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

Seyit Ahmet Ertürk¹, Zekiye Hasbek², Hatice Özer³

¹TR. Ministry of Health, Tokat State Hospital, Nuclear Medicine Unit, Tokat, Turkey
²Sivas Cumhuriyet University Faculty of Medicine, Department of Nuclear Medicine, Sivas, Turkey
³Sivas Cumhuriyet University Faculty of Medicine, Department of Pathology, Sivas, Turkey

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 ($\text{SUV}_{\text{max}}$), mean standardized uptake value ($\text{SUV}_{\text{mean}}$), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) values of patients positive with HER-2 were 9.95, 5.3, 30.44, and 139.16, respectively, whereas patients negative with HER-2 were 9.3, 5.4, 36.62, and 190.42, 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 $\text{SUV}_{\text{max}}$ and $\text{SUV}_{\text{mean}}$ 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, $\text{SUV}_{\text{max}}$, $\text{SUV}_{\text{mean}}$, 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 $\text{SUV}_{\text{max}}$, $\text{SUV}_{\text{mean}}$, 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 sıklaşa kullanılmaktadır. Bizim çalışmadaki amaçımız patolojik olarak mide kanseri tanı konmuş hastalarda $^{18}$F-FDG PET/BT tetkikinde elde edilen veriler ile HER-2 ekspresyonunu arasındaki ilişkisinin araştırılmasıdır.

Address for Correspondence: Seyit Ahmet Ertürk MD, T.R. Ministry of Health, Tokat State Hospital, Nuclear Medicine Unit, Tokat, Turkey
Phone: +90 346 258 02 61 E-mail: seytahmet1988@gmail.com ORCID ID: orcid.org/0000-0002-6030-9662
Received: 21.01.2021 Accepted: 12.05.2021

©Copyright 2021 by Turkish Society of Nuclear Medicine
Molecular Imaging and Radionuclide Therapy published by Galenos Yayınevi.
**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 tumorogenesis 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).

$^{18}$F-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 ¹⁸F-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 ¹⁸F-FDG was administered to the patients during the ¹⁸F-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\textsubscript{max}), mean standardized uptake value (SUV\textsubscript{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\textsubscript{max} measurement of metastatic lymph nodes and distant metastatic lesions was not evaluated.

The SUV was calculated with the following formula:

\[
\text{SUV} = \frac{\text{Activity in ROI (mCi/mL) \times Bodyweight (gram)}}{\text{ Injected Dose (mCi)}}
\]

TLG reflects the metabolic activity of the entire tumor and was calculated by multiplying the MTV by the SUV\textsubscript{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
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\text{max}, SUV\text{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\text{max} of patients was 10.73±6.35 [minimum (min): 3.2, maximum (max): 49.6]; tumor SUV\text{mean} value was 6.07±3.92 (min: 1.7, max: 30.7); TLG value was 295.98±464 (min: 4.428, max: 3438.400); and MTV value was 44.4±41.01 (min: 1.64, max: 228). The median SUV\text{max} of patients positive with HER-2 was 9.95 (min: 3.2, max: 49.6), whereas the median SUV\text{max} of patients with negative HER-2 was 9.3 (min: 3.3, max: 31.7) ($p=0.959$). The median SUV\text{mean} value of patients positive with 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

| 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% |

| Table 1. Continued |
|---|---|---|
| **HER-2 expression score** | **Number (n)** | **Percentage (%)** |
| 0 | 58 | 50.4% |
| 1+ | 13 | 11.3% |
| 2+ | 29 | 25.2% |
| 3+ | 15 | 13% |
| Total | 115 | 100% |

HER-2: Human epithelial growth factor receptor-2, $^{18}$F-FDG PET/CT: $^{18}$Fluoride-fluorodeoxyglucose positron emission tomography/computed tomography.
cm in patients with negative HER-2 (p=0.802) (Table 2). 18F-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. 18F-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). 18F-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).

18F-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 18F-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 18F-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\textsubscript{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 and the incidence of distant metastasis

| Table 2. Relationship between HER-2 and age, gender, metabolic PET parameters, tumor diameter, presence of distant metastasis and lymph node metastasis in 18F-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\textsubscript{max} (median) | 9.95 | 9.3 | 0.959 |
| SUV\textsubscript{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 18F-FDG PET/CT |
| Present | 20 (45.5%) | 22 (31%) | 0.086 |
| Absent | 24 (54.5%) | 49 (69%) |
| Lymph node metastasis 18F-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, 18F-FDG PET/CT: 18Fluoride-fluorodeoxyglucose positron emission tomography/computed tomography, SUV\textsubscript{max}: Maximum standardized uptake value, SUV\textsubscript{mean}: Mean standardized uptake value
were higher in patients with positive HER-2. Contrarily, a statistically significant relationship was found between the distant metastasis in 18F-FDG PET/CT examination and SUV\textsubscript{max}, SUV\textsubscript{mean}, age, histopathologic subtype, and CEA levels.

### Table 3. The relationship between the presence of distant metastasis in 18F-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 18F-FDG PET/CT | Patients without distant metastasis in 18F-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\textsubscript{max} | 11.1                                               | 8.2                                                  | 0.002*  |
| SUV\textsubscript{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, 18F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, SUV\textsubscript{max}: Maximum standardized uptake value, SUV\textsubscript{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 18F-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 18F-FDG PET/CT before the first stage of chemotherapy and the HER-2 status of the patient. In their study, mean SUV\textsubscript{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\textsubscript{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\textsubscript{max} values of 109 patients who were operated on for gastric cancer and had preoperative 18F-FDG PET/CT, SUV\textsubscript{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\textsubscript{max} value obtained in PET/CT and HER-2 status of patients, and the cumulative death incidence was 60% in patients whose SUV\textsubscript{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 18F-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\textsubscript{max} when the signet ring cell carcinomas were included. The mean SUV\textsubscript{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\(_{\text{max}}\) values when signet ring cell carcinomas were excluded, and the mean SUV\(_{\text{max}}\) 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\(_{\text{max}}\) 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\(_{\text{max}}\) 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\(_{\text{max}}\) values were linearly correlated with CA 19-9 values. Therefore, the CA 19-9 value was a parameter used to predict the SUV\(_{\text{max}}\) value. Likewise, the SUV\(_{\text{max}}\) 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 \(^{18}\text{F}-\text{FDG}\) PET/CT examination and SUV\(_{\text{max}}\), SUV\(_{\text{mean}}\), 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.

**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.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer 1993;55:891-903.
3. Parkin DM. Epidemiology of cancer: global patterns and trends. Toxicol Lett 1998;102-103:227-34.
4. Digkiat A, Wagner AD. Advanced gastric cancer: Current treatment landscape and future perspectives. World J Gastroenterol 2016;22:2403-2414.
5. Boku N. HER2-positive gastric cancer. Gastric Cancer 2014;17:1-12.
6. Meric-Bernstam F, Johnson AM, Dumbrava EEI, Raghav K, Balaji K, Bhatt M, Murthy RK, Rodon J, Piha-Paul SA. Advances in HER2-Targeted Therapy: Novel Agents and Opportunities Beyond Breast and Gastric Cancer. Clin Cancer Res 2019;25:2033-2041.
7. Nicole McMillian N, Lenora Pluchino MA, Ajani JA, D TA, Chair V, Bentrem DJ, et al. Gastric Cancer Continue NCCN Guidelines Panel Disclosures. 2019.

8. Fox JJ, Austran-Blanc E, Morris MJ, Gavane S, Nehmeh S, Van Nuffel A, Gönen M, Schöder H, Humm JL, Scher HI, Larson SM. Practical approach for comparative analysis of multileision molecular imaging using a semiautomated program for PET/CT. J Nucl Med 2011;52:1727-1732.

9. Bartley AN, Washington MK, Ventura CB, Ismaila N, Colasacco C, Benson AB 3rd, Carrato A, Gulley ML, Jain D, Kakar S, Mackay HJ, Streutker C, Tang L, Troxell M, Ajani JA. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Am J Clin Pathol 2016;146:647-669.

10. Hofmann M, Stoss Q, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschoff J, Henkel T. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008;52:797-805.

11. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 2014;138:241-256.

12. Park JS, Lee N, Beom SH, Kim H5, Lee CK, Rha SY, Chung HC, Yun M, Cho A, Jung M. The prognostic value of volume-based parameters using 18F-FDG PET/CT in gastric cancer according to HER2 status. Gastric Cancer 2018;21:213-224.

13. Kim JS, Young Park S. (18)F-FDG PET/CT of advanced gastric carcinoma and association of HER2 expression with standardized uptake value. Asia Ocean J Nucl Med Biol 2014;2:12-18.

14. Celli R, Colunga M, Patel N, Djekidel M, Jain D. Metabolic Signature on 18F-FDG PET/CT, HER2 Status, and Survival in Gastric Adenocarcinomas. J Nucl Med Technol 2016;44:234-238.

15. Chen R, Zhou X, Liu J, Huang G. Relationship Between 18F-FDG PET/CT Findings and HER2 Expression in Gastric Cancer. J Nucl Med 2016;57:1040-1044.

16. Bai L, Guo CH, Zhao Y, Gao JG, Li M, Shen C, Guo YM, Duan XY. SUVmax of 18F-FDG PET/CT correlates to expression of major chemotherapy-related tumor markers and serum tumor markers in gastric adenocarcinoma patients. Oncol Rep 2017;37:3433-3440.

17. Zhou H, Dong A, Xia H, He G, Cui J. Associations between CA19-9 and CA125 levels and human epidermal growth factor receptor 2 overexpression in patients with gastric cancer. Oncol Lett 2018;16:1079-1086.