The relationship between HER 2 expression and ^{18}F-FDG in gastric carcinoma

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Abstract

Objective: The aim of this retrospective study was to evaluate the relationship between human epidermal growth factor receptor 2 (HER2) expression and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake in positron emission tomography with computed tomography (PET/CT) in gastric carcinoma. **Materials and Methods:** Gastric carcinoma patients who had ^{18}F-FDG PET/CT scans before treatment were enrolled in this study. Ninety PET/CT images were evaluated before resection or neoadjuvant treatment of 69 patients with gastric carcinoma who had HER2 examination tests. The maximum standardized uptake value (SUVmax) at early (SUV1) and delayed images (SUV2) if any were calculated. In addition, liver SUVmax was measured from the normal liver parenchyma at the dual time (SUV1liver and SUV2 liver). Tumor-to-liver SUVmax ratio (TLR), retention indexes (RI) from SUVmax, and TLR values obtained from dual-time images were calculated. **Results:** Histological type of 69 patients were 85.5% adenocarcinoma, 10.1% signet ring cell carcinoma, 2.9% adenosquamous carcinoma, 1.4% mucinous adenocarcinomas. Human epidermal growth factor receptor 2 negative group included 56 (81.2%) patients and the positive group had 10 (14.35%) patients. We did not find any statistical difference for the values of SUVmax and tumor-to-liver SUVmax on all histological types of gastric carcinoma on the dual-phase PET scan. High-level SUV1 was found in the HER2 positive group (8.01±3.11) than negative group (6.15±3.76) in early PET/CT imaging (P=0.043) for adenocarcinoma patients. A positive correlation was observed between HER2 and SUV1 in adenocarcinoma patients (r=0.254,P=0.042). An inverse correlation was determined for histological grade with SUV1 (r=-0.29,P=0.048), TLR1 (r=-0.29,P=0.048) and TLR2 (r=-0.324, P=0.03). **Conclusion:** Patients with HER2 expression in gastric adenocarcinomas had higher SUVmax values, but no significant difference was found between the groups when the tumor/liver ratio was measured by SUVmax from normal liver parenchyma when background activity was excluded. Signet ring cell carcinoma type and the presence of the signet ring component had no effect on ^{18}F-FDG uptake.

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Introduction

Human epidermal growth factor receptor 2 (HER2) is known as CerbB-2 or ERBB2 is a protooncogene on the 17q21 chromosome. It codes a transmembranous protein having tyrosine kinase activity, and it causes cell growth and differentiation [1]. In gastric carcinoma, it is thought to cause higher proliferation activity of tumor cells [2]. Amplification of the HER2 gene was first discovered in breast cancer and overexpression of the product was significantly associated with worse prognosis[3]. Many studies have shown that HER2 is also found in certain other malignancies, including colorectal cancer, ovarian cancer, prostate cancer, lung cancer, and particularly stomach and gastroesophageal cancer [4]. Currently, HER2 is routinely looked at in gastric carcinoma to evaluate patient selection and response to anti-HER2 antibody therapy. However, the HER2 evolution is different from testing in breast cancer because of differences in tumor biology, intratumorally heterogeneity of HER2 expression, incomplete membrane staining is widely seen in gastric tumors [5].

The aim of this study was to evaluate the relationship between HER2 expression and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake in positron emission tomography with computed tomography (PET/CT) in gastric carcinoma.

Materials and Methods

Patients

In this study, we retrospectively reviewed the medical records of all gastric carcinoma

patients who had ^{18}F-FDG PET/CT scan as part of a staging workup before treatment at our institution and the HER2 test were enrolled in this study. Ninety PET/CT images before resection orneoadjuvant treatment of 69 patients (mean age: 60.52±11.34 years, 20 female and 49 males) with gastric carcinoma who had HER2 examination tests were evaluated. Gastric carcinoma was diagnosed by endoscopic biopsy or from gastrectomy specimen in all patients before ^{18}F-FDG PET/CT imaging. This retrospective study was approved by the local Ethics Committee (Decision no: 2934).

^{18}F-FDG PET/CT protocol and image analysis

For PET/CT imaging, blood glucose levels were checked after patients were fasted for at least six hours, then 3.7-5.2MBq/kg (0.1-0.2mCi/kg) ^{18}F-FDG was injected intravenously. Also, an oral contrast agent was used. All patients were rested in a quiet room during the waiting period after injection. They emptied their bladder before the scan. Whole-body ^{18}F-FDG PET/CT imaging at 1 hour was acquired from the skull base to the mid-thighs in supine position with a Gemini GXL PET/CT scanner (Philips Healthcare, Cleveland, Ohio, USA). A CT image was obtained firstly from the integrated PET/CT scanner with the use of a standardized protocol involving automatically calculated mAs for the patient's weight, 120kV, a tube rotation time of 0.75s per rotation, a pitch of 0.85, and a section thickness of 3.3mm. After this, PET images were acquired immediately and reconstructed using CT data with iterative reconstruction for attenuation correction.

For semi-quantitative assessment of PET/CT scans, nuclear medicine specialist with ten years of experience evaluated with visual inspection in transaxial, coronal, and sagittal planes using a commercial workstation (IntelliSpace Portal; Philips Healthcare, USA). Twenty-six PET/CT scans were reported as negative studies that is no evidence of recurrence or metastasis. In 64 scans, 77 lesions were examined. Forty-four patients had dual-phase PET/CT scans. The regions of interest over the lesion were drawn. The maximum standardized uptake value (SUVmax) at early (SUV1) and delayed images (SUV2) if any, were automatically calculated. In addition, liver SUVmax was measured from the normal liver parenchyma at the dual time (SUV1liver and SUV2liver). In order to tumor-to-liver SUVmax ratio (TLR) calculation, SUVmax of the primary tumor was divided to liver SUVmax as follows:

$TLR1=SUV1/SUV1_{liver}$

$TLR2=SUV2/SUV2_{liver}$

Retention indexes (RI) from SUVmax and TLR values, obtained from dual time images, were calculated as RI=(SUV2-SUV1)100/(SUV1) and RI (TLR) =(TLR2-TLR1)100/(TLR1).

HER2 test

Test for HER2 protein overexpression was done by immunohistochemical method. The patients were divided into two groups as "Negative" and "Positive" according to HER2 protein overexpression. The 0 and 1+ results were negative, 3+ was positive, and 2+ was equivocal. HER2 2+ situation was confirmed by Silver-enhanced in situ hybridization (SISH) method. There were not enough tissues for SISH evaluation in 3 patients who were excluded from the study.

Statistical analysis

Statistical analysis was performed using the NCSS Statistical Software version 2007 (Kaysville, UT, USA). Quantitative parameters were analyzed by mean and standard deviation. Qualitative parameters were analyzed by frequencies and percentages. Fluorine-18-FDG parameters were compared according to the pathological parameters by classifying the patients. Fluorine-18-FDG parameters were SUV1, SUV2, TLR1, TLR2, RI, and RI(TLR). Pathological parameters were histological type, grade, presence of lymphatic, vascular, and perineural invasions, presence of lymph node metastasis, and HER2 status. T-test, Mann-Whitney U-test, Oneway-ANOVA test, Tukey Post Hoc tests, and Kruskal-Wallis test for these variables were used. The Spearman's rho correlation test for nonparametric parameters and Pearson correlation test for parametric parameters were performed. When the value of P is less than 0.05, it was considered significant.

Results

Histological type of 69 patients were 59 (85.5%) adenocarcinoma, 7 (10.1%) signet ring cell carcinoma, 2 (2.9%) adenosquamous carcinoma, 1 (1.4%) mucinous adenocarcinoma. In addition, 15 (21.7%) adenocarcinoma patients had signet ring cell components up to 40%, and 5 (7.2%) adenocarcinomas had mucinous components up to 45%. Furthermore, histological grade in 54 patients, lymphatic invasion in 57 patients, vascular invasion in 28 patients, perineural invasion in 53 patients, lymph node metastasis in 57 patients were also studied in pathological evaluation. According to histological grade, patients were divided into three groups as 8 (11.6%) well-differentiated, 12 (17.4%) moderately differentiated, 34 (49.3%) poorly differentiated. Lymphatic, vascular and perineural invasions were found positive 53 (76.8%), 16 (23.2%), 35 (50.7%), respectively. Lymph node metastasis was seen in 44 (63.8%) patients.

Human epidermal growth factor receptor 2 status of patients is expressed according to the pathological materials (Table 1). HER2 negative group included 56 (81.2%) patients and the positive group had 10 (14.35%) patients. When the discordance between endoscopy and resection for HER2 status was detected, the result obtained from the resection specimen was accepted.

Table 1. *HER2 status of patients.*

HER2 situation	Endoscopic biopsy, n (%)	Gastrectomy specimen, n (%)
0	7 (10.1%)	17 (24.6%)
1+	26 (37.7%)	20 (%29)
2+	17 (24.6%)	13 (%18.8)
3+	7 (10.1%)	6 (%8.7)

Ninety PET/CT scans were evaluated in 69 patients. Twenty-six scans were negative that is no evidence of recurrence or metastasis. Seventy-seven lesions were evaluated in this study, as expressed in Table 2.

We did not find any statistical difference for the values of SUVmax and tumor-to-liver SUVmax on all histological types of gastric carcinoma on the dual-phase PET scan. Signet ring cell component in adenocarcinoma did not cause a statistical difference (P>0.05). When we compared the HER2 status group, there was no statistical difference among all patients. However, we found higher SUV1 levels in the HER2 positive group (8.01±3.11) than the negative group (6.15±3.76) in early PET/CT imaging (P=0.043) for adenocarcinoma patients (Figure 1). On the other hand, there was not a difference in delayed imaging parameters.

We found a weak positive correlation between HER2 and SUV1 in adenocarcinoma patients (r=0.254,P=0.042). In addition, we determined an inverse correlation for histological grade with SUV1 (r=-0.29,P=0.048), TLR1 (r=-0.29,P=0.048) and TLR2(r=-0.324,P=0.03). There were no correlations among the other parameters (Figure 2).

Table 2. *Distribution of lesions in PET/CT scan.*

Lesion localization	n (%)
Primary gastric lesion	33 (42.85%)
Intraabdominal lymph node metastasis	10 (12.98%)
Liver metastasis	8 (10.38%)
Lung metastasis	6 (7.79%)
Adrenal gland metastasis	4 (5.19%)
Bone metastasis	3 (3.89%)
Supraclavicular lymph node metastasis	2 (2.59%)
Other (brain, muscle and soft tissue metastasis)	11 (14.28%)

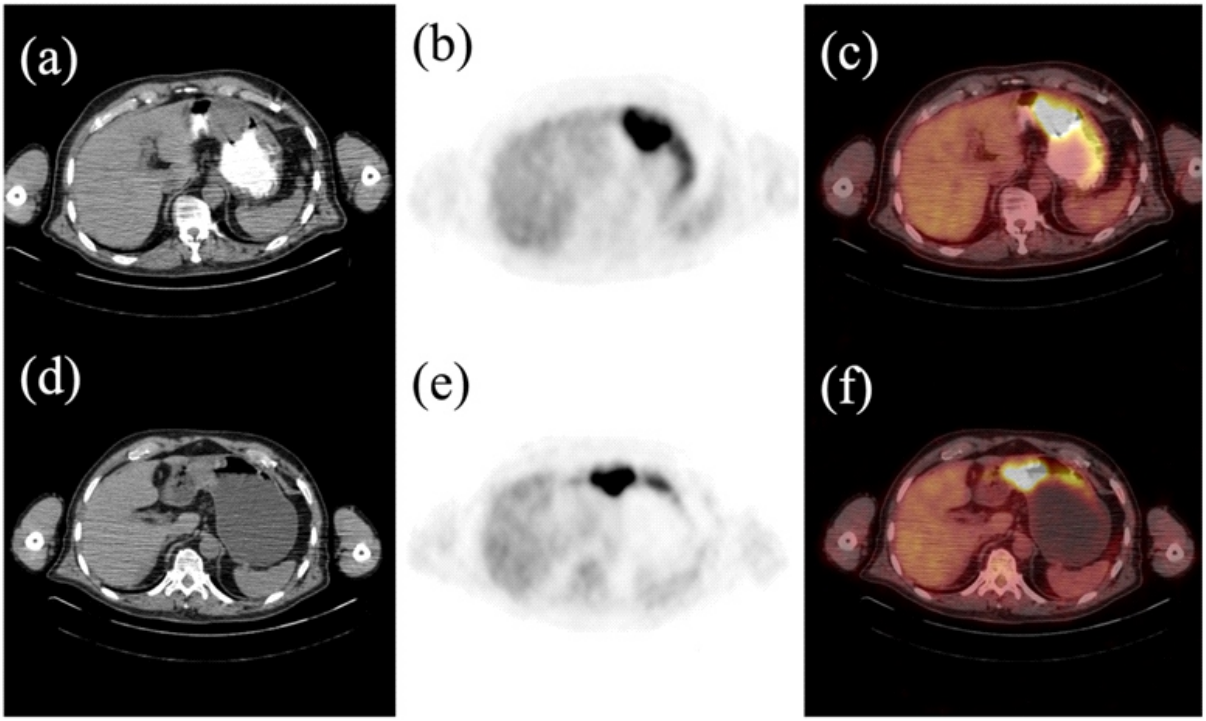

Figure 1. Figure 1. a) HER2 positive patient with adenocarcinoma. Lymphovascular-perineural invasion was found in the total gastrectomy specimen. The ^{18}F-FDG parameters were 10.73 SUV1, 14.44 SUV2, 4.88 TLR1, 6.02 TLR2, 34.58% RI, and 23.36% RI (TLR).

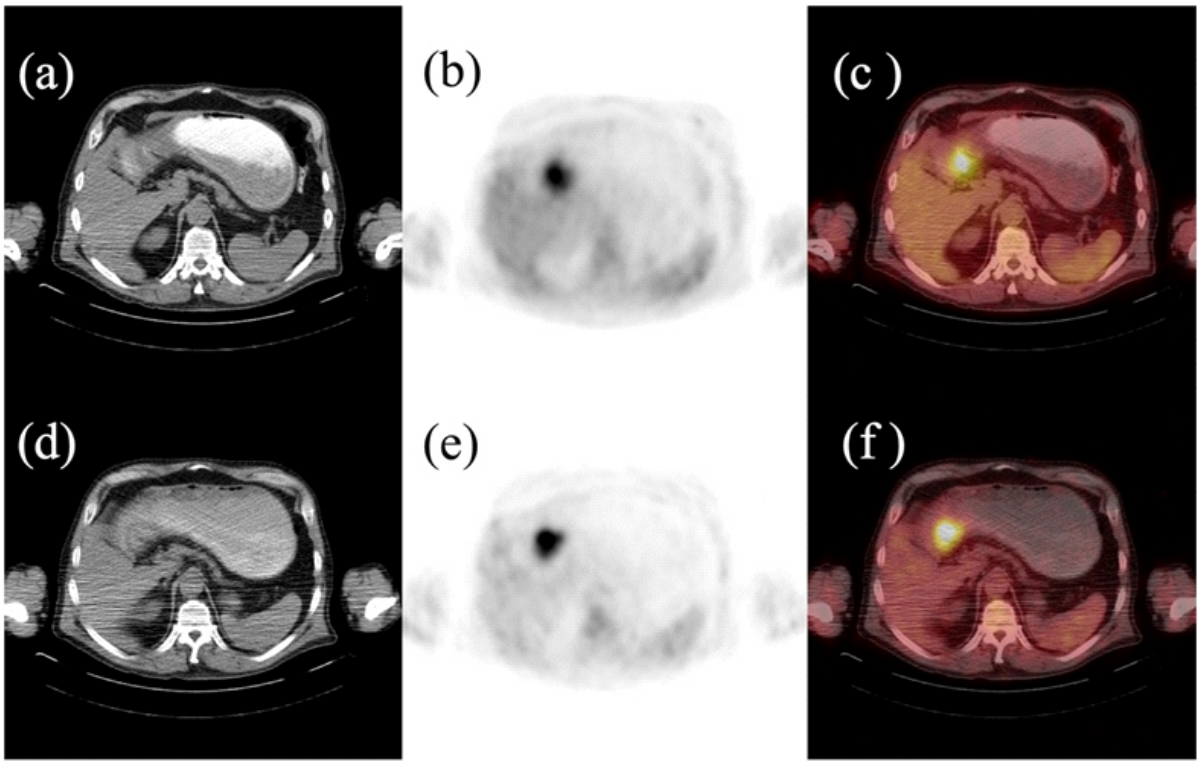

Figure 1. b) HER2 negative patient with high-grade adenocarcinoma. Lymphatic and perineural invasion without lymphatic metastasis was found in the subtotal gastrectomy specimen. The ^{18}F-FDG parameters were 5.76 SUV1, 9.49 SUV2, 2.53 TLR1, 4.37 TLR2, 64.76% RI, and 73.11% RI (TLR).

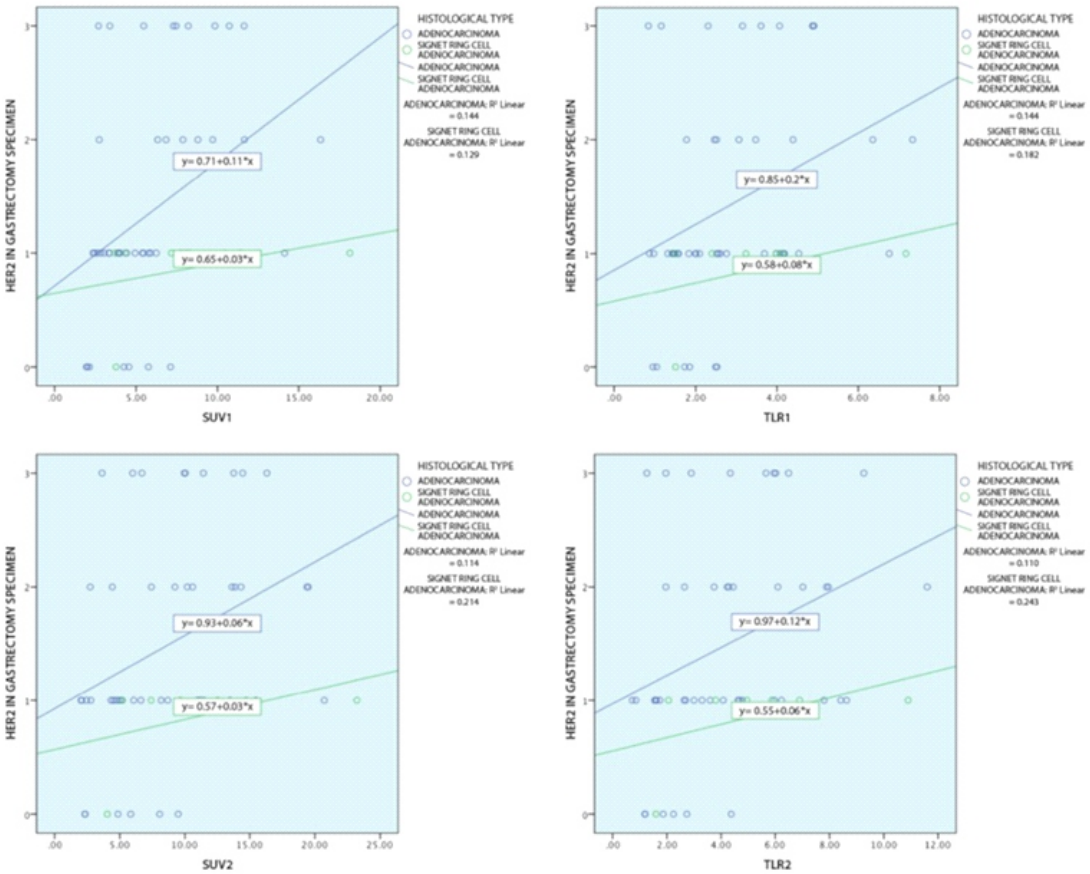

Figure 2. The relation of HER2 status in gastrectomy specimen and ^{18}F-FDG parameters according to histological type.

Discussion

Gastric carcinoma is common cancer having aggressive progression, exhibiting differences in epidemiological and clinical presentation. About 8% of new cases are detected each year[6]. Human epidermal growth factor receptor 2 expression ratios in gastric cancer have identified different percentages in some research, 27% using fluorescence in situ hybridization method in 200 Japanese patients [7] and12% of 131 cases using chromogenic in situ hybridization method, and in 24% of 100 cases with gastroesophageal junction tumor [8]. This study found 14.35% HER2 expression using the immunohistochemical method proven by SISH. This wide range of HER2 positivity may be the cause of heterogeneity of the tumor cells with regards to HER2 expression. It was found at a higher ratio in intestinal-type than the diffuse/mixed type and also in gastroesophageal junction tumors [9].

As known, ^{18}F-FDG uptake into cells occurs by glucose transporter (GLUT-1) in the tumor. Glucose transporter expression is lower in signet ring cell carcinoma subtype in gastric cancer; thus, they did not show significant ^{18}F-FDG uptake [10]. In our study, there was no such correlation. While we could not find a correlation between HER2 and SUVmax values when all subtypes were included, we found a correlation between SUVmax and HER2 when patients with signet ring cells were excluded.

Many studies showed higher SUVmax values in HER2 positive patients than HER2 negative patients, similar to our study [11,12]. Park et al. (2018) suggested that ^{18}F-FDG PET/CT volume-based parameters may play an additional role in classifying the prognosis of stage IV gastric cancer [13]. Ock et al. (2016) expressed that HER2 is not a prognostic factor in patients receiving chemotherapy without an anti-HER2 agent, yet ^{18}F-FDG parameters are prognostic factors [11]. However, there are also contradictory publications in the literature. The researchers found that there is no relationship between SUVmax and HER2 expression in both gastric cancer and gastroesophageal cancer. In addition, they expressed those metabolic indicators obtained from PET/CT scan is a better predictor than histological indicators [14]. Another study found higher SUVmax values in the HER2 negative group than positive group (8.619±5.878 vs. 3.789±2.613, respectively; P=0.021) when signet-ring cell carcinomas were excluded [15]. The heterogeneity and imbalances in the patient population and distribution may have led to discordant results and may have weakened some analyzes.

To avoid variables affecting SUV calculations used an internal comparison method obtained from normal liver parenchyma SUVmax value. Because the liver normally has heterogeneous ^{18}F-FDG uptake, we calculated SUVmax measured with a 2D ROI placed on an appropriate slice of the normal liver parenchyma.Although there was a correlation between HER2 and SUVmax, we did not detect any correlation between the tumor-to-liver SUVmax ratio and HER2. In breast carcinoma, tumor-to-liver SUV ratio was found a significant parameter for HER2-positive subtype identification (P=0.0049) in 66 patients with 83% sensitivity and 79% specificity [16]. In a study including patients with stage III gastric cancer, researchers noted that SUVmax, SUVpeak, TLRmax, and TLRpeak were significantly associated with the overall survey and recurrence-free survival. In addition, they expressed that high TLRmax and TLRpeak were significantly unfavorable prognostic factors for recurrence-free survival (both P<0.05) even after adjusting for age, lymph node metastasis, depth of tumor invasion, and chemotherapy [17]. In a study, researchers found that TLR is superior to tumor SUVmax in predicting treatment response and overall survival in patients with esophageal squamous cell carcinoma undergoing concurrent chemoradiotherapy and high TLR value was also an independent predictor of poor treatment response and shorter overall survival [18]. So far, we have not come across any study examining the relationship between HER2 and TLR in gastric tumors in the literature. In this respect, our study is the first research.

In conclusion, we found that the signet ring cell carcinoma type and the presence of the signet ring component had no effect on ^{18}F-FDG uptake. However, patients with HER2 expression in gastric adenocarcinomas had higher SUVmax values, no significant difference was found between the groups when measured tumor/liver ratio by SUVmax from normal liver parenchyma and background activity was excluded. In addition, a weak inverse correlation was detected between histological grade and ^{18}F-FDG uptake in adenocarcinomas. Although the relationship between HER2 expression and ^{18}F-FDG has been found in a few studies in the literature, we think that the reliability of studies conducted for the prediction of HER2 status will increase in larger patient series, especially by evaluating the parameters by proportioning the lesions to the normal liver.

Ethics

The present study protocol was reviewed and approved by the local Review Board of Istanbul Training and Research Hospital Ethics Committee. (Decision no: 2934). Informed consent was obtained by all subjects when they were enrolled.

The authors declare that they have no conflicts of interest.

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