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Original Article

The Correlation of Tumor Markers, Neutrophil/Lymphocyte Ratio and FDG PET/CT Measures in Pancreatic Cancer

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ABSTRACT

Background This review will outline the correlation of tumor markers and NLR (Neutrophil/lymphocyte ratio) with measures such as MTV (mean total volume), TLG (total lesion glycolysis), and SUV (standard uptake value) in ^{18}F FDG PET/CT in pancreatic carcinoma with the goal of selection of appropriate treatment modality and decrease rates of treatment failure and recurrences in pancreatic carcinoma by using tumor markers. In this way, we can predict the results of imaging modalities, using easy lab technics such as NLR and tumor markers.

Material and Methods 45 patients newly diagnosed with pancreatic cancer were included in the study. The diagnosis was confirmed by cytology. Their tumor marker levels (CA 19.9, CEA and AFP), NLR and PET/CT measurements (SUVmax, SUVmean, TLG, MTV) were obtained. Patients that were already diagnosed, followed up, or treated by the oncology department, were excluded.

Results When tumor markers were compared with PET/CT measurements (SUVmax, SUVmean, TLG, MTV and tumor size) there were no significant difference between them. Also, total uptake values of organs (liver, spleen, pancreas) were not related with tumor marker levels. However, there were positive significant correlation between tumor size and SUVmax, SUVmean, TLG (p=0.02, r:0.347; p=0.022, r:0.340; p=0.008, r:0.392).

Conclusions Tumor markers may help diagnosing or managing of pancreatic malignities, but we cannot predict PET/CT results according to tumor marker levels. So, tumor markers must be used as an adjunctive method for diagnosing malignities. They cannot be major determiner for malignities. Diagnosing and following up malignities should be supported by other laboratory technics and imaging methods.

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Introduction

Pancreatic cancer is an important health problem because of its aggressive behavior, it causes death in 95% of patients. Five-year overall survival (OS) rate after surgery is only about 10 to 20 percent whereas it is less than for metastatic pancreatic cancer.[1,2]

Cancer antigen 19.9 (CA 19.9) is a tumor marker present at high levels in some of malignities like bile duct, hepatocellular, colorectal, gastric, esophagus and pancreas cancer. It can be used to confirm the diagnosis of pancreas cancer, to evaluate the response to the treatment and the recurrence of pancreatic cancer.[3-5] Also, it can be elevated in benign conditions such as biliary tract obstruction, cholangitis, acute or chronic pancreatitis, liver cirrhosis, cystic fibrosis, thyroid diseases, inflammatory bowel disease or in normal, healthy population high levels can be detected.[6] It's known that 5% of population is unable to synthesize CA 19.9 even if there are malign conditions.[7]

Carcinoembryonic antigen (CEA) is a glycoprotein, and it has immunosuppressive and tumor cell adhesion properties, thus it facilitates metastasis and invasion of tumor cells.[8-13] In healthy individuals, CEA is present at very low levels in the blood because its production stops before birth. Although it is not tumor specific, its concentrations are raised in some types of cancer.[14-18]

Alfa-feto protein (AFP) is also produced during fetal development by the yolk sac and the liver. It plays a major role to screen liver cancer, preoperatively evaluation or postoperative monitoring and it can show advanced disease. Its levels can be raised not only in hepatocellular carcinoma, but also in other benign diseases and malignancies of testes and other germ cells.[19-21]

Neutrophil/lymphocyte ratio (NLR) is an indicator of systemic inflammation. We know that inflammation may play important roles in the development and progression of malignities. The presence of an elevated peripheral NLR has been recognized as a poor prognostic factor in various cancers.

PET/CT (positron emission tomography-computed tomography) is an imaging method that combines functional imaging with anatomical images. The most common radiotracer on PET is 18F-flurodeoxyglucose (18F-FDG), which is a glucose analogue. Pancreatic malignities are usually associated with an overexpression of glucose transporter 1 and it causes increased 18F-FDG uptake on PET/CT.[22] A main limitation of this imaging modality is the low spatial resolution and possibility of false positive uptake in normal structures or benign diseases, such as inflammatory processes.[23]

SUV max (maximum standardized uptake value) is a semi quantitative measure commonly used in 18F-FDG PET/CT. MTV (metabolic tumor volume), is a volumetric measurement of tumor cells with increased 18F-FDG uptake. The MTV on 18F-FDG PET/CT also demonstrates the metabolic activity, thereby it predicts the response to treatment and helps to determine the prognosis in head and neck cancers. In addition to SUVmax and MTV, TLG (total lesion glycolysis) constitutes another measurement derived from FDG PET/CT that can be useful for predicting prognosis in some of malignities.[24-27]

This study will outline the correlation of tumor markers and NLR with measures such as MTV, TLG, and SUV in 18F FDG PET/CT in pancreatic carcinoma to select appropriate treatment modalities and decrease rates of treatment failure and recurrences in pancreatic carcinoma by using tumor markers. In this way, we can predict the results of imaging modalities, using easy laboratory technics such as NLR and tumor markers.

Material and Methods

This cross-sectional study was conducted between April 2016 and December 2018 in internal medicine outpatient clinics of the Afyonkarahisar Health Science University, Turkey. It was approved by the institutional review board of Afyonkarahisar Health Science University with the number 2019/145.

Forty-five patients newly diagnosed with pancreatic cancer were included in the study. The diagnosis was confirmed by cytology. Their tumor marker levels (CA 19.9, CEA and AFP), NLR and PET/CT measurements (SUVmax, SUVmean, TLG, MTV) were obtained. The interval between the FDG-

Table 1. Mean values of tm markers and PET/CT measurements

	Minimum	Maximum	Mean	Std Deviation
Age	36	84	62	10.1
Tumor size (mm)	19	97	41.6	17.4
CA 19.9 (U/mL)	0.60	10.000	1329.7	2923.1
CEA (ng/mL)	0.99	71.29	10.2	14.2
AFP (ng/mL)	0.86	9.48	2.5	1.4
NLR	0.76	27.72	5.56	6.55
SUVmax	3.0	17.2	8.1	3.5
SUVmean	2.0	10.7	4.5	1.9
TLG	14.8	1248	161.3	188.3
MTV	4.5	156	38.3	35.5

NLR: neutrophil/lymphocyte ratio, TLG: total lesion glycolysis, MTV: metabolic tumor volum

PET/CT evaluation and determining tumor markers was no more than one week. Tumor size was obtained by measure of greatest diameter of tumor with computed tomography. Patients that already diagnosed, followed up or treated by oncology department, were excluded. 18F-FDG-PET/CT scans were performed in accordance with a standard whole-body oncological protocol in each institution following the guidelines of the European Association of Nuclear Medicine.

Statistical analysis

The data collected were analyzed by SPSS for IBM, version 23.0 (SPSS, Turkey). Patient characteristics were reported using frequency and descriptive analyses. Tests of normality was determined by Shapiro-Wilk test. Correlation between variables was analyzed with Spearman's test. A p-value of less than 0.05 was considered to statistically significant.

Results

Overall, 45 patients (20 men and 25 women) were included in this study. The mean age of patients was 62±10.1 year. The mean serum levels of tumor markers and NLR and PET/CT measurements are shown in Table 1.

Mean serum levels of CA 19.9 was 1329.7±2923.1 U/mL. 17 of the patients had normal CA 19.9 levels (under 37 U/Ll). 4 of them had levels above 10,000 U/mL.

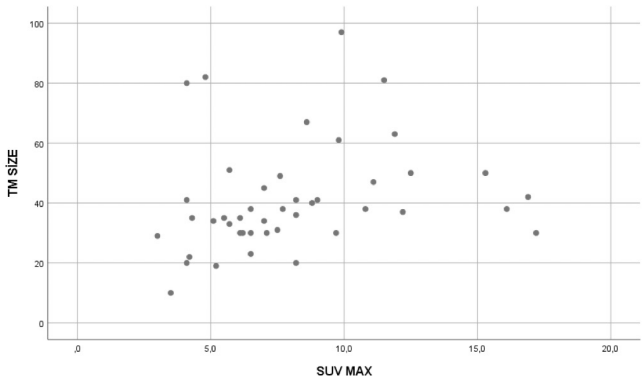
Mean CEA levels were 10.2±14.2 ng/mL and nineteen patients had normal CEA levels (under 5 ng/mL). However, AFP levels of all patients were at normal range (under 10 ng/mL). Mean NLR were 5.56±6.55. Three patients had very high levels of NLR (above 25) since they had bacterial co-infections.

When tumor markers were compared with PET/CT measurements there were no significant difference between them *(Table 2)*. Also, total uptake values of organs (liver, spleen, pancreas) were not related with tumor marker levels.

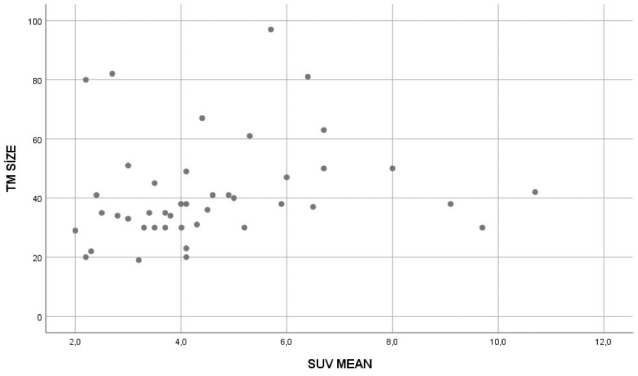
Table 2. P values of correlations between tumor markers, NLR and PET-CT measurements

	SUVmax	SUVmean	TLG	MTV	Tumor Size	Liver	Spleen	Pancreas
CA 19.9	0.503	0.464	0.961	0.845	0.660	0.751	0.439	0.811
CEA	0.322	0.228	0.487	0.379	0.499	0.643	0.319	0.071
AFP	0.854	0.884	0.152	0.166	0.095	0.105	0.498	0.708
NLR	0.315	0.186	0.468	0.478	0.912	0.512	0.252	0.696

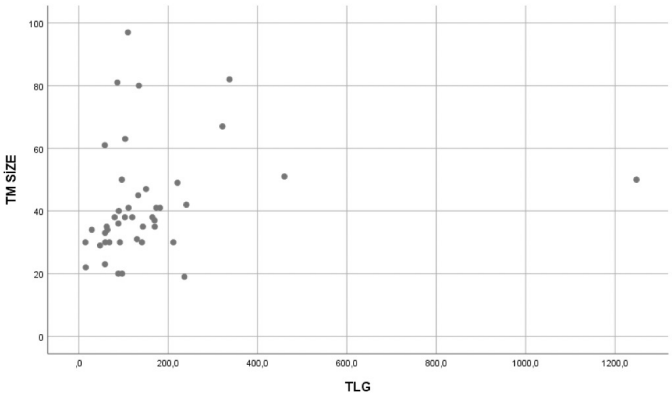
SUVmax: maximum standardized uptake value, SUVmean: Mean standardized uptake value, TLG= total lesion glycolysis, MTV=metabolic tumor volume, NLR= neutrophil lymphocyte ratio (P<0.05 significant)



Graphic 1. Correlation between tumor size and SUVmax



Graphic 2. Correlation between tumor size and SUVmean



Graphic 3. Correlation between tumor size and TLG

Interestingly, we found that a negative correlation between CA 19.9 levels and SUVmax, SUVmean but it was not statistically significance (p=0.503, r:-0.102; p=0.464, r:-0.112). Likewise, between CEA levels and TLG, MTV there were negative insignificant correlation (p=0.487, r:-0.106; p=0.379, r:-0.134). Negative correlation continued between AFP and TLG, MTV also tumor size. Its level was also negligible (p=0.152, r: -0.217; p=0.166, r: -0.210; p=0.095, r: -0.252). Between NLR and SUVmax, SUVmean there were negative insignificant correlation (p=0.315, r:-0.153; p=0.186, r:-0.201).

As expected, there were positive significant correlation between tumor size and SUVmax, SUVmean, TLG as shown in graphic 1,2 and 3. (p=0.02, r:0.347; p=0.022, r:0.340; p=0.008, r:0.392).

Discussion

Tumor markers are used for detecting, diagnosing, managing certain types of cancer and also determining the progression of disease.

Carbohydrate antigen 19.9 also called cancer antigen 19.9 or sialylated Lewis antigen is a tumor marker that is used firstly in the management of pancreatic cancer.[28] But it may be falsely positive in cases of biliary inflammation or obstruction.[29] However, CA 19.9 may be undetectable in Lewis antigen-negative individuals even if they have advanced cancer. In our study 17 of patients have normal CA 19.9 value.

As in this study, CA 19.9 serum level of 100 U/mL suggestive of unresectability or metastatic disease.[30] Our 4 patients that have distant metastasis, have up to 10,000 U/mL value of CA 19.9.

In pancreatic cancers, levels of CEA may reflect the tumor size, differentiation and metastasis.[31] Also, its pancreatic juice levels can be used as a tumor marker.[16,32-34] Preoperatively, high serum levels of CA 19.9 and CEA can be an indication of nonresectability or low chance of survival. While CA19.9 level is increased in both malignant and benign diseases, CEA increases only in malignant diseases.[35] In our study mean value of CEA was 10.2±14.2 ng/mL. Only 19 patients' results were under 5 ng/mL, it can be explained by the presence of CEA-related glycoproteins. Unlike the literature, we did not find any correlation between CEA levels and tumor size.

AFP has a high specificity for a hepatocellular carcinoma. It can be used for screening hepatocellular carcinoma and its levels also can be elevated in liver cirrhosis and chronic hepatitis.[36] We found that all AFP values were under 10 ng/mL. According to these results, we can predict that in pancreas malignities even if

there is distant metastasis (like liver metastasis), elevated AFP values are not always expected.

It is known that inflammation plays a very significant role in the development of cancer and may affect cancer patients' survival.[37] Systemic inflammation supports tumor metastasis and progression.[38] Because inflammatory cells and mediators generate a tumor related inflammatory microenvironment which plays vital roles in tumor progression and pathogenesis.[39] The previous meta-analyses had showed that the prognostic value of preoperative NLR for patients with cancers, such as epithelial ovarian or upper urothelial tract, hepatocellular carcinoma and all solid tumors.[40-43] In the same way, Li et al.[44] indicated that high NLR was associated with poor overall survival, disease free survival, recurrence free survival in colorectal cancer. They had defined high NLR as values higher than 5.[44,45] Also Fujii et al.[46] found that high NLR were significantly associated with high SUVmax in the primary tumor of breast. They demonstrated that high NLR may be predictive of poor prognosis among patients with breast cancer 46. In our study, the mean value of NLR was 5.56±6.55. Contrarily, we did not detect any significant relation between NLR and SUVmax, SUVmean.

Sun et al.[47] showed that SUVmax levels were associated with tumor size in pancreatic cancer patients.[47] Like them, we also defined relation between tumor size and SUVmax, SUVmean, TLG.

As a result, tumor markers may help diagnosing or managing of pancreatic malignities but we can not predict PET/CT results according to tumor marker levels. So, tumor markers must be used as an adjunctive method for diagnosing malignities. They can not be major determiner for malignities. Diagnosing and following up malignities should be supported by other laboratory technics and imaging methods.

Unfortunately, our study has some limitations. First of all, it is a retrospective study and involves small sample size and all patients were selected from same hospital. Therefore, to say a relation between tumor markers and PET/CT measurements, multi-center, large sample prospective studies are needed.

Conflict of interest

The authors declared that there are no potential conflicts of interest.

Authors' Contribution

Study Conception: MH; Study Design: MH; Supervision: EH, HD; Funding: EB; Materials: ABS, NU, FCH; Data Collection and/or Processing: RK; Statistical Analysis and/or Data Interpretation: RK, EB; Literature Review: EH, HD; Manuscript Preparation: MH; and Critical Review: EH, HD.

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