Relationship between Histone Deacetylase (HDAC) Overexpression and ^{18}F-FDG PET/CT Parameters in Patients with Gastric Cancer, and Prognostic Importance of HDAC Overexpression

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ABSTRACT

Histon Deacetylases (HDACs) exert a pro-oncogenic effect by keeping genes that cause differentiation, apoptosis, and cell cycle arrest in a transcriptionally quiescent state. Moreover to achieve our aim, we investigated the relationship between the patients' HDAC protein expression rates and their prognosis. In no patients, tumors were located in the cardia and corpus. While the median HDAC1 protein score was 3.5 in the early stage patients, it was 8 in the advanced stage (stage 1-2) patients, and 12 in the metastatic stage (stage 4) patients. There was a significant correlation between HDAC protein positivity and tumor localization (p= 0.030). Significant correlation was observed between histopathological stages and median HDAC1 protein scores. (p= 0.021). The HDAC1 protein score increased as the patients' stage progressed. Given the relationship between HDAC1 proteins and the survival of the patients, the 2-year survival rate was high in HDAC1 positive patients; however, it was not statistically significant. According to the results of our study, in HDAC1-positive gastric cancer patients, there was no significant relationship between SUVmax showing tumor metabolism in 18F-FDG PET/CT.

Keywords: HDAC, HDACI, 18F-FDG PET/CT, Gastric cancer

INTRODUCTION

Gastric cancer is one of the most common causes of cancer-related deaths worldwide.[1] It is the fifth most common cancer after lung, breast, colorectal and prostate cancers and the second most common cause of cancer-related deaths after lung cancer.[1,2] Gastric cancer can be affected by many environmental, genetic and epigenetic factors. Epigenetic changes are reversible changes and occur in the function of genes without causing changes in the DNA sequence, such as acetylation of histones.[3] The acetylation state of histones is determined by a reversible balance between histone acetyltransferase (HAT) and histone deacetylase enzymes (HDAC).HDACs (Histone deacetylases) exert a pro-oncogenic effect by keeping genes that cause differentiation, apoptosis, and cell cycle arrest in a transcriptionally quiescent state.HDACs have become the target molecule of cancer research because they abnormally increase in various cancers.[4-6]

In this study, we aimed to investigate the clinical effect of the HDAC enzyme, which is involved in the acetylation balance of histones, the epigenetic mechanism in the development of gastric cancer. To achieve our aim, we investigated the relationship between the patients' HDAC protein expression rates and their prognosis. In addition, the relationship between patients' prognosis and HDAC protein expression rates was assessed with the visual and quantitative parameters obtained through ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computer Tomography (PET/CT) performed in the preoperative period.

PATIENTS AND METHODS

In the study, 83 patients who were diagnosed with gastric cancer by endoscopic biopsy between 2015 and 2021 and underwent 18F-FDG PET/CT examination for staging before receiving chemotherapy/radiotherapy and/or undergoing surgery were included. Patients who had previously received any treatment (chemotherapy/radiotherapy, etc.), and/or those who had other primary cancers, and those who had PET/CT imaging performed in other centers were not included in the study. In addition, patients whose histopathological diagnosis was other than adenocarcinoma and/or who were diagnosed with adenocarcinoma but whose blocks could not be accessed in the archive of the Medical Pathology Department of our hospital due to in- and out-hospital consultation, were not included in the study.

Patient files in the archives of the Medical Oncology Department were accessed in order to evaluate the life expectancy of the patients followed up in our hospital.

Immunohistochemical Examination

The H-E stained preparations of the patients obtained from the archive of the Medical Pathology Department were re-examined under the light microscope. Preparations in which the tumor was best sampled and had adjacent normal mucosa, with minimal necrosis and bleeding, were selected, and 2.5-micron-thick Tomo brand adhesive slide sections were taken from the blocks of these preparations using the Leica microtome device. Slide sections were deparaffinized in an Electro-Mag oven at 65^{0}C degrees for 1.5 hours.

The HDAC-1 antibody (Santa Cruz Biotechnology, INC, Clone: 10E2) was diluted by 1/100 with dilution water. Immunohistochemical staining was performed automatically on the Ventana BenchmarkXT device (incubation time: 44 min). After the washing process, the preparations removed from the device were transferred to the Sakura brand sealing device. After the sealing process, they were evaluated under a light microscope.

Evaluation: Nuclear staining in tumor cells was used as the basis for evaluating HDAC-1 staining. The intensity of nuclear staining was quantitatively scored as follows: 0: no staining; 1+: weak staining; 2+: moderate staining; 3+: strong staining. The percentage of staining was quantitatively scored as follows: 0: < 5%; 1: 5-25%; 2: 26%-50; 3: 51-75%; 4: > 75%. Then, the total score was obtained by multiplying the staining intensity score by the staining percentage score. If the total score obtained was ≥ 4, HDAC1 expression was considered as high (HDAC1High), and if it was < 4, HDAC1 expression was considered as low (HDAC1Low). From the blocks belonging to the patients whose files were obtained from the archives of the pathology laboratory, 2.5-micron-thick Tomo brand adhesive sections were taken using the Leica brand microtome device. Slide sections were deparaffinized in an Electro-Mag oven at 65 degrees for 1.5 hours. The HDAC-1 antibody (Santa Cruz Biotechnology, INC, Clone: 10E2) was diluted by 1/100 with dilution water. Immunohistochemical staining was performed on the Ventana Benchmark XT device (incubation time: 44 min). After the washing process, the preparations removed from the device were transferred to the Sakura brand sealing device. After the sealing process, microscopic examination was started.

Both the staining intensity (0: no staining; 1+: weak staining; 2+: moderate staining; 3+: strong staining) and the percentage of stained cells (0: < 5%, 1: 5-25%, 2: 26-50%, 3: 51-75%, 4: > 75%) were scored quantitatively. Then, the total score was calculated by multiplying the staining intensity score by the staining percentage score. If the total score obtained was ≥ 4, HDAC1 expression

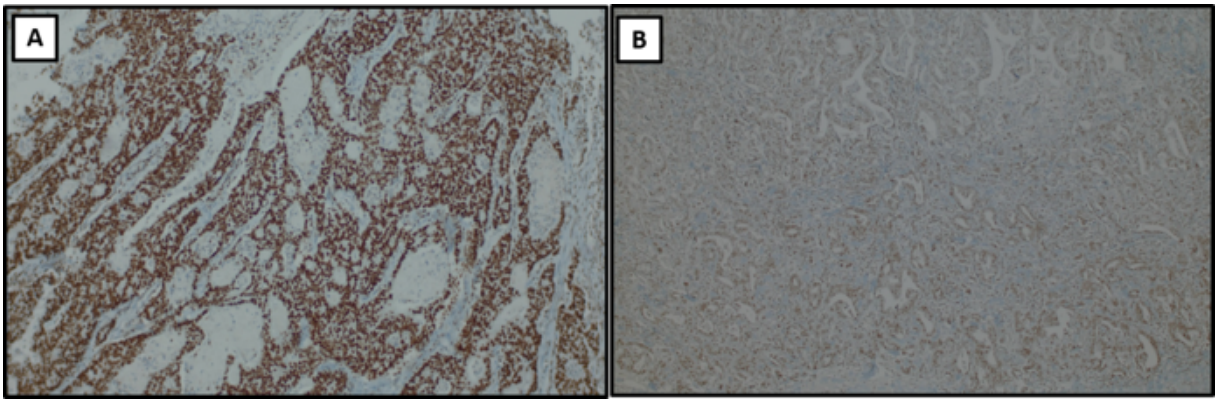

Figure 1. Strong staining **(A)** and weak staining **(B)** with HDAC (HDAC; X100)

was considered as high (HDAC1High), and if it was < 4, HDAC1 expression was considered as low (HDAC1Low)[7,8] (Figure 1).

^{18}F-FDG PET/CT Imaging Protocol: The patients were asked to fast for at least 4-6 hours, and their blood glucose levels were measured before imaging was performed. Only patients with fasting blood glucose levels below< 200 mg/dL were injected with radiopharmaceuticals. During 18F-FDG PET/CT examinations, the patients were administered an average of 10 mCi 18F-FDG. All the patients stayed in the relaxation room for 45-60 minutes after the injection.

The General Electric Discovery PET/CT 600 device was used for imaging. CT imaging was performed with a spiral 16-slice scanner at 120 kV and 172 mAs for attenuation correction and anatomical correlation. Three-dimensional PET imaging was performed, covering the body parts from the skull to the proximal thigh. PET imaging was conducted for approximately 2 minutes in each bed position. Axial, coronal and sagittal fusion images were created using the iterative reconstruction method. The maximum standardized uptake values (SUVmax) were calculated based on the PET images. An adaptive threashold setting of 42% of maximum regional metabolic activity was used for the PET images, and the region of interest (ROI) was placed with in the primary tumor in the stomach by avoiding the peripheral area.

The following formula was used to calculate the SUVmax:

[Activity in ROI (mCi/mL) × Body Weight (grams)] ÷ Injected Dose (mCi)

This study was conducted in accordance with the principles of the Declaration of Helsinki. Before the study was conducted, ethical approval was obtained from the Cumhuriyet University Faculty of Medicine) non-Interventional Clinical Research Ethics Committee (decision number: 2021-03-22).

Statistical Analysis

The obtained data were analyzed with the Statistical Package for the Social Sciences 23.0 program (SPSS Inc., Chicago). Kolmogorov Smirnov test was used to find out whether the data were distributed normally. For the data with parametric conditions, while the independent samples t-test was used to compare two independent groups, the F test [analysis of variance (ANOVA)] was used to compare more than two groups. To determine which group differed from the others, Tukey tests were used for those with homogeneity assumption, and Tamhane T2 tests were used for those without homogeneity assumption. The Mann-Whitney U test was used for two independent groups. The Kruskal-Wallis test was used for more than two independent groups if any or all of the assumptions were not met. The Chi-square test was used for statistical analysis of the categorical variables. Kaplan–Meier test was used for survival analysis of the patients. The margin of error was accepted as 0.05.

RESULTS

In the present study, 83 patients were included. Of them, 29 (34.9%) were women and 54 men (65.1%) were men. They were in the age group of 36-93 years. While their mean age was 63.5 years, their median age was 64 years. While 45 (55.2%) of them were under the age of 65, 38 (44.8%) were aged 65 and over. According to the Lauren classification, the histopathological subtypes of the patients were as follows: diffuse type: 15 (18.1%), intestinal type: 63 (75.9%), and mixed type: 5 (6%). According to the histopathological grade, among the patients, 9 (13.6%) were well differentiated, 24 (36.4%) were moderately differentiated, and 33 (50%) were poorly differentiated. The grade of 17 patients was unknown.

18F-FDG PET/CT taken after diagnosis demonstrated that, 54 (74%) of patients had metastatic lymph nodes in the abdomen, 4 (5.5%) of patients had metastatic lymph nodes and liver metastases in the abdomen, 2 (2.7%) of patients had liver metastases. 1 (1.4%) of patients had peritoneal metastases, 2 (2.7%) had abdominal metastatic lymph nodes and peritoneal metastasis, and 2 (2.7%) of patients had abdominal metastatic lymph nodes, liver and lung metastases. 1 (1.4%) of patients had metastatic lymph nodes in the abdomen and acid in the abdomen. One of patient (1.4%) had metastatic lymph nodes in the abdomen and mediastinum, 1 (1.4%) of patient had metastatic lymph nodes in the abdomen and mediastinum, and metastases in the liver, 1 (1.4%) of patient had metastatic lymph nodes, bone and peritoneum metastases in the abdomen. 1 (1.4%) of patient had metastatic lymph nodes in the abdomen, metastases in the lung and peritoneum, 1 (1.4%) of patient had metastatic lymph nodes in the neck, mediastinum and abdomen and metastases in the liver, 1 (1.4%) of patient had metastatic lymph nodes in the abdomen with liver and brain metastases, 1 (1.4%) of patient had lung metastases. There was no metastasis in 10 of the patients.

The SUVmax of gastric tumors of the patients ranged between 1 and 31.7, and the median value was calculated as 8.6. Metastasis SUVmax ranged between 1 and 19.2, with a median of 6.9.

Tumors were located in the cardia in 16 (19.3%) patients, in both the cardia and corpus in 5 (6%) patients, in the corpus in 14 patient (16.9%), in the corpus-antrum in 8 (9.6%) patients, in the antrum in 29 (34.9%), in the antrum-pylor in 6 (7.2%), in the pylor in 4 (4.8%) patient, diffusely located in 1 (1.2%) patient.

Evaluation of the patients' tumor tissues according to the HDAC1 percentage demonstrated that they were HDAC1 positive in 74 (89.2%) patients and HDAC1 negative in 9 (10.8%) patients.

The mean SUVmax of the primary gastric tumor was calculated as 8.6. However, there was no correlation between the positivity of HDAC1 protein from the tumor site and SUVmax, whether it was above or below this value (p= 0.369). While 53 (71.6%) of 74 HDAC1 positive patients developed metastases, 21 patients (29.4%) had no metastases. Of the 9 HDAC1 negative patients, 6 (66.6%) had metastases and 3 (33.4%) did not. There was no significant correlation between the positivity of HDAC1 protein and the presence of metastasis (p= 0.757).

Of the 74 HDAC1 positive patients, 14 (18.9%) had tumors located in the cardia, 4 (5.4%) had tumors located in the cardia-corpus, 13 (17.6%) had tumors located in the corpus, 8 (10.8%) tumors located in the corpus-antrum, 26 (35.1%) tumors located in the antrum, 6 (8.1%) tumors located in the antrum-pylor, 3 (4.1%) tumors located in the pylor and there was no diffuse localization. Of the 9 HDAC1 negative patients, 2 (22.2%) had tumors located in the cardia, 1 (11.1%) had diffusely located tumors, 1 (11.1%) had cardia and corpus located tumors, 1 (11.1%) had corpus located tumors, 3 (33.3%) had antrum located tumors and 1 (11.1%) had tumors located in the pylor of the gastric. There was no a significant correlation between HDAC protein positivity and tumor localization (p= 0.121) (Table 1). According to the Lauren Classification, 14 (93.3%) of 15 patients with diffuse-type gastric cancer were HDAC1 positive and 1 (6.7%) was HDAC1 negative. Of the 63 patients with intestinal-type gastric cancer, 55 (87.3%) were HDAC1 positive and 8 (12.7%) were HDAC1 negative. All five patients with mixed-type gastric cancer were HDAC1 positive. However, there was no significant relationship

Table 1. Relationship between HDAC1 positivity and tumor localization

Tumor localization	HDAC1 negativity	HDAC1 positivity	p
Cardia	2 (12.5%)	14 (87.5%)	0.121
Cardia-corpus	1 (20%)	4 (100%)	
Korpus	1 (7.1%)	13 (92.9%)	
Korpus- Antrum	0 (0%)	8 (100%)	
Antrum	3 (10.3%)	26 (89.7%)	
Antropylor	0 (0%)	6 (100%)	
Pylor	1 (25%)	3 (75%)	
Diffüz	1 (100%)	0 (0%)	
Total	9 (10.8%)	74 (89.2%)	

between the HDAC1 protein positivity and Lauren Classification (p= 0.576) (Table 2).

Of the 74 HDAC1 positive patients, 49 (66.3%) had lymph node metastases whereas 25 (33.7%) had no lymph node metastasis. Of the 9 HDAC1 negative patients, 6 (66.7%) had lymph node metastases while 3 (33.4%) had no lymph node metastasis. However, there was no statistically significant correlation between the HDAC1 protein positivity and the presence of lymph node metastasis (p= 0.978).

Among the 57 HDAC1 positive patients, 30 (52.6%) were poorly differentiated, 20 (35%) were moderately differentiated, and 7 (12.4%) were well differentiated. In the group of 9 HDAC1 negative patients, 3 (33.4%) were poorly differentiated, 4 (44.4%) were moderately differentiated, and 2 (22.2%) were well differentiated. There was no significant correlation between the HDAC1 protein positivity and tumor grade (p= 0.514). We could not access 17 patients' data. Among the 29 female patients, 26 (89.7%) were HDAC1 positive and 3 (10.3%) were HDAC1 negative. While 48 (88.9%) of the 54 male patients were HDAC1 positive, 6 (11.1%) were HDAC1 negative. There was no significant relationship between the HDAC1 protein positivity and the sex variable (p= 0.785).

Among the 45 patients younger than 65 years of age, 40 (88.9%) were HDAC1 protein-positive and 5 (11.1%) were HDAC1 negative. In the group of 38 patients aged 65 and over, 34 were HDAC1 positive (89.5%), while 4 (10.5%) were HDAC1 negative. There was no significant correlation between the positivity of HDAC1 protein and the age of the patients, whether they were < 65 years old or ≥ 65 years old (p= 0.932). Out of the total 83 patients, 73 had metastases, while 10 did not. The mean SUVmax of the primary tumor was calculated as 9.83±6.2 and 11.2 ± 6.5 in the patients with and without metastasis respectively. There was no statistically significant difference between the patients with and without metastatic gastric cancer in terms of the mean SUVmax of the tumors (p= 0.417). There was no significant difference between the mean SUVmax of the tumors in terms of the localization of primary tumors (p= 0.933). The median SUVmax was 10.5 (range: 1-31.7) in the patients whose histopathological subtype was an intestinal type. The median SUVmax was 4.9 (range: 1-25.7) in patients with diffuse type and 5.8 (range: 2.9-16.5) in patients with mixed type. According to the Lauren classification, there was a significant difference between the median SUVmax of the histopathological subtypes. The median SUVmax was higher in the patients with intestinal-type gastric cancer than was in the patients with other types (p= 0.001).

While the median HDAC1 protein score was 3.5 in the early-stage patients, it was 8 in the advanced stage (stage 1-2) patients, and 12 in the metastatic stage (stage 4) patients. A significant correlation was observed between histopathological stages and median HDAC1 protein scores (p= 0.021). The HDAC1 protein score increased as the patients' stage progressed (Table 3).

While the median SUVmax was 5.1 (range: 4-6.2) in the early-stage patients, it was 7.85 (range: 1-30) in the locally advanced-stage patients and 10.7 (range: 3.5-31.7) in the metastatic-stage patients. A significant correlation was observed between the histopathological stages and the median SUVmax. (p= 0.048). An increase was observed in the median SUVmax as the patients' stage progressed.

According to the Lauren classification, out of the 15 patients with diffuse gastric cancer, 11 (73.3%) had metastasis, while 4 (26.7%) had no metastasis. Of the 63 intestinal-type gastric cancer patients, 52 (82.5%) had metastasis while 11 (17.5%) did not.

Table 2. Relationship between HDAC1 positivity/negativity, and demographic and histopathological characteristics of the patients

Characteristics	Total	HDAC1 negative (< 4) n (%)		HDAC1 positive (≥ 4) n (%)	p
Sex	Men	54	6 (11.1%)	48 (88.9%)	0.915
	Women	29	3 (10.3%)	26 (89.7%)	
Age (years)	< 65	45	5 (11.1%)	40 (88.9%)	0.932
	≥ 65	38	4 (10.5%)	34 (89.5%)	
Location of the tumor	Cardia	16	2 (12.5%)	14 (87.5%)	0.121
	Cardia-Corpus	5	1 (20%)	4 (80%)	
	Korpus	14	1 (7.1%)	13 (92.9%)	
	Korpus- Antrum	8	0 (0%)	8 (100%)	
	Antrum	29	3 (10.3%)	26 (89.7%)	
	Antropylor	6	0 (0%)	6 (100%)	
	Pylor	4	1 (25%)	3 (75%)	
	Diffüz	1	1 (100%)	0 (0%)	
Histologic degree	G1 well differentiated	9	2 (22.2%)	7 (77.8%)	
	G2 moderately differentiated	24	4 (16.7%)	20 (83.3%)	
	G3 little differentiated	33	3 (9.1%)	30 (90.9%)	
Lauren Classification	Intestinal	63	8 (12.7%)	55 (87.3%)	0.709
	Diffuse	15	1 (6.7%)	14 (93.3%)	
	Mixed	5	0 (0%)	5 (100%)	
	Lymph Node				
Metastasis	No	28	3 (10.7%)	25 (89.3%)	0.978
	Yes	55	6 (10.9%)	49 (89.1%)	
Primary Tumor	< 8.6		4 (15.4%)	22 (84.6%)	0.369
SUVmax (median)	≥ 8.6		5 (8.8%)	52 (91.2%)	
Presence of Metastases	Yes	24	1 (10%)	9 (90%)	0.927
	No	59	8 (11%)	65 (89%)	

Among the 5 mixed-type patients, 3 (60%) had metastasis, but 2 (40%) did not. According to the Lauren Classification, there is a significant relationship between metastasis development and cancer types. Metastasis was more common in patients with intestinal-type gastric cancers. However, metastasis rates were lower in patients with diffuse-type gastric cancer (p= 0.0001).

Given all the patients, the median overall survival time was 22 months. 1-year survival rate was 73%, 2-year survival rate was 48%, and 5-year survival rate was 27%. Given the relationship between HDAC1 proteins and the survival of the patients, the 2-year survival rate was high in HDAC1 positive patients; however, it was not statistically significant (Table 4) (Figure 2).

Table 3. Relationship between the median HDAC1 scores and histopathological stages of the patients

Stage	Early Stage	Locally Advanced Stage	Metastatic Stage	p
HDAC1 score Median (Range)	3.5 (3-4)	8 (1-12)	12 (2-12)	0.021*
SUVmax Median (Range)	5.1 (4-6.2)	7.85 (1-30)	10.7 (3.5-31.7)	0.048*

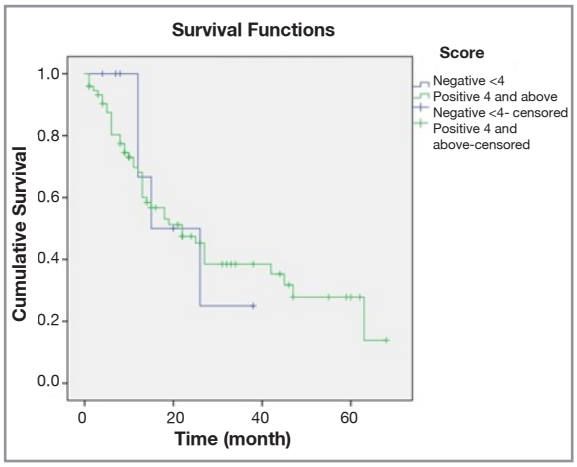

Figure 2. Association of HDAC1 positive/negative with prognosis

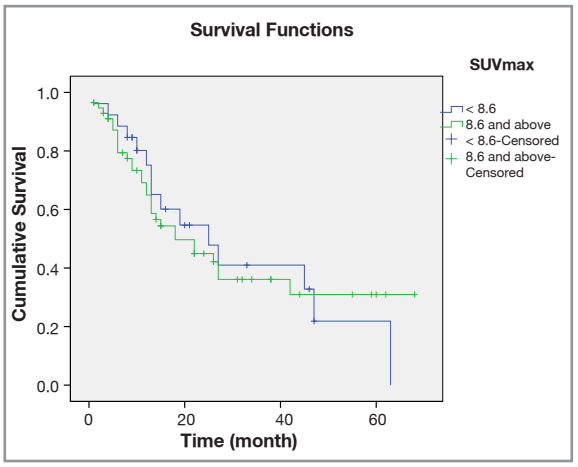

Figure 3. Relationship between tumor SUVmax and prognosis

Based on the relationship between the SUVmax calculated from the primary tumor lesion and the survival time of the patients, it was observed that patients with low SUVmax had a longer overall survival time. However, this difference was not found to be statistically significant (p= 0.646) (Figure 3).

DISCUSSION

The fact that HDAC1 overexpression causes gastric cancer and that HDAC1 inhibitors give hope that they can be used in the treatment of gastric cancers has increased the interest in this enzyme. Although there are not enough clinical studies in the literature on the relationship between HDAC1 overexpression and gastric cancer, we found only one study in which the relationship between HDAC1 protein and PET/CT data was investigated.[9] Therefore, we expect that the results of our study be of value.

While 74 (89.2%) of the 83 patients participating in our study had HDAC1 protein positivity, only 9 (10.8%) patients were HDAC1 negative. Therefore, our study clearly demonstrates that HDAC1 is overexpressed in gastric cancer and it probably plays an important role in gastric carcinogenesis. According to the results of Choi, et al.'s study[10] in which gastric cancer and normal gastric tissues of 25 patients were studied, HDAC1 expression significantly increased in 17 (68%) cancer tissues.

The amount of HDAC1 in cancerous tissue increased by 1.8 times compared to the matched gastric tissue and, on average,four times compared to normal gastric tissue. According to the results of Jiang et al.'s study conducted with 252 patients[7], HDAC1 positivity was observed in 60% of the gastric cancerous tissues. This rate was considerably higher than that in normal gastric cells (19.7%). In Mutze et al.'s study that included 127 patients with gastric cancer[8], 69 (54%) of the patients were stained positive for HDAC1.

In our study, no relationship was determined between HDAC1 positivity and gastric tumor SUVmax, metastasis SUVmax, presence of metastasis, localization of the tumor, tumor grade, or Lauren classification of the tumor. There was also a significant correlation between HDAC1 protein score and tumor stage (p= 0.021). The stage progressed

Table 4. Relationship between HDAC1 positivity/negativity and prognosis

HDAC1 (No)	Two-year survival rate	Median	p
Negative (9)	25%	15 months	0.917
Positive (74)	48%	22 months	

as the HDAC1 protein score increased. This observation aligns with Cao et al.'s study [11], where the amount of HDAC1 protein increased as the stage progressed.

Although in our study, there was no significant relationship between HDAC1 protein levels and lymph node metastasis, in Mutze's, Sudo's, Weichert's, Jiang's and Chen et al.'s studies, the rate of lymph node metastasis was high in patients whose HDAC1 protein level was high.[7,8,9,12,13]

Although there was no relationship between HDAC1 protein levels and tumor differentiation in our study, in Chen et al.'s study[9], HDAC1 protein levels in the patients with well-differentiated tumors were higher than those in patients with moderately/poorly differentiated tumors. In Mutze et al.'s study[8], no significant relationship was determined between HDAC1 levels and tumor differentiation.

Although we did not find a significant relationship between the HDAC1 protein levels and the age variable in our study, in their study, Mutze et al. found a significant relationship between the HDAC1 positivity and advanced age (p= 0.01).[8] As in our study, in Mutze et al.'s study, no relationship was determined between HDAC1 protein levels and the sex variable.[8]

In our study, there was no significant relationship between the gastric tumor SUV(max) and presence/absence of metastasis (p= 0.417). In their study, Mochiki et al.[14] determined a significant relationship between the gastric tumor SUV(max) and presence/absence of metastasis. However, in our study, there was a significant relationship between the gastric tumor SUVmax and Lauren classification (p= 0.0001). SUVmax was higher in patients with intestinal type gastric cancer. In addition, a significant relationship was determined between the stage and the mean SUVmax (p= 0.048). As the stage progressed, the mean SUVmax calculated from the tumor increased.

In our study, no significant difference was determined between the SUVmax calculated from the tumors of the patients and HDAC1 protein levels. However, in Jiang et al.'s study[7], tumors with high HDAC1 protein levels also had high SUVmax, and the p value was calculated as < 0.05.

Similar to our study, Chen et al.'s study[9] conducted with 408 gastric cancer patients and 211 normal gastric control groups[9] showed that patients with HDAC1 protein-positive gastric cancer had a better prognosis and longer overall survival time, and the p value was calculated as 0.01. However, in Sudo et al.'s study[13] conducted with 140 patients and Weichert[12], Jiang[7], and Cao's[11] study conducted with 143 patients, HDAC1 protein decreased overall survival time.

In their study, Mutze, et al.[8] concluded that although HDAC1 protein levels did not have a significant relationship with overall survival time, patients with high HDAC1 expression levels had a shorter overall survival time. Additionally,among the patients who responded to treatment, those with high HDAC1 expression had shorter overall survival time.[8]

According to the results of our study, although it was not statistically significant, 2-year survival rates were higher in HDAC1 positive patients.

The median overall survival time was 22 months in our patients. While the 1-year overall survival rate was 73%, the 2-year overall survival rate was 48%.

One of the most important factors limiting (limitations) our study was the small number of patients. We were unable to determine the tumor grade in 17 of the patients because some patients were diagnosed only with biopsy, and some were not operated for various reasons. We were unable to analyze prognostic statistical data because some patients did not come to follow-ups.

Conclusion

According to the results of our study, HDAC1 protein levels were high in the majority (89.2%) of the gastric cancer patients. Although not statistically significant, HDAC1 positive patients had longer survival times than HDAC1 negative patients. These results recall the question of whether the use of HDAC1 inhibitors would be more effective primarily in patients diagnosed with dysplasia/metaplasia via endoscopy, if the effect of HDAC1 is positive after the tumor has developed. Recently it is thought that further in vitro and clinical studies are needed on the therapeutic efficacy of HDAC

protein, which has been a target for drug development in gastric cancers.

According to the results of our study, in HDAC1-positive gastric cancer patients, there was no significant relationship between SUVmax showing tumor metabolism in 18F-FDG PET/CT and SUVmax showing tumor metabolism, and the variables such as presence/absence of metastasis, patient age and sex. We also determined that in the patients with a high gastric tumor SUVmax intestinal-type gastric cancers were more common and that more metastases were observed in patients with a high tumor SUVmax regardless of tumor type. We think that more meaningful results can be achieved by increasing the number of patients in studies to be conducted in the future.

Funding: *This project was supported by Cumhuriyet University Scientific Research Projects Commission as a Medical Specialization Project (Number: T-2021-924).*

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