# The Relationship Between HER2 Status Acquired From Pathological Data and Metabolic Parameters From Pre-treatment 18F-FDG PET/CT in Gastric Adenocarcinomas

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## Abstract

# Aim

This study aimed to investigate the relationship between pathological data with strong importance to Human Epidermal Growth Factor Receptor 2 (HER2) status, and pre-treatment 18F-FDG PET/CT semi-quantitative metabolic parameters in gastric adenocarcinomas and their impact on survival.

# Methods

A retrospective analysis was conducted on 117 patients with gastric cancer who underwent 18F-FDG PET/CT for staging. PET/CT results were evaluated for SUVmax, SUVmean, metabolic tumor volume (MTV), total lesion glycolysis (TLG), HER2 status, pathological data, and tumor markers.

# Results

Of the 117 patients, 17.1% were HER2 + and 82.9% were HER2-. SUVmax was significantly lower in tubular adenocarcinoma (TA) patients with signet ring cell (SRC) component compared to those without SRC component. Tumor size > 5 cm positively correlated with MTV and TLG in patients who underwent total resection. Vascular invasion and local invasion (T3/T4) were associated with higher SUVmax. Patients with distant metastasis had significantly higher SUVmax, SUVmean, and TLG. Stage 3/4 patients showed positive correlations with CEA and CA19-9 values. The tumor's localization in the cardia correlated significantly with HER2 positivity in the TA group. Survival analysis revealed higher 1-year and 3-year survival rates in the HER2 + group compared to the HER2- group.

# Conclusion

18F-FDG PET/CT evaluation for staging provides non-invasive guiding findings for treatment and prognosis. The histological components should be performed in tubular adenocarcinomas PET/CT can predict histological components, local invasion, and vascular invasion. Evaluating metabolic parameters in the primary tumor focus using PET/CT can demonstrate the presence of distant metastasis. The relationship between tumor localization in the cardia and HER2 positivity may be useful in predicting anti-HER2 antibody treatment options. Further extensive studies are needed on this topic.

## Introduction

Gastric adenocarcinoma is the fifth most common type of cancer and ranks fourth in cancer-related deaths [1]. Although the primary treatment method is surgery, chemotherapy, and immunotherapy are emphasized in advanced-stage diseases. Pathological findings in gastric cancers play a crucial role in determining prognosis. Key factors include tumor stage, tumor size, lymph node involvement, presence of metastasis, and Human Epidermal Growth Factor Receptor 2 (HER2) overexpression [2, 3]. Human Epidermal Growth Factor Receptor 2 (HER2) is a tyrosine kinase family member that plays a significant role in the oncogenesis of breast and gastric cancers. While HER2/neu positivity is considered a poor prognostic factor in breast cancer, it is associated with progression and aggressive tumor biology in gastric cancer [4, 5]. HER2 positivity is observed in 7–34% of gastric cancers, making anti-HER2 treatment options, particularly trastuzumab therapy, an important consideration [5, 6].

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is a widely utilized imaging technique in the field of oncology. It combines functional and anatomical imaging, providing valuable information for cancer staging, treatment planning, and response assessment. 18F-FDG PET/CT plays a crucial role in the detection of distant metastases, including lymph node involvement and distant organ spread. Its ability to detect occult metastatic lesions, which may not be apparent in conventional imaging modalities, is particularly valuable in guiding appropriate treatment strategies and prognostic assessment [7].

Studies have shown an association between tumor markers such as CA19-9 and CEA with SUVmax values in certain types of cancer, and there are also studies suggesting a relationship between SUVmax and tumor markers in gastric cancer [8, 9, 10, 11].

There are studies investigating the relationship between pathological data and positron emission tomography/computed tomography (PET/CT) parameters. However, these studies have conflicting results.

This study aims to examine the relationship between 18F-FDG PET/CT semi-quantitative metabolic parameters (SUVmax, SUVmean, MTV, TLG), tumor pathological data, HER2, CA19-9, CEA and their impact on survival in gastric cancer. The results of this study can contribute to our understanding of the role of 18F-FDG PET/CT in the treatment of gastric cancer and the prognostic value of metabolic parameters.

## Materials and Methods

Between January 2015 and August 2022, 750 patients who underwent PET/CT with a diagnosis or suspicion of gastric adenocarcinoma in our hospital were retrospectively screened. A total of 117 patients, including 83 males and 34 females, were included in the study. The inclusion criteria were confirmed pathological diagnosis of gastric adenocarcinoma, HER2 test analysis, and no prior treatment before imaging. Staging was performed based on the TNM classification for carcinoma of the stomach according to the 8th edition of the American Joint Committee on Cancer guidelines [12]. In patients with, total resection material surgical staging was possible. Patients with distant metastasis were classified as stage 4.

Patients with a second primary malignancy and those who did not undergo HER2 testing were excluded from the study.

18F- FDG PET/CT examination included the evaluation of SUVmax, SUVmean, metabolic tumor volume (MTV), total lesion glycolysis (TLG), and the presence of distant metastases. Pathological data were examined, including HER2 status, perineural invasion, local invasion, vascular invasion, tumor size and location, lymph node metastasis, histological subtype, and histological component. Age and gender were obtained by the institutional records system, and patient survival status and date of death were obtained from the national death notification system (DNS).

# Histopathological Method:

All specimens underwent HER-2 immunohistochemical (IHC) staining. Cases with suspicious HER-2 scores (score 2) and positive scores (score 3) were further investigated for HER-2 gene amplification using the dual silver in situ hybridization (SISH) method.

# Immunohistochemistry:

Two-micron thick sections were obtained from formalin-fixed and paraffin-embedded tissues. The sections were placed on positively charged electrostatic slides (Isotherm Technical Laboratory Glass Materials) and incubated at

58ºC for approximately 4 hours until the paraffin dissolved. All sections were placed in an automated IHC staining device (Ventana, Benchmark, Ultra). Anti-HER-2/neu (4B5) rabbit monoclonal antibody (Ventana, Catalog No. 790–2991) and the compatible Ultraview Universal DAB Detection Kit were used for IHC staining.

# In-situ Hybridization (ISH):

Two-micron thick sections obtained from paraffin-embedded tissues were placed on positively charged electrostatic slides (Isotherm Technical Laboratory Glass Materials) and incubated at 58ºC for approximately 4 hours until the paraffin dissolved. All sections were then transferred to an automated staining device (Ventana, Benchmark, Ultra) and the Ventana inform HER2 Dual ISH Automated System was applied. The Ultraview SISH DNP Detection Kit was used for HER-2 gene detection, resulting in black signals through silver deposition, while the Ultraview Red ISH DIG Detection Kit was used for chromosome 17, resulting in red signals using Naftol and Fast Red.

# IHC Evaluation:

Hofmann et al. published the scoring system for the HER-2 (4B5 clone) IHC marker evaluation [13, 14]. The staining pattern, location, intensity, and extent were considered. Membranous staining with a complete/basolateral/lateral pattern was considered positive. The negative evaluation was given to cytoplasmic, nuclear, luminal, or basal staining. The results were reported as negative (score 0 and score 1), suspicious (score 2), and positive (score 3).

# ISH Evaluation:

For cases with suspicious (score 2) and positive (score 3) HER-2 IHC results, HER-2 gene amplification was investigated using the dual silver in situ hybridization (SISH) method [15, 16]. In the identified neoplastic cell group, gene and chromosome signals were counted in 40 consecutive cells at x40 magnification. Cases with an average HER-2 gene copy number ≥ 6 or an HER-2 gene/chromosome 17 ratio of 2 and above were considered positive. Those with an HER-2 gene/chromosome 17 ratio below 2 were considered negative. Cells showing both gene and chromosome signals were included in the evaluation. Amplified tumor cells with overlapping gene signals were assessed by comparing them to a normal signal size. Signals touching each other or closer than one signal size were considered "paired signals" and counted as a single signal. In samples with an expected signal in the internal control cells, multiple overlapping signals in tumor cells that could not be counted separately were considered clusters. A small cluster was considered as 6 signals, and a large cluster as 12 signals. Cells without signals, cells with signals in a single color, and signals observed outside the cells were not included in the evaluation.

# 18 F-FDG PET/CT Imaging Technique:

After fasting for a minimum of six hours, all patients underwent PET/CT, and their blood sugar levels were assessed. An intravenous dose of 8–12 mCi (29–44 MBq; or approximately 8.1 MBq of FDG per kilogram of body weight) of 18F-FDG was administered when the serum glucose level was less than 200 ng/dl. Whole-body PET/CT imaging was performed using a full-ring high-resolution (HI-REZ) LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). The procedure included a non-enhanced CT scan followed by positron emission tomography scanning. The PET image datasets were created using the ordered subsets expectation maximization approach combined with CT-based attenuation correction was used to iteratively recreate PET image datasets.

# 18F-FDG PET/CT Image Analysis:

A General Electric Advantage Workstation (AW workstation Volume Viewer 3 software; GE Healthcare, Waukesha, WI, USA) was used for all image analysis. In three planes (transaxial, coronal, and sagittal), the maximum intensity projection and attenuation-corrected PET/CT fusion images were assessed. The tumor’s maximum SUV, mean SUV(SUVmean), MTV, and TLG were noted. Using the formula [injected dose(MBq) body weight (g)], maximum SUV

were determined based on body weight. To determine MTV, the tumor contours were semi-automatically identified by employing a threshold of 42% of the SUVmax within the lesion. The SUVmean was multiplied by the MTV to compute total lesion glycolysis. A volumetric zone of interest was defined to encompass the main tumor completely. On checking the sagittal and coronal images, the volumetric region of interest border was semi-automatically adjusted if the volume extended beyond the borders of the primary lesion.

# Ethics Committee Approval:

The study was authorized by the local ethics committee of Prof. Dr. Cemil Tascioglu City Hospital in Istanbul, Turkey (2023/19), and informed consent was received from all patients who participated in this study. All procedures in human-participant studies were carried out in compliance with the institutional research committee's ethical standards and the Helsinki Declaration of 1964.

# Statistical Analysis:

SPSS 25.0 for Windows software was used for statistical analysis. Descriptive statistics were provided for categorical variables in terms of frequency and percentage, and for numerical variables in terms of mean, standard deviation, minimum, maximum, and median. The proportions between groups were compared using the Chi-square test. Since the numerical variables did not meet the assumption of normal distribution, independent group comparisons were conducted using the Mann-Whitney U test, and multiple group comparisons were conducted using the Kruskal-Wallis test. A statistical alpha significance level of $p < 0.05$ was accepted.

## Results

# Patient Population

A total of 117 patients were included in our study, with 83 (70.9%) males and 34 (29.1%) females. The age of the patients ranged from 26 to 89. Among them, 76 patients had only endoscopic biopsy material, while 41 patients had total resection material available. Perineural invasion, local invasion, vascular invasion, tumor size, and lymph node metastasis, stage were evaluated in patients with total resection material.

There were 31 patients with poorly differentiated tumors, 45 patients with moderately differentiated tumors, and 7 patients with well differentiated tumors. Additionally, there were 7 patients with signet ring cell histology. Histologically, 22 patients had a signet ring cell component, and 8 patients had a mucinous cell component. Among the patients, 17.1% were HER2-positive (13.7% with a score of 3, 3.4% with a score of 2), and 82.9% were HER2-negative (73.5% with a score of 0, 9.4% with a score of 1; table 1)

| Table 1. Patient Characteristic | | | |
|---|---|---|---|
| | | n | % |
| **Gender** | Male | 83 | 70,9 |
| | Female | 34 | 29,1 |
| **Age (year, mean ± SD (Min-Max)** | | 62,2±12,6 (26-89) | |
| **Biopsy Method** | Endoscopic | 76 | 65,0 |
| | Total Resection | 41 | 35,0 |
| **HER Score** | 0 | 86 | 73,5 |
| | 1 | 11 | 9,4 |
| | 2 | 4 | 3,4 |
| | 3 | 16 | 13,7 |
| **HER Status** | | | |
| | Negative | 97 | 82,9 |
| | Positive | 20 | 17,1 |
| **Tumor Size (mm, mean ±SD (Min-Max)** | | 56,3±33,8 (15-150) | |
| **Tumor Size (cm)** | <5 | 19 | 46,3 |
| | ≥5 | 22 | 53,7 |
| **Perineural Invasion** | | 17 | 41,5 |
| | Absent | | |
| | Present | 24 | 58,5 |
| **Vascular Invasion** | | | |
| | Absent | 18 | 43,9 |
| | Present | 23 | 56,1 |
| **Local Invasion** | | | |
| | T1-T2 | 10 | 24,4 |
| | T3-T4 | 31 | 75,6 |
| **Lymph Node Status** | Metastasis | 31 | 75,6 |
| | Reactive | 10 | 24,4 |
| **Histological Subtype** | Poorly differentiated | 31 | 32,0 |
| | Moderately differentiated | 45 | 46,4 |
| | Well-differentiated | 7 | 7,2 |

| | | | |
|---|---|---|---|
| | Mixed | 2 | 2,1 |
| | Mucinous | 5 | 5,2 |
| | Signet ring cell | 7 | 7,2 |
| **Histological Component** | Mucinous | 8 | 26,7 |
| | Signet ring cell | 21 | 70,0 |
| | Signet ring cell + Mucinous | 1 | 3,3 |
| **Tumor Location** | Cardia | 28 | 23,9 |
| | Corpus-Fundus | 36 | 30,8 |
| | Antrum | 33 | 28,2 |
| | Diffuse | 20 | 17,1 |
| **Distant Metastasis** | Absent | 73 | 65,2 |
| | Present | 39 | 34,8 |
| **Stage** | Stage 1-2 | 22 | 29,7 |
| | Stages 3-4 | 52 | 70,3 |
| **Current Status** | Alive | 30 | 25,6 |
| | Deceased | 87 | 74,4 |

# Correlation Between Patient Characteristics and PET Parameters

In our study, we investigated the relationship between tumor size and metabolic parameters in gastric cancer patients. We found that MTV (metabolic tumor volume) and TLG (total lesion glycolysis) values were significantly higher in tumors larger than 5 cm compared to tumors smaller than 5 cm (74.2 ± 79.1 vs. 25.0 ± 19.5, p-value: 0.008). However, there was no significant relationship observed between SUVmax with tumor size. Seventy-six patients were diagnosed with gastric adenocarcinoma based on endoscopic findings, and 41 patients underwent total resection. Although there were only 7 patients with signet ring cell (SRC) histological subtype, 22 out of 83 patients with tubular adenocarcinoma (TA) had an SRC component. SUVmax was significantly lower in TA patients with an SRC component (9.4 ± 7.78) compared to those without the SRC component (13.33 ± 12.27) (p:0.037). We found that patients with vascular invasion had a significantly higher mean SUVmax compared to those without vascular invasion (10.2 ± 15.3 vs. 2.8 ± 2.0, p-value: 0.010). Additionally, patients with T3/T4 local invasion exhibited significantly higher SUVmax values compared to patients with T1/T2 (8.3 ± 13.3 vs. 2.4 ± 0.9, p-value: 0.047). Furthermore, in patients with stage 3–4 disease, the mean MTV was significantly higher compared to those with stage 1–2 (52,2 ± 47,8 vs. 47,7 ± 75,0, p-value: 0.030). Based on the statistical analysis conducted, no statistically significant relationship was found between vascular invasion, local invasion, and the parameters of MTV (Metabolic Tumor Volume) and TLG (Total Lesion Glycolysis). Lastly, patients with distant organ metastasis demonstrated significantly higher SUVmax, SUVmean (mean standardized uptake value), and TLG (total lesion glycolysis) values compared to those without metastasis (14.6 ± 13.4 vs. 10.8 ± 9.5, p-value: 0.029; 6.4 ± 3.3 vs. 4.6 ± 3.2, p-value: 0.003; 327.9 ± 379 vs. 267.2 ± 485.7, p-value: 0.014, respectively; Table 2). There was no significant correlation between age, gender, perineural invasion, lymph node metastasis, and tumor location.

Table 2
Relationship between PET parameters and patient characteristics

| Variable | | *n* | SUVmax (mean + SD*) | p | SUVmean (mean + SD*) | p | MTV** (mean + SD*) | p | TLG*** (mean + SD*) | p |
|---|---|---|---|---|---|---|---|---|---|---|
| Gender | Male | 83 | 12,2 ± 12,0 | 0,487 | 5,0 ± 3,1 | 0,258 | 50,2 ± 56,3 | 0,511 | 312,3 ± 505,3 | 0,801 |
| | Female | 34 | 12,4 ± 7,9 | | 6,0 ± 4,0 | | 42,4 ± 45,1 | | 298,3 ± 521,4 | |
| Age | < 60 | 49 | 12,0 ± 10,7 | 0,487 | 5,0 ± 3,5 | 0,171 | 51,8 ± 60,4 | 0,862 | 316,5 ± 504,2 | 0,449 |
| | ≥ 60 | 68 | 12,5 ± 11,2 | | 5,6 ± 3,3 | | 45,3 ± 48,1 | | 305,5 ± 517,3 | |
| Tumor Size | < 5 cm | 19 | 11,6 ± 15,4 | 0,084 | 4,6 ± 3,0 | 0,111 | 25,0 ± 19,5 | 0,008 | 130,7 ± 138,6 | 0,021 |
| | ≥ 5 cm | 22 | 16,7 ± 13,8 | | 6,4 ± 4,1 | | 74,2 ± 79,1 | | 573,6 ± 772,5 | |
| Perineural Invasion | Absent | 17 | 3,0 ± 2,0 | 0,062 | 5,9 ± 3,7 | 0,543 | 45,6 ± 47,5 | 0,853 | 308,6 ± 373,9 | 0,672 |
| | Present | 24 | 9,7 ± 15,0 | | 5,3 ± 3,7 | | 55,5 ± 74,0 | | 410,7 ± 738,2 | |
| Vascular Invasion | Absent | 18 | 2,8 ± 2,0 | 0,01 | 40,9 ± 74,3 | 1,000 | 50,2 ± 79,5 | 0,258 | 364,6 ± 611,6 | 0,813 |
| | Present | 23 | 10,2 ± 15,3 | | 350,0 ± 1377,8 | | 52,4 ± 50,2 | | 371,3 ± 622,2 | |
| Local Invasion | T1-T2 | 10 | 2,4 ± 0,9 | 0,047 | 57,3 ± 97,3 | 0,723 | 39,7 ± 51,8 | 0,261 | 264,6 ± 449,9 | 0,347 |
| | T3-T4 | 31 | 8,3 ± 13,3 | | 59,1 ± 1174,1 | | 55,2 ± 67,6 | | 401,8 ± 656,0 | |
| Lymph Node Metastasis | Metastatic | 31 | 8,1 ± 13,3 | 0,26 | 268,4 ± 1173,5 | 0,797 | 43,8 ± 42,2 | 0,627 | 310,9 ± 537,9 | 0,952 |

*Standart Deviation, **Metabolic Tumor Volume, ***Total Lesion Glycolysis

Statistically significant p-values are indicated with red colored entries

| Variable | | *n* | SUVmax (mean + SD*) | p | SUVmean (mean + SD*) | p | MTV** (mean + SD*) | p | TLG*** (mean + SD*) | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | Reactive | 10 | 2,9 ± 1,4 | | 30,4 ± 29,6 | | 75,1 ± 106,5 | | 546,6 ± 801,0 | |
| Stage | 1–2 | 22 | 14,0 ± 13,5 | 0,795 | 5,4 ± 3,3 | 0,471 | 47,7 ± 75,0 | 0,030 | 329,4 ± 572,1 | 0,133 |
| | 3–4 | 52 | 13,6 ± 12,2 | | 6,1 ± 3,6 | | 52,2 ± 47,8 | | 369,6 ± 510,1 | |
| Tumor Localization | Cardia | 28 | 13,0 ± 6,9 | 0,158 | 5,9 ± 3,5 | 0,286 | 40,9 ± 38,9 | 0,898 | 226,7 ± 191,1 | 0,709 |
| | Corpus-Fundus | 36 | 13,1 ± 14,3 | | 5,2 ± 3,1 | | 47,8 ± 48,9 | | 316,6 ± 551,4 | |
| | Antrum | 33 | 9,8 ± 8,2 | | 4,7 ± 3,5 | | 53,0 ± 66,3 | | 337,2 ± 625,2 | |
| | Diffuse | 20 | 13,7 ± 12,4 | | 5,8 ± 3,5 | | 49,4 ± 57,0 | | 359,8 ± 538,6 | |
| Distant Metastasis | Absent | 78 | 10,8 ± 9,5 | 0,029 | 4,6 ± 3,2 | 0,003 | 46,3 ± 55,3 | 0,234 | 267,2 ± 485,7 | 0,014 |
| | Present | 39 | 14,6 ± 13,4 | | 6,4 ± 3,3 | | 47,4 ± 44,6 | | 327,9 ± 379,1 | |
| *Standart Deviation, **Metabolic Tumor Volume, ***Total Lesion Glycolysis | | | | | | | | | | |
| Statistically significant p-values are indicated with red colored entries | | | | | | | | | | |

# Correlation Between Patient Characteristics and HER2 Expression, Tumor Markers, and Overall Survival

The correlation between patient characteristics and HER2 expression, tumor markers, and overall survival was investigated in this study. No significant associations were found between HER2-positive patients and PET parameters, indicating that HER2 expression does not have a direct impact on PET findings. In terms of tumor location, there was no significant relationship between HER2 positivity and tumor location in the overall patient group. However, when analyzing tubular adenocarcinomas without any other components, a significant association was found between HER2 positivity and tumors located in the cardia region (p:0.022), suggesting a potential correlation specific to this subtype (Fig. 1). Regarding disease stage, patients with stage 3–4 disease had significantly higher CA19-9 and CEA values compared to those with stage 1–2 (p:0.008, p:0.013). However, no statistically significant relationship was observed between tumor markers and PET parameters, indicating that these markers may not be reliable indicators of PET findings. This study was to examine the correlation between patient characteristics, including vascular invasion, histological subtype, and stage, with overall survival in gastric adenocarcinomas. The

results revealed significant differences between deceased and surviving patients in terms of these factors. Firstly, the analysis showed that the rate of vascular invasion was statistically significantly higher in deceased patients compared to survivors ($p = 0.009$). Furthermore, there were statistically significant differences in histological type between deceased and surviving patients ($p = 0.045$). Specifically, the occurrence of histological subtypes such as poorly differentiated, mucinous, and signet ring cells was significantly higher in deceased patients compared to survivors. Additionally, the rate of Stage 3–4 disease was significantly higher in deceased patients compared to survivors ($p < 0.001$). These findings highlight the importance of vascular invasion, growth pattern, histological subtype, and disease stage as significant factors influencing overall survival in gastric adenocarcinomas. In terms of HER2 status and survival, there was no significant difference observed between HER2-positive and HER2-negative patients (log-rank p:0.69). Similarly, when considering tubular adenocarcinomas, there was no significant relationship between HER2 positivity and survival (log-rank p:0.19), indicating that HER2 expression may not be a reliable prognostic factor in these cases (Fig. 2).

# Discussion

The studies on gastric adenocarcinomas to determine the relationship between PET/CT parameters and HER2 status revealed contradictory findings, which highlighted the need for further research. We aimed to examine the relationship between histopathological data and PET/CT parameters. and their impact on survival in gastric cancer. Regarding tumor size, there are studies claiming that SUVmax is higher in tumors > 5cm [21, 22], while other studies have shown no such correlation [17, 18]. In our study, we only found a correlation between MTV and TLG with tumor size, but no significant relationship was found with SUVmax. The common feature of studies showing a correlation is that they focused only on tubular adenocarcinomas and excluded signet ring cell carcinomas.

There are studies indicating differences in FDG uptake in tubular adenocarcinomas based on their histopathological type. It has been observed that tubular adenocarcinomas exhibit higher FDG uptake compared to mucinous and signet ring cell cancers, and this increase has been suggested to be associated with glut 1 expression [17, 18, 19]. However, in our study, we identified that some patients classified as tubular adenocarcinomas also included components of signet ring cells or mucinous cells. Additionally, despite being categorized as well, moderately, or poorly differentiated tumors, we noticed that groups with histopathological signet ring cell components had lower SUV values.

A meta-analysis reported a lower HER2 positivity rate in signet ring cell cancers. However, one of the main reasons for the varying results in many studies investigating the relationship between HER2 and PET parameters is the lack of examination of histological components and the unknown impact of these components on the disease [20].

In the context of vascular invasion, some studies, including Kim et al., have reported high SUVmax values in patients with lymphovascular invasion [21] while several others have not found a significant correlation [22, 23, 24, 25]. Similarly, in a study by Arslan et al., no relationship was observed between SUVmax of the primary tumor and distant metastasis in tubular adenocarcinomas. However, when focusing on signet ring cell carcinomas, patients with distant metastasis exhibited higher SUVmax values [26]. In our study, a significant correlation was found between distant metastasis and SUVmax when considering all groups together.

The relationship between HER2 status and PET/CT parameters has also been explored in various studies. Chen et al. found no association between HER2 status and SUVmax in their study, but when excluding patients with signet ring cell carcinomas, they observed higher SUVmax values in HER2-negative patients compared to HER2-positive patients [22]. Conversely, other studies by Kim et al. and Park et al. reported significantly higher SUVmax values in HER2-

positive patients [21, 27]. In line with our findings, studies by Ertürk et al. and Celli et al. did not find a statistically significant relationship between HER2 status and SUVmax [23, 24].

In our study, we identified a significant relationship between HER2 positivity and tumor location in the cardia region among tubular adenocarcinomas without signet ring cells or mucinous components. However, other studies did not consistently observe this relationship [21, 22, 23, 24].

The study's constraints encompass its retrospective design and the limited sample size of patients.

## Conclusion

Evaluation of F18 PET/CT performed for staging purposes provides non-invasive guiding findings for treatment and prognosis. Histological components should be performed in tubular adenocarcinomas. Histological components, local invasion, and vascular invasion can be predicted using PET/CT. The presence of distant metastasis can be demonstrated by evaluating metabolic parameters in the primary tumor focus using PET/CT. The relationship between tumor localization in the cardia and HER2 positivity may be useful in predicting anti-HER2 antibody treatment options. Further extensive studies are needed on this topic.

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# Figures

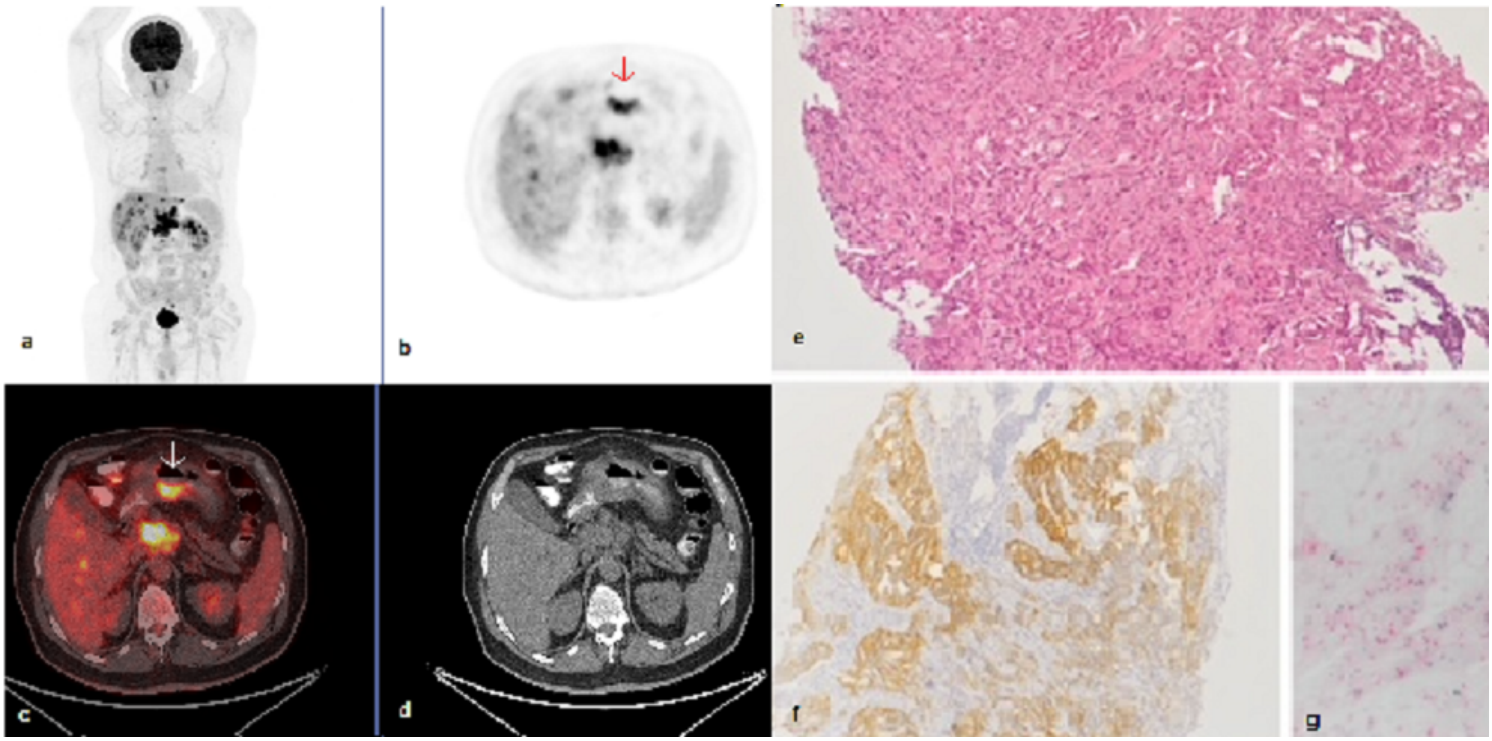
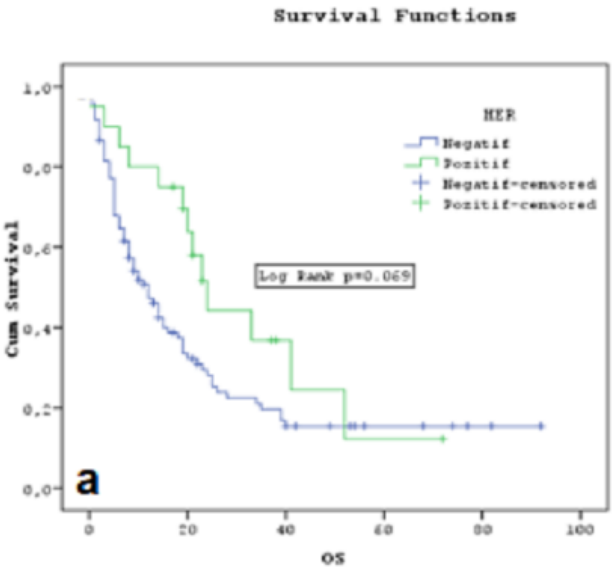


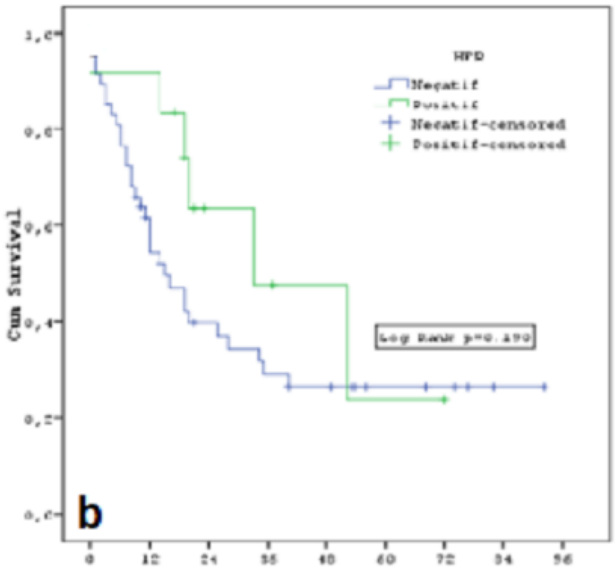

**Figure 1**

A 71-year-old female patient with moderately differentiated tubular adenocarcinoma without components, has endoscopic biopsy material. SUVmax: 13.98 in the corpus fundus tumor of the patient with a HER2 positive score of 3. a.MIP: Maximum Intensity Projection image, b.Axial PET, c.Fusion, d.CT, e.Moderately differentiated adenocarcinoma (HE, x100), f.Strong membranous basolateral staining with CerbB2 (3+) (x100), g. SISH method, CerbB2/chromosome 17≥2 (x400)




| | Median (SE)/ 95% CI | Log rank p |
|---|---|---|
| HER2 negative | 12(2,1)/ 7,9-16,1 | 0,069 |
| HER2 positive | 24(2,7)/18,8-29,2 | |
| Total | 14(2,9)/8,4-19,6 | |

| | HER2 negative | HER2 positive |
|---|---|---|
| | **OS % SE** | **OS % SE** |
| 1 year | 47,3 (5,2) | 80,0 (8,9) |
| 3 year | 19,7 (4,5) | 36,8 (12,2) |
| 5 year | 15,5 (4,1) | 12,3 (10,8) |




| | Median (SE)/ 95% CI | Log rank p |
|---|---|---|
| HER2 negative | 15(3,1)/8,9-21,1 | 0,190 |
| HER2 positive | 33(14,3)/5,1-60,9 | |
| Total | 19(2,8)/13,4-24,6 | |

| | HER2 negative | HER2 positive |
|---|---|---|
| | **OS % SE** | **OS % SE** |
| 1 year | 54,4 (7,4) | 91,7 (8,0) |
| 3 year | 29,1 (7,1) | 47,6 (17,7) |
| 5 year | 24,4 (6,7) | 23,8 (19,0) |

## Figure 2

Kaplan Meier survival analysis prepared according to HER2 status a: Analysis by including the whole group b: Analysis of only tubular gastric cancer with no histological component. SE: Standart Error, OS: Overall Survival, CL: Confidence Interval, HER2: Human Epithelial Growth Factor 2