Original Article

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The Relationship Of Suv Value In Pet-Ct With Tumor Differentiation And Tumor Markers In Gastric Cancer

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ABSTRACT

Purpose: In this study, we aimed to investigate the relationship between the use of FDG-PET/CT, SUVmax value of tumor and tumor differentiation and tumor markers in initial staging of patients with gastric cancer.

Materials and Methods: The study included 50 patients (14 F, 36 M, mean age; 63 ± 11 years, age range; 31-80 years) who have undergone initial staging with FDG-PET/CT after the diagnosis of gastric cancer with endoscopic biopsy between January and June 2013. Serum AFP, CA 19-9, CEA and CRP levels were measured in patients prior to imaging. PET/CT images were evaluated for primary tumor, locoregional spread and distant organ metastases, and classified by TNM staging. Semiquantitative data were collected by SUVmax measurement in pathological regions of involvement. Data were analyzed statistically.

Findings: FDG-PET/CT showed primary gastric cancer with a sensitivity of 87%. Imaging findings were normal in three patients (1/3; mucinous adenocarcinoma, 2/3; signet-ring cell adenocarcinoma). With FDG-PET/CT, 3/50 patients were classified into Stage 1B, 3/50 patients into Stage 2, 5/50 patients into Stage 3A, 5/50 patients into Stage 3B, 5/50 patients into 3C and 29/50 patients into Stage 4. The mean SUVmax; was calculated as 11.35 ± 4.3 (poorly differentiated adenocarcinoma; 5.4 ± 1.7, moderately differentiated adenocarcinoma; 10.3 ± 4.8) for the primary tumor and 14.9 ± 6.3 for tumor metastasis. There was a positive correlation between the measured SUVmax and stage and the grade of primary tumor ($p < 0.05$). While the relationship between SUVmax and serum AFP and CRP levels was statistically significant ($p < 0.05$), the relationship between it and serum CA 19.9 and CEA levels was not statistically significant ($p > 0.05$).

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Result: In our study, the SUVmax value of primary tumor was found to be connected with the degree of differentiation of primary tumor and biochemical tumor markers CRP and AFP. The fact that SUVmax value of the primary tumor is high is important in terms of giving clues about the presence of the said factors affecting the prognosis of the disease.

Key Words: Gastric cancer, FDG-PET/CT, initial staging, SUVmax, tumor markers

INTRODUCTION

Throughout the world, gastric cancer is the third leading cause of cancer-related deaths in men after lung cancer; and also, the second one in women after breast cancer[1]. It is difficult to diagnose it in the early period because it frequently gives symptoms with weight loss and anemia [2]. Therefore, early diagnosis and accurate staging are important.

The gold standard method for diagnosis of gastric cancer is still endoscopy and biopsy. However, computed tomography (CT), endoscopic ultrasonography (EUS) and diagnostic laparoscopy increased their values as other methods. Generally, the most important problem of these methods is that there is insufficient evidence for the diagnosis of metastatic lymph nodes due to their relatively low detection rate [3]. Positron emission tomography (PET) is a molecular imaging method that provides physiological information required for clinical diagnosis based on change in tissue metabolism. Many of the malignant tumors can be noninvasively visualized through PET carried out with fluoro-2-deoxyglucose (FDG) labeled with F-18 isotope due to increased glucose metabolisms [4]. FDG-PET/CT is a imaging modality in which the limited spatial resolution of PET is compensated by CT, and anatomical and morphological information is completed with metabolic and molecular information and has a leading role in staging, treatment response evaluation, prognosis determination and restaging stages in various types of malignancies [5,6]

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Alpha fetoprotein (AFP), carcinogenic antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA) and C-reactive protein (CRP) are the tumor markers used traditionally for the early diagnosis, prognosis prediction, and post-treatment recurrence investigation of gastric cancer [7]. The prognostic significance of CRP in esophageal, gastric, liver, pancreatic, colorectal and prostate cancers is frequently mentioned [8].

In this study, we investigated the initial staging performance of FDG-PET/CT in patients with gastric cancer, as well as the relationship of PET/CT findings with the degree of tumor differentiation and tumor markers.

MATERIALS AND METHODS

The study group consists of 50 patients (14 F, 36 M, mean age; 63 ± 11 years, age range; 31-80 years) diagnosed with gastric cancer by endoscopic biopsy who underwent initial staging with FDG-PET/CT before the treatment, between January and June 2013. To avoid the false positive states of tumor markers; patients diagnosed with chronic inflammatory/infectious disease, collagen tissue disease and concurrent second primary cancer were excluded from study prior to imaging. Informed consent form was obtained from the patients before the PET/CT study. In cancer staging, "revised AJCC cancer staging manual 7th ed. system was used [9].

FDG-PET/CT imaging protocol

Fasting blood glucose levels of patients were measured before PET/CT study. PET/CT scan was not performed in patients with fasting blood glucose levels higher than 150 mg/dl. The patients were injected with 8-12 mCi (296-444 MBq) of iv FDG, 60 minutes after making them drink 25 ml of oral contrast (Omnipaque 300mg/50mL, GE Healthcare) agent in 1 liter of water. One hour after the injection, non-diagnostic CT imaging was performed for anatomic localization and attenuation correction. CT imaging was performed using the 70 mAs and 120 keV values from the the thigh to the cranium with the patient in supine position. Following CT imaging, PET imaging was performed with the patient in the same position from the proximal thigh to the base of

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the skull, with 9 bed positions and with 2-minute periods for each bed position. Biograph 16 TruePoint model PET/CT device (Siemens, Germany) was used in all patients for FDG-PET/CT.

Evaluation of Images

PET/CT images were evaluated together by two experienced nuclear medicine specialists. Prior to the evaluation of PET/CT images, the evaluators were informed about the patient's medical history, the results of the patient's previous anatomical imaging studies, the complaints of the patients, the tumor markers and the histopathological examination results. The final decision was made by consensus when the two evaluators had different views during the evaluation of the images.

In FDG-PET/CT images, all focal hypermetabolic activity involvements that are higher than ground activity except FDG's physiological involvement areas were accepted as pathological involvement. Focal hypermetabolic areas in the gastric tissue were evaluated as local lesion and focal hypermetabolic areas in the liver with higher concentrations than adjacent parenchymal tissues were evaluated as liver metastasis. Focal linear activties detected along with the gastric mucosa were accepted as changes related to inflammation. Focal or diffuse increased activity involvements in the mesenteric area that does not correspond to the bowel wall were accepted as peritoneal carcinomatosis. Moderately diffuse or segmental hypermetabolic areas were considered as physiological involvement and focal increased hypermetabolic areas were accepted as metastasis in areas that correspond to the bowel wall. While metastases other than liver metastases were accepted as distant metastases, liver metastases were evaluated separately. SUVmax of each pathological lesion read was measured and recorded.

Tumor markers

Biochemical measurements of tumor markers including AFP, CA 19-9, CEA and CRP were made in each patient after histological diagnosis and before imaging. Immunochemical method and “Beckman Coulter Immunoassay (DXI 800, CA, USA)” device were used for serum AFP, CA 19-9 and CEA measurements. Serum CRP level

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was measured by nephelometric method using “Siemens BN Behring analyzer (Siemens Healthcare Diagnostics, Germany)” device.

Statistical analysis

Statistical analysis and descriptive statistics were performed using the "SPSS for Windows 15.0" software package (SPSS Inc., Chicago, IL, USA). Data were presented as number, percentage, mean and standard deviation. The Kolmogorov Smirnov Test was used to determine whether the variables were in compliance with normal distribution. Mann-Whitney U Test was used for group analyses of two groups of numerical variables such as serum CEA or CRP level, and Kruskal Wallis Test was used for the group analyses of those with more than two groups. Chi-Square Test and Fisher's Exact Test were used in the analysis of categorical variables. As in the investigation of the relationship between serum AFP level and SUVmax level of the primary tumor, Spearman Correlation Analysis was used to determine whether two numerical variables were correlated to each other. Statistical significance level was accepted as $p < 0.05$.

Ethical Dimension of the Research

The compatibility of the study with ethical principles was evaluated by the Ethics Committee of **** University Faculty of Medicine. This article was approved by the Ethics Committee of the Non-Drug Clinical Trials of ***** University Faculty of Medicine with 28.02.2013 date and with number 39 and decision number 13. Written permission was received from the directors of the **** University Training and Research Hospital in order for the study to be carried out. The patients involved in the research provided verbal and written consent about their willingness to participate.

FINDINGS

The study group consisted of 50 patients [36 M (72%), 14 F (28%)] diagnosed with gastric cancer after endoscopic biopsy. The mean age of the patients was 62.9 ± 11.0 and the age range was 31-80 years. As a result of histopathological examination of biopsy materials; 11/50 patients (22%) were reported as moderately differentiated

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adenocarcinoma, 7/50 patients (14%) as poorly differentiated adenocarcinoma, 2/50 patients (4%) as neuroendocrine differentiated adenocarcinoma, 3/50 patients (6%) signet-ring cell carcinoma, 3/50 patients (6%) as mucinous adenocarcinoma and 24/50 patients (48%) were reported as untyped/other adenocarcinoma. Demographic characteristics and histopathological examination findings of the patients are summarized in Table 1. After initial staging by PET/CT, surgical treatment decision was taken for 24/50 (48%) of the patients and 26/50 (52%) of the patients were accepted as inoperable. Of the 24 patients for whom surgical intervention was determined, 14 had total gastrectomy and 10 had distal subtotal gastrectomy. D2 lymp node dissection was applied in all total gastrectomies wheres as lmyph node dissection was D1 in distal gastrectomies.

PET/CT findings

Prior to the treatment, presence of primary tumor (T), nodal invasion (N), and distant metastasis (M) were evaluated according to FDG-PET/CT findings. The tumor stage was found to be Tx in 26/50 patients (52%), T1b in 3/50 patients (6%), T2 in 1/50 patients (2%) and T4a in 20/50 patients (40%). When evaluated in terms of lymph node spread; 26/50 patients (52%) were Nx, 4/50 patients (8%) were N0, 7/50 patients (14%) were N1, 6/50 patients (12%) were N2, 4/50 patients (8%) were N3a and 3/50 patients (6%) were N3b. While the presence of distant metastases (liver in 23 patients and extrahepatic metastases in 6 patients) was detected in 29/50 patients (58%), there was no finding detected in imaging in 21/50 patients (42%) that could be compatible with distant metastasis. In conclusion, according to clinical TNM staging; 3/50 patients (6%) were classified into Stage 1B, 3/50 patients (6%) into Stage 2, 5/50 patients (10%) into Stage 3A, 5/50 patients (10%) into Stage 3B, 5/50 patients (%10) into Stage 3C and 29/50 patients (58%) into Stage 4 (Table 1). The sensitivity of FDG-PET/CT in demonstrating primary tumor was 87%. Of the 3 patients whose primary gastric tumor cannot be demonstrated by PET/CT, 1 was reported as mucinous type adenocarcinoma and 2 as signet-ring cell adenocarcinoma. (Figure 1).

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Mean SUVmax used as semiquantitative index was calculated as 11.35 (3.20 - 26.91) for all patients. Difference between the mean SUVmax (14.9 ± 6.3) of the patients with distant metastasis (29/50 patients) and the mean SUVmax (7.4 ± 4.4) measured on patients without distant metastasis were statistically significant. ($p<0.05$). Similarly, the difference between the mean SUVmax (13.5 ± 6.7) (Figure 2) measured in the patients with liver metastasis (23/50 patients) and the mean SUVmax (9.8 ± 6.2) measured in patients without liver metastasis was also found to be statistically significant. ($p<0.05$). It was observed that the mean SUVmax value increased as the degree of differentiation of the tumor increased. The mean SUVmax was measured as 5.4 ± 1.7 in the poorly differentiated adenocarcinomas, while the mean SUVmax measurement was 10.3 ± 4.8 in the moderately differentiated adenocarcinomas. The difference between these two groups was statistically significant. ($p<0.01$). There was also a statistically significant relationship positively increasing between the disease stage and the SUVmax measurement result of the primary tumor. ($p<0.01$).

Compliance with tumor markers

Serum AFP positivity rate was 30% (15/50 patients) in patients involved in this study. While the mean SUVmax measurement of patients with serum AFP levels within normal range was 10.26 ± 6.3, this value was 13.9 ± 6.9 in patients with elevated AFP. We have detected weak positive correlation between the primary tumor SUVmax and AFP reading of patients (r: 0.238, $p<0.05$) with liver metastasis (Figure 3).

Serum CA 19-9 measurement result was positive in 44% of the patients (22/50 patients). However, there was no statistically significant relation detected in correlation analysis between serum CA 19-9 level and disease stage, presence of distant metastasis and SUVmax measured in primary tumor.

Serum CEA measurement result was found to be positive in 56% (28/50 patients) of the patients. There was a significant weak correlation between serum CEA level and disease stage (r: 0.203, $p<0.05$). No statistically significant relationship was

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found between the serum CEA measurement results of patients and the SUVmax readings of the primary tumor.

Serum CRP level has exceeded the upper limit of the normal reference range in 52% of patients (26/50 patients). More than half of the patients with high serum CRP (16/26 patients) had a late stage disease. There was a positive correlation between SUVmax of the primary tumor and serum CRP level. However, this correlation was not statistically significant.

DISCUSSION

In our study, we have demonstrated that the SUVmax value obtained from PET-CT in patients with gastric cancer was correlated with tumor differentiation, presence of liver metastasis, presence of distant metastasis and biochemical tumor markers.

Up to today, surgical treatment has been the treatment of choice in the middle stage and even in some advanced stage gastric cancers. Therefore, early diagnosis, correct clinical staging and selection of appropriate surgical procedure are of prognostic importance [10].

The criterion in which CT is used in metastatic lymph nodes is size increase. However, also in infective and inflammatory processes, lymph nodes may increase in size and this leads to false evaluations . Several studies comparing CT and PET in terms of preoperative lymph node staging in gastric cancer have shown that PET is not superior to CT in terms of sensitivity. This is mainly caused by the PET's failure to distinguish pathologic lymph node from the adjacent primary tumor due to its low resolution. However, it was reported that pathological lymph nodes can be detected more accurately when PET and CT are combined [11].

The literature reports that PET/CT is not used in T staging and can show the primary tumor with a sensitivity of 58-94% [12]. FDG involvement has been shown to be significantly lower in signet-ring cell adenocarcinoma, mucinous adenocarcinoma and poorly differentiated adenocarcinoma subtypes of gastric cancer [13]. Some investigators have reported that although PET/CT has a lower diagnostic efficacy in

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signet-ring cell and mucinous adenocarcinomas, it can distinguish sufficiently between other histological types [14]. Signet-ring cell and mucinous adenocarcinoma causing false negative results on PET/CT were found to have insufficient GLUT-1 expression in tumor cell membranes [11,15] Similarly, histopathology of patients in our study group whose primary tumor could not be visualized was reported as mucinous adenocarcinoma in one patient and signet ring cell adenocarcinoma in two patients.

SUVmax is a semiquantitative parameter calculated by taking into account the amount of FDG administered to the patient, the patient's weight and the physical decay of FDG . It has been observed that the value of SUVmax is higher in fast-growing tumors with high glucose use than in slow-growing tumors [16].

Previous studies reported that there was a correlation between the degree of differentiation of the tumor and the level of FDG involvement in gastric cancer, that the SUVmax value was significantly lower in well-differentiated types compared to the poorly differentiated types, and also that there could be a significant difference in SUVmax in cases with lymph node metastasis. [17]. Some diverse results were also present in the literature. In a previous study authors found that moderately differentiated (grade 2) gastric adenocarcinomas had higher SUVmax values compared to poorly differentiated ones (grade 3) [13]. Our results support that study as we found that there was a significant difference between the poorly differentiated adenocarcinomas and moderately differentiated adenocarcinomas in terms of in SUVmax (5.4 ± 1.7 vs 10.3 ± 4.8, $p<0.05$). In addition, it was shown that there was a strong and significant relationship between SUVmax value of the primary tumor and the stage of the disease and distant metastasis. These findings partially support the previous literature findings.

Serum AFP levels are frequently a marker for germ cell tumor, hepatocellular cancer and AFP producing gastric cancer [18]. There are publications reporting that high serum AFP in gastric cancer is associated with liver metastasis [18,19]. High serum AFP is also known as a poor prognosis indicator in patients with liver metastasis [19]. In our series, a relation was found between high serum AFP and histopathological

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tumor type. However, a statistically significant relation between serum AFP values and SUVmax values in patients with liver metastasis is shown.

CA 19-9 is a tumor marker with an adhesion molecule. It was reported that this marker is 16-44% positive in gastric cancer [20]. This rate was found to be 44% in our patient group. High serum CA 19-9 in gastric cancer was associated with lymph node metastasis and peritoneal metastasis [21]. In a study, a statistically significant relation was found between high serum CA 19-9 and the disease stage, tumor size, serosal invasion, peritoneal metastasis and acid [22]. Another study has shown a correlation between high serum CA 19-9 and lymph node involvement, disease stage, vascular invasion and tumor size [23]. In another study, a relation was found between high serum CA 19-9 and liver metastasis, depth of tumor invasion, primary tumor size, and resectability of primary tumor [20]. In our study group, no statistically significant correlation was found between serum CA 19-9 level and tumor stage, distant metastasis and SUVmax.

CEA is the most studied tumor marker in terms of correlation with gastrointestinal malignancies. At the present time, serum CA 19-9 and CEA measurements are routinely used in the management of gastric cancer. Preoperative CEA level can also be used for the prediction tumor prognosis [20]. According to the literature, high serum CEA levels are detected in 15.9-57.6% of patients with gastric cancer. [20]. High level of serum CEA was found in 56% of our patient group and it is within the limits reported in previous studies. Some authors reported that serum CEA positivity is associated with liver metastasis, but not associated with histopathological type or tumor stage [24]. In a study, it was found that there was a significant relation between serum CEA positivity and the patient's gender (males have a higher rate of positivity), disease stage, tumor size, lymph node metastasis, liver metastasis, serosal invasion as well as peritoneal metastasis [25]. Another study found a relation between high serum CEA level and advanced stage disease, large tumor size, serosa invasion, liver metastasis and resectability of the primary tumor [22]. In a study conducted on 663

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patients with gastric cancer, a significant relation was found between high serum CEA and liver metastasis, peritoneal involvement and advanced stage disease [20]. Another study conducted in a large patient population (549 gastric cancer cases) showed a significant correlation between high serum CEA and liver metastasis, primary tumor resectability and tumor depth [26]. In this study, a strong correlation was found between the disease stage and the presence of liver metastases and high serum CEA. On the other hand, no significant relation was found between the histopathological subtype and SUVmax value of the primary tumor and high serum CEA. In this study, no statistically significant relation was found between the serum CEA measurement results of patients and the SUVmax readings of the primary tumor.

The production of CRP is regulated by IL-1, IL-6 tumor necrosis factor from proinflammatory cytokines. It is known that circulating products of these cytokines increase the synthesis of CRP in hepatocytes [27]. CRP is also produced by some tumor cells [28]. High serum CRP has also been reported in patients with gastric cancer [18]. Findings based on many studies have shown that high serum CRP levels can be used as an indicator of poor prognosis in lung, prostate, ovarian and gastrointestinal malignancies [29]. Serum CRP level is a cheap survey that can be easily measured in routine [30]. High serum CRP detected in malignant cases is probably a secondary response to tumor necrosis, regional tissue damage, and the associated inflammation. [31]. In this study group, serum CRP level read was high in 52% of the patients. In addition, a positive but statistically non-significant correlation was found between the SUVmax of the primary tumor and the serum CRP level.

There are some limitations of our study. First, the sample size of our study is relatively small and our findings need to be supported by studies with a larger sample sizes. Second, although our findings are valid for gastric cancer, no significant correlation was found for mucinous and signet ring cell subtypes.

In our study, the SUVmax value of primary tumor was found to be connected with the degree of differentiation of primary tumor and biochemical tumor markers

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CRP and AFP. The fact that SUVmax value of the primary tumor is high is important in terms of giving clues about the presence of the said factors affecting the prognosis of the disease.

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FIGURE LEGENDS

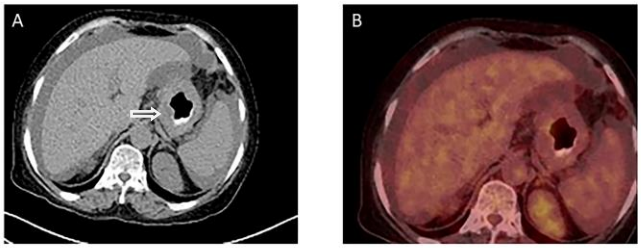

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Figure 1. a,b. (a) Wall thickening and an appearance of the mass are observed in the primary tumor area (arrow head) of the case with a signet ring cell type gastric adenocarcinoma in axial section CT image **(b)** In the PET/CT fusion image of the same patient; it is observed that metabolic F18-FDG involvement in primary tumor and other areas in the image is within normal limits.

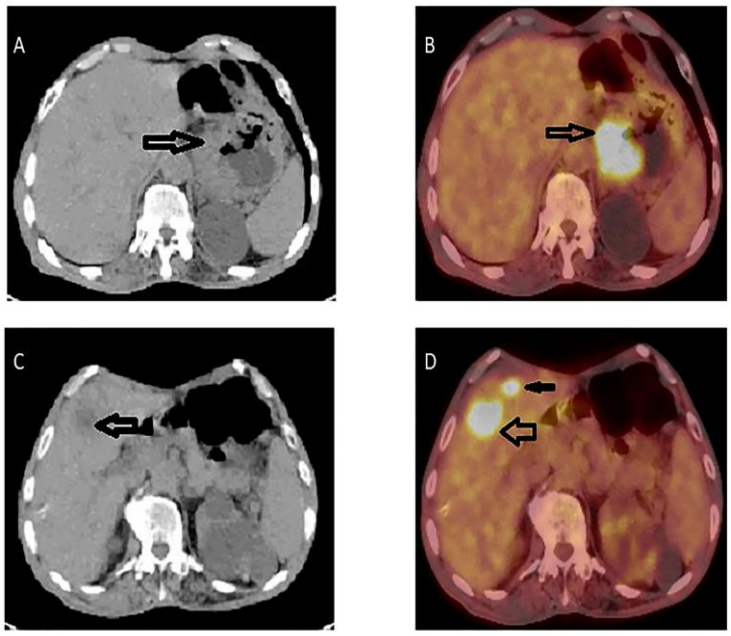

Figure 2. a-d. The case of adenocarcinoma located in gastric cardia region. **(a**) Wall thickening (arrow) is observed in axial section CT image **(b)** Hypermetabolic FDG involvement (arrow) is observed in primary tumor (SUVmax: 12.29) in axial section PET/CT fusion image **(c)** Tumor metastasis in liver is observed as hypodense area (arrow) in axial section CT image **(d)** Axial PET/CT fusion image shows focal hypermetabolic FDG involvement (SUVmax: 15.9) in liver metastases (arrows).

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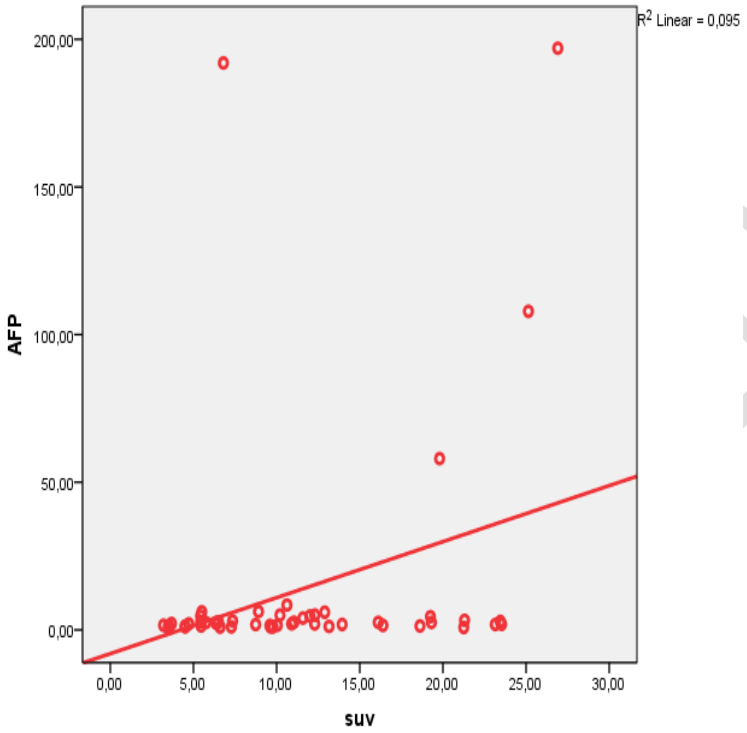

Figure 3. Linear correlation graph of the relationship between serum AFP levels measured in 50 patients with gastric cancer forming the study group and SUVmax readings of the primary tumor

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