sample volume calculation before the study determined the sample size as 96.

Results

A total of 115 patients [85 men (73.9%), 30 women (26.1%)] were included in this study, with the patient tumor characteristics presented in Table 1. The histopathological subtypes of patients by Lauren classification revealed 9 (7.8%) with diffuse type, 101 (87.8%) with intestinal type, and 5 (4.3%) with mixed type. The group with intestinal-type gastric carcinoma revealed 4 (3.5%) patients with intramucosal carcinoma. The group with diffuse-type gastric carcinoma revealed four (3.5%) patients with signet ring cell carcinoma and five (4.3%) with poorly cohesive carcinoma. Patients with adenocarcinoma revealed 29 with poorly differentiated adenocarcinoma, 30 with

Table 1. Age, gender, histopathological diagnosis, tumor location, presence of distant metastasis, and lymph node metastasis in ^{18}F-FDG PET/CT, HER-2 expression distribution of patients

	Number (n)	Percentage (%)
Gender		
Male	85	73.9%
Female	30	26.1%
Total	115	100%
Age (mean ± standard deviation)	66.70±10.52	-
Histopathologic diagnosis		
Diffuse type	9	7.8%
Signet ring cell carcinoma	4	3.5%
Poorly cohesive carcinoma	5	4.3%
Intestinal type	101	87.8%
Invasive adenocarcinoma	97	84.3%
Intramucosal carcinoma	4	3.5%
Mixed carcinoma	5	4.3%
Total	115	100%
Tumor localization		
Cardia	34	29.6%
Non-cardia	81	70.4%
Corpus	29	25.2%
Antrum	45	39.1%
Lesser curvature	4	3.5%
Fundus	1	0.9%
Greater curvature	1	0.9%
Diffuse	1	0.9%
Total	115	100%
Distant metastasis in ^{18}F-FDG PET/CT		
Absent	73	63.5%
Present	42	36.5%
Total	115	100%
Lymph node metastasis ^{18}F-FDG PET/CT		
Absent	55	47.8%
Present	60	52.2%
Total	115	100%
HER-2 expression status		
Negative	71	61.7%
Positive	44	38.3%
Total	115	100%
HER-2 expression score		
0	58	50.4%
1+	13	11.3%
2+	29	25.2%
3+	15	13%
Total	115	100%

HER-2: Human epidermal growth factor receptor-2, ^{18}F-FDG PET/CT: ^{18}Fluoride-fluorodeoxyglucose positron emission tomography/computed tomography

moderately differentiated adenocarcinoma, and 2 with well-differentiated adenocarcinoma.

HER-2 immunohistochemical examinations were performed in all patients, wherein 58 (50.4%) were negative, 13 (11.3%) were 1+, 29 (25.2%) were 2+, and 15 (13%) were 3+. According to the HER-2 immunohistochemical examination of patients, 71 (61.7%) were negative and 44 (38.3%) were positive.

No statistically significant relation was found between HER-2 and age, gender, SUV_{max}, SUV_{mean}, MTV, TLG, tumor diameter, presence of distant metastasis and lymph node metastasis in ^{18}F-FDG PET/CT, tumor histopathologic subtype, tumor grade, and tumor localization (p=1.0, 0.507, 0.959, 0.751, 0.661, 0.627, 0.802, 0.086, 0.418, 0.371, 0.713, and 0.677, respectively). Median tumor SUV_{max} of patients was 10.73±6.35 [minimum (min): 3.2, maximum (max): 49.6]; tumor SUV_{mean} value was 6.07±3.92 (min: 1.7, max: 30.7); TLG value was 295.981±464 (min: 4.428, max: 3438.400); and MTV value was 44.4±41.01 (min: 1.64, max: 228). The median SUV_{max} of patients positive with HER-2 was 9.95 (min: 3.2, max: 49.6), whereas the median SUV_{max} of patients with negative HER-2 was 9.3 (min: 3.3, max: 31.7) (p=0.959). The median SUV_{mean} value of patients with positive HER-2 was 5 (min: 1.7, max: 30.7), whereas 5.4 for patients with negative HER-2 (min: 1.7, max: 19.5) (p=0.751). The median MTV value of patients with positive HER-2 was 30.44 (min: 1.64, max: 205), whereas 36.62 for patients with negative HER-2 (min: 1.86, max: 228) (p=0.661). The median TLG value of patients positive with HER-2 was 139.16 (min: 4.428, max: 3438.400), where 190.424 for patients with negative HER-2 (min: 8.624, max: 2553.600) (p=0.627). The separate statistical group evaluation of patients with positive and negative HER-2 in terms of distant metastasis revealed 45.5% of patients with positive HER-2 had distant metastasis on PET/CT examination, whereas 31% of patients with negative HER-2 had distant metastasis (p=0.117). The mean tumor diameter of patients with positive HER-2 was 4.93±2.11 cm, whereas 5.25±2.68

cm in patients with negative HER-2 (p=0.802) (Table 2). ^{18}F-FDG PET/CT examination of patients with positive HER-2 revealed 20 (45.5%) patients with distant metastasis and 24 (54.5%) without distant metastasis. ^{18}F-FDG PET/CT examination of patients with negative HER-2 revealed 22 (31%) patients with distant metastasis and 49 (69%) without distant metastasis (p>0.05, p=0.086).

Table 2. Relationship between HER-2 and age, gender, metabolic PET parameters, tumor diameter, presence of distant metastasis and lymph node metastasis in ^{18}F-FDG PET/CT, tumor grade, tumor localization, CA 19-9 levels, and CEA levels

	HER-2 (+) n (%)	HER-2 (-) n (%)	p
Age	66.7±10.2	66.7±10.8	1.0
Gender			
Female	11 (25%)	19 (26.8%)	0.507
Male	33 (75%)	52 (73.2%)	
SUV_{max} (median)	9.95	9.3	0.959
SUV_{mean} (median)	5	5.4	0.751
MTV (median)	30.44	36.62	0.661
TLG (median)	139.16	190.424	0.627
Tumor diameter	4.93±2.11 cm	5.25±2.68 cm	0.802
Distant metastasis in ^{18}F-FDG PET/CT			
Present	20 (45.5%)	22 (31%)	0.086
Absent	24 (54.5%)	49 (69%)	
Lymph node metastasis ^{18}F-FDG PET/CT			
Present	24 (54.5%)	36 (50.7%)	0.418
Absent	29 (45.5%)	35 (49.3%)	
Tumor grade			
Grade 1	2 (9.5%)	3 (6.8%)	0.713
Grade 2	13 (61.9%)	24 (54.5%)	
Grade 3	6 (28.6%)	17 (38.6%)	
Tumor localization			
Cardia	14 (31.8%)	20 (28.2%)	0.677
Non-cardia	30 (68.2%)	51 (71.8%)	
Corpus	11 (25%)	18 (25.4%)	
Antrum	16 (36.4%)	29 (40.8%)	
Lesser curvature	1 (2.3%)	3 (4.2%)	
Fundus	1 (2.3%)	0	
Greater curvature	0	1 (1.4%)	
Diffuse	1 (2.3%)	0	
CA 19-9	33.52	11.79	**0.016***
CEA	3.23	2.31	0.158

HER-2: Human epidermal growth factor receptor-2, ^{18}F-FDG PET/CT: ^{18}Fluoride-fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value, SUV_{mean}: Mean standardized uptake value

^{18}F-FDG PET/CT examination of patients with positive HER-2 revealed 24 (54.5%) patients with lymph node metastasis and 20 patients (45.5%) without lymph node metastasis. ^{18}F-FDG PET/CT examination of patients with positive HER-2 revealed 36 (50.7%) patients with lymph node metastasis in and 35 (49.3%) without lymph node metastasis (p=0.418).

No statistically significant relationship was found between HER-2 status and tumor grade. Two (9.5%) patients with positive HER-2 had grade 1, 13 (61.9%) had grade 2, and 6 (28.6%) had grade 3. Three (6.8%) of the patients with negative HER-2 had grade 1, 24 (54.5%) had grade 2, and 17 (38.6%) had grade 3 (p=0.713). No statistically significant relationship was found between the HER-2 status and tumor localization (p=0.677).

The median CA 19-9 value of patients with positive HER-2 was 33.52 U/mL (min: 2.52, max: 36310), whereas 11.79 U/mL in patients with negative HER-2 (min: 0.95, max: 1000), which was statistically significant (p=0.016). However, no significant relationship was found between the CEA and HER-2, and the median CEA value of patient with positive HER-2 was 3.23 ng/mL (min: 0.75, max: 415.3), whereas 2.31 ng/mL in patients with negative HER-2 (min: 0.53, max: 1000) (p=0.158) (Table 2).

^{18}F-FDG PET/CT evaluation of the relationship between the distant metastasis and tumor histopathological subtype revealed no distant metastases in nine patients with diffuse-type tumor, whereas four had lymph node metastasis. A total of 60 patients with intestinal-type tumors did not have metastases, whereas 41 had distant metastases. Four patients with mixed tumors did not have distant metastases, whereas one patient had distant metastases, which was statistically significant (p=0.039).

The relationship between presence of distant metastasis in ^{18}F-FDG PET/CT and CA 19-9 levels revealed a median CA 19-9 level of 31.34 U/mL (min: 4.30, max: 36.310) in patients with distant metastasis, whereas 11.55 U/mL (min: 0.95, max: 1.000) in patients without distant metastasis (p=0.011). The relationship between the presence of distant metastasis in ^{18}F-FDG PET/CT and CEA levels revealed a median CEA level of 9.20 ng/mL (min: 0.74, max: 1.000) in patients with distant metastases, whereas 2.26 ng/mL (min: 0.53, max: 280) in patients without distant metastases (p=0.001) (Table 3).

Discussion

Study results revealed the mean SUV_{max} value of patients with positive HER-2 of 9.95, whereas 9.3 in patients with negative HER-2, which was not statistically significant. CA 19-9 levels and the incidence of distant metastasis

were higher in patients with positive HER-2. Contrarily, a statistically significant relationship was found between the distant metastasis in ^{18}F-FDG PET/CT examination and SUV_{max}, SUV_{mean}, age, histopathologic subtype, and CEA levels.

Table 3. The relationship between the presence of distant metastasis in ^{18}F-FDG PET/CT and age, gender, metabolic PET parameters, tumor diameter, grade, and localization, CA 19-9, and CEA levels

	Patients with distant metastasis in ^{18}F-FDG PET/CT	Patients without distant metastasis in ^{18}F-FDG PET/CT	p
Age	69.3±9.35	65.2±10.9	**0.042***
Gender			
Female	12 (28.6%)	18 (24.7%)	0.402
Male	30 (71.4%)	55 (75.3%)	
SUV_{max}	11.1	8.2	**0.002***
SUV_{mean}	6.3	4.5	**0.001***
MTV	32.75	35.82	0.822
TLG	187.62	133.635	0.180
Tumor diameter	5.5	4.75	0.552
Tumor grade			
Grade 1	0	5 (100%)	0.297
Grade 2	9 (24.3%)	28 (75.7%)	
Grade 3	3 (13%)	20 (87%)	
Tumor localization			
Cardia	14 (41.2%)	20 (58.8%)	0.502
Non-cardia	28 (34.6%)	53(64.4%)	
Corpus	10 (34.4%)	19 (65.6%)	
Antrum	16 (35.6%)	29 (64.4%)	
Lesser curvature	2 (50%)	2 (50%)	
Fundus	0	1 (100%)	
Greater curvature	0	1 (100%)	
Diffuse	0	1 (100%)	
Histopathologic diagnosis			
Diffuse type	0	9 (100%)	**0.039***
Intestinal type	41 (40.6%)	60 (59.4%)	
Mixed carcinoma	1 (20%)	4 (80%)	
CA 19-9	31.34	11.55	**0.011***
CEA	9.20	2.26	**0.001***

*p<0.05, HER-2: Human epidermal growth factor receptor-2, ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, SUV_{max}: Maximum standardized uptake value, SUV_{mean}: Mean standardized uptake value

A limited number of publications evaluated the HER-2 status in patients with gastric cancer, together with the parameters obtained in the ^{18}F-FDG PET/CT examination. One of these limited studies was by Park et al. (12) compared the parameters obtained in PET/CT in 124 patients with gastric cancer who had ^{18}F-FDG PET/CT before the first stage of chemotherapy and the HER-2 status of the patient. In their study, mean SUV_{max} values were 12.1 in patients with gastric cancer having positive HER-2, whereas 7.4 in patients with gastric cancer having negative HER-2, which was statistically significant. Patients with positive HER-2 with higher metabolic tumor burden among those treated with Trastuzumab had worse overall survival but without difference in progression-free survival. In the same study, SUV_{mean}, MTV, and TLG values were also higher in a patient with positive HER-2, whereas no statistically significant differences were found in our study. However, only metastatic and recurrent patients with gastric cancer were included in this study, whereas all patients with or without metastases who underwent PET/CT scans for primary staging were included in our study. The difference between the studies between HER-2 examination and PET/CT parameters is due to the difference in the patient population. In a study by Kim and Young Park (13) comparing HER-2 expression status and SUV_{max} values of 109 patients who were operated on for gastric cancer and had preoperative ^{18}F-FDG PET/CT, SUV_{max} values were significantly higher in patients with positive HER-2.

According to the study conducted by Celli et al. (14), similar to our study, no statistically significant difference was found between the SUV_{max} value obtained in PET/CT and HER-2 status of patients, and the cumulative death incidence was 60% in patients whose SUV_{max} value was above 6.6 during the study period, whereas the cumulative death incidence was 18% in patients below 6.6. Similar to our study, no significant relationship was found between the tumor size, presence of lymph node metastasis in patients, and HER-2 status. In the same study, the average age of patients with positive HER-2 was 70 years, whereas the mean age of patients with negative HER-2 was 67 years, which was not statistically significant. In our study, the mean age of patients with positive HER-2 was 66.7±10.2 years, whereas the mean age of patients with negative HER-2 was 66.7±10.8 years. Similarly, no statistically significant difference was found between the mean ages.

The study of Chen et al. (15) compared the data obtained in the ^{18}F-FDG PET/CT examination with the HER-2 status in 64 patients with gastric cancer who were not operated on. This study revealed a statistically significant correlation between the HER-2 expression and SUV_{max} when the signet ring cell carcinomas were included. The mean SUV_{max}

values of patients with positive HER-2 were 6.893±5.495, whereas 3.673±2.352 in patients with negative HER-2. A significant relationship was found between the HER-2 status and SUV_{max} values when signet ring cell carcinomas were excluded, and the mean SUV_{max} values of patients with positive HER-2 were 8.619±5.878, whereas 3.789±2.613 in patients with negative HER-2. They were able to detect HER-2 status with 64.4% accuracy when the SUV_{max} cut-off value was 6.2. Therefore, PET/CT examination is used to predict HER-2 status when signet ring cell carcinomas were excluded. However, our study revealed that the relationship between the HER-2 and PET/CT parameters remained even when signet ring cell carcinomas were excluded.

The study conducted by Bai et al. (16) revealed a mean SUV_{max} value in patients with gastric adenocarcinoma of 9.22 in HER-2 positive tumors and 5.02 in HER-2 negative tumors, which was statistically significant. In this study, only operable patients were evaluated, and inoperable patients were not evaluated. However, in our study, both operable and inoperable patients were evaluated. The difference between the studies between HER-2 examination and PET/CT parameters is due to the difference in the patient population. In the same study, SUV_{max} values were linearly correlated with CA 19-9 values. Therefore, the CA 19-9 value was a parameter used to predict the SUV_{max} value. Likewise, the SUV_{max} value is used to predict the HER-2 status. The study conducted by Zhou et al. (17) including 256 gastric cancer patients revealed no statistically significant correlation between the CA 19-9 levels and HER-2. However, they concluded that HER-2 and CA 19-9 levels are independent prognostic factors in patients with gastric cancer. In our study, the median CA 19-9 value of patients with positive HER-2 was 33.52, whereas 11.79 in patients with negative HER-2, which was statistically significant (p=0.011).

Study Limitations

One of the main limitations of our study was that HER-2 immunohistochemical analysis was performed on all patients, gene amplification analysis was performed with the *in situ* hybridization technique in addition to 17 of the patients with 2+HER-2 immunohistochemical analysis result; however, this analysis was not done to the 12 patients. All patients had a pathological diagnosis and macroscopic type of tumor and tumor diameter parameters were included in the operated patients, but these parameters were not included in the non-operated patients.

Conclusion

A significant relationship was not found between the PET/CT parameters and HER-2 status in patients with gastric cancer; however, a statistically significant relationship was found between the HER-2 expression level and CA 19-9 values. Contrarily, a statistically significant relationship was found between the distant metastasis in ^{18}F-FDG PET/CT examination and SUV_{max}, SUV_{mean}, age, histopathologic subtype, and CEA levels, thus evaluating these data primarily in the treatment plan and follow-up of patients is important. In addition, the rate of distant metastasis increases with age in patients with gastric cancer, and increased CA 19-9 and CEA levels raise suspicion of distant metastasis in patients. However, the use of immunohistochemical and *in situ* hybridization techniques together with the addition of survival data in a wider patient population of this study will contribute more to the literature.

Ethics

Ethics Committee Approval: This study was approved by Cumhuriyet University Non-interventional Clinical Research Ethics Committee with decision number 2019-09/05.

Informed Consent: Verbal and written consent forms were obtained from all study participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.E, Z.H., H.Ö., Concept: S.A.E, Z.H., H.Ö., Design: S.A.E, Z.H., H.Ö., Data Collection or Processing: S.A.E., Z.H., Analysis or Interpretation: S.A.E., Z.H., Literature Search: S.A.E., Z.H., Writing: S.A.E, Z.H.,H.Ö.

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