Evaluation of the Effectiveness of Bevacizumab Treatment in Patients with Metastatic Colorectal Cancer with PET-CT

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Abstract: *Purpose:* To evaluate the response to therapy with PET-CT in metastatic colorectal cancer patients treated with Bevacizumab and chemotherapy.

Methods: Twenty-two patients with metastatic colorectal cancer that were treated with bevacizumab and 6 cycles of chemotherapy were evaluated by whole-body PET-CT scan before and after the treatment in accordance with the European Organization for Research and Treatment of Cancer criteria.

Results: While 31.8% of patients responded to treatment (complete response + partial response), 68.2% did not respond to treatment (stable disease + progressive disease). The mean hepatic, extra hepatic, abdomen, lung and bone metastases SUVmax values were higher after treatment in comparison to the pre-treatment values. There was an increase in SUVmax values in those who did not respond to the treatment, while a decrease was observed in those who responded to the treatment. Survival was significantly increased in all patients that responded to the treatment. The difference in terms of gender, histological subtype, histological grade, primary tumor location, presence of metastases in regional lymph nodes and liver at the time of diagnosis or the response to the treatment was not statistically significant.

Conclusions: In this study we detected metabolic response before anatomical response with PET-CT in one third of metastatic colorectal cancer patients treated with Bevacizumab and chemotherapy. This finding suggests that PET-CT may be used as a measure to follow therapy response and predict the prognosis in metastatic colorectal cancer patients.

Keywords: Metastatic colorectal cancers, Bevacizumab, Chemotherapy, Response to therapy, PET-CT.

INTRODUCTION

Colorectal cancer is the most common cancer of the gastrointestinal tract. The diagnosis of colorectal carcinoma is based on colonoscopy and biopsy. The preoperative staging with imaging modalities is usually limited because most patients will benefit from colectomy to prevent intestinal obstruction. The extent of the disease can be evaluated during surgery.

Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (F-18 FDG PET-CT) is a popular hybrid imaging method used in the evaluation of oncological patients. It is superior to all other radiological methods because of its ability to show metabolic/functional changes in the tumor tissue in the early stages, when morphological changes have not yet occurred [1-3]. PET-CT has been widely used in diagnosis, staging, restaging, evaluation of response to therapy, planning of the radiotherapy and chemosensitivity determination in many types of cancer [1-7].

Vascular endothelial growth factor (VEGF) is the most potent and specific angiogenic factor that regulates normal and pathological angiogenesis. Increased expression of VEGF is associated with increased risk of metastasis, recurrence and poor prognosis in many types of cancers, including colorectal cancer [8]. Bevacizumab, which is a monoclonal antibody targeted against VEGF, is the first anti-angiogenic agent approved by the American Food and Drug Administration for use in patients with metastatic colorectal cancer [9-11].

Our aim in this study was to evaluate colorectal cancer patients' response to bevacizumab and chemotherapy by using PET-CT.

MATERIALS AND METHODS

The local ethics committee approved the study. The mean age of the 22 colorectal cancer patients included in our study was 62.8 ± 7.7, and 17 of the patients

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(77.3%) were male while 5 (22.7%) were female. The PET-CT images of 22 patients that were taken before and after bevacizumab and 6 cycles of chemotherapy treatment [Standard doses of FOLFIRI (irinotecan 180 mg/m^2 day 1, leucovorin 400 mg/m2 day 1, 5-fluorouracil (FU) bolus 400 mg/m^2 day 1, 5-FU infusion 2400 mg/m^2 over 46 h) plus bevacizumab 5 mg/kg on day 1 were given on a 14-day cycle] were retrospectively evaluated in the workstation. The whole-body ^{18}F-FDG PET/CT images were done by using a PET/CT scanner (Philips Gemini TF), consisting of dedicated lutetium yttrium oxyorthosilicate (LYSO) full ring PET scanner and 64 slice CT. Standard patient preparation included at least 6 hours fasting and serum glucose level of less than 150 mg/dl before ^{18}F-FDG administration. PET/CT imaging was performed 60 minutes after intravenous injection of 3. 7MBq/kg (0.1mCi/kg) of ^{18}F-FDG (Monrol, Eczacıbaşı). At 60 minute after administration of ^{18}F-FDG, low dose CT (50mAs, 120 kV) covering area from scull to the mid-thighs was performed for the purpose of attenuation correction and precise anatomical localization. Subsequently, emission scan was acquired immediately following the CT for 2-3 min per bed position in the three-dimensional mode. A nuclear medicine specialist performed both by visual and semi-quantitative evaluations PET and CT images (non-corrected and attenuation-corrected) in the rotating maximum-intensity projection and in the cross-sectional planes view (transverse-sagittal-coronal).The PET-CT results were reported as normal or abnormal FDG uptake. The anatomical localization of regions with abnormal FDG uptake was clarified with the help of the fusion of CT images.

Pre-treatment PET-CT images were accepted as baseline and were compared with post-treatment images. The metastatic lesions detected in basal PET-CT images were evaluated in terms of size and FDG uptake after the treatment (Table **1**). Moreover, we also investigated whether there were new metastatic lesions, and made a progression/regression distinction. We used the European Organization for Research and Treatment of Cancer (EORTC) criteria to evaluate the response to the treatment.

Table 1: Pre-Treatment and Post-Treatment Distribution of Metastases in PET-CT

	Pre-Treatment	Post-Treatment
	N %	N %
Hepatic Metastasis	10 (45.5)	9 (40.9)
Extra Hepatic Metastasis		
Abdominopelvic region (Peritoneum, lymph nodes, mesenteric)	14 (63.6)	15 (68.2)
Lung	9 (40.9)	9 (40.9)
Bone	5 (22.7)	5 (22.7)

The SPSS 20.0 software package was used for statistical analysis of the data. The categorical variables were expressed as number and percentage, while continuous variables were expressed as mean and standard error. The relationship between categorical variables (gender, histopathology, histological grade, localization and treatment response) was evaluated by using the chi-square test. The McNemar test was used to evaluate the relationship between the presence of metastatic lesions before and after the treatment. The Kolmogrov-Smirnov test was used to test whether the variables were distribution normally and the paired t-test was used to compare the parametric data (SUVmax values before and after treatment and metastatic lesion size), (Table **2**, Figure **1A-B**). The statistical significance level was set to 0.05 in all tests.

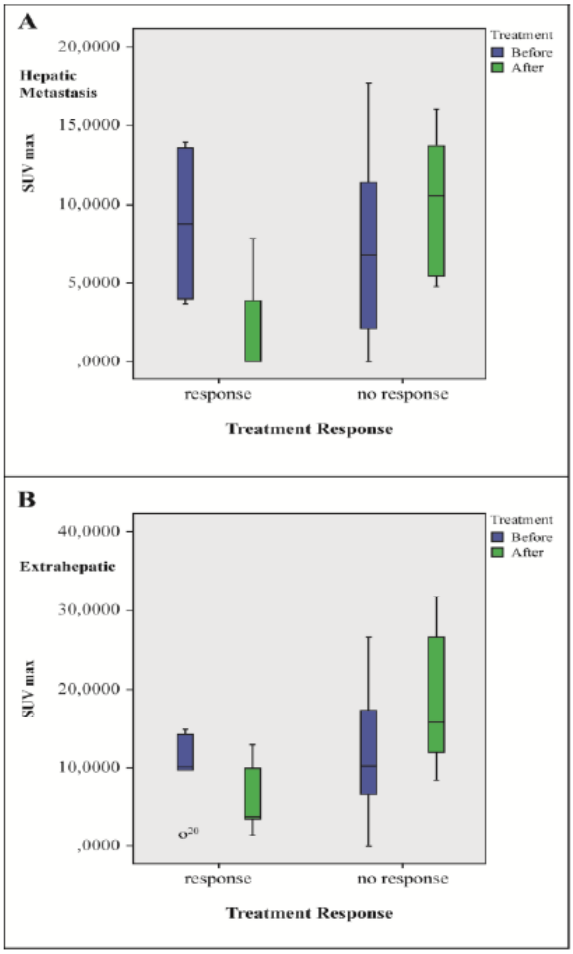

Figure 1(A-B): Boxplot graph showing pre-treatment and post-treatment SUVmax values of hepatic (**A**) and extrahepatic (**B**) metastases and treatment outcomes.

Table 2: The Evaluation of the Pre-Treatment and Post-Treatment Mean SUVmax Values of Metastatic Colorectal Cancer

Colorectal Cancer Metastasis Location	PET-CT TIme	Number of Patients with Metastasis (N)	Mean SUVmax Values	Standard Error	P Value
Liver	Pre-treatment	10 (45.5%)	7.66	+/- 1.92	0.473
	Post-treatment	9 (40.9%)	8.80	+/- 1.52	
Extrahepatic abdominopelvic	Pre-treatment	14 (63.6%)	11.19	+/- 1.75	0.244
	Post-treatment	15 (68.2%)	13.97	+/- 2.35	
Lung	Pre-treatment	9 (40.9%)	4.22	+/- 1.26	0.129
	Post-treatment	9 (40.9%)	6.39	+/- 1.36	
Bone	Pre-treatment	5 (22.7%)	8.90	+/- 2.29	0.241
	Post-treatment	5 (22.7%)	13.48	+/- 5.18	

RESULTS

Adenocarcinoma was the most common histological subtype of colorectal cancer (81.8%, N=18), followed by mucinous adenocarcinoma (13.6%, N=3) and signet ring cell carcinoma (4.5%, N=1). There were 8 (36.4%) well differentiated, 11 (50%) moderately differentiated, and 3 (13.6%) poorly differentiated cases. In 10 patients (54.5%) the tumors were localized in rectum, while in 12 (45.5%) patients the tumors were localized incolon. Twenty-one patients (95.5%) underwent surgical treatment, while 1 patient (4.5%) did not. During initial diagnosis, 18 patients (81.8%) were positive for regional lymph node metastasis, while 5 patients (22.7%) were positive for liver metastasis. Moreover, the comparison of PET-CT scans taken before and after treatment showed regression in 7 cases (31.8%) and progression in 15 cases (68.2%).

The PET-CT scans taken after the treatment showed that liver metastases completely disappeared in 3 patients (Figure **2A-D**). However, new liver metastases were observed in 2 patients who did not have liver metastasis in their baseline PET-CT scans (Figure **3A-F**).

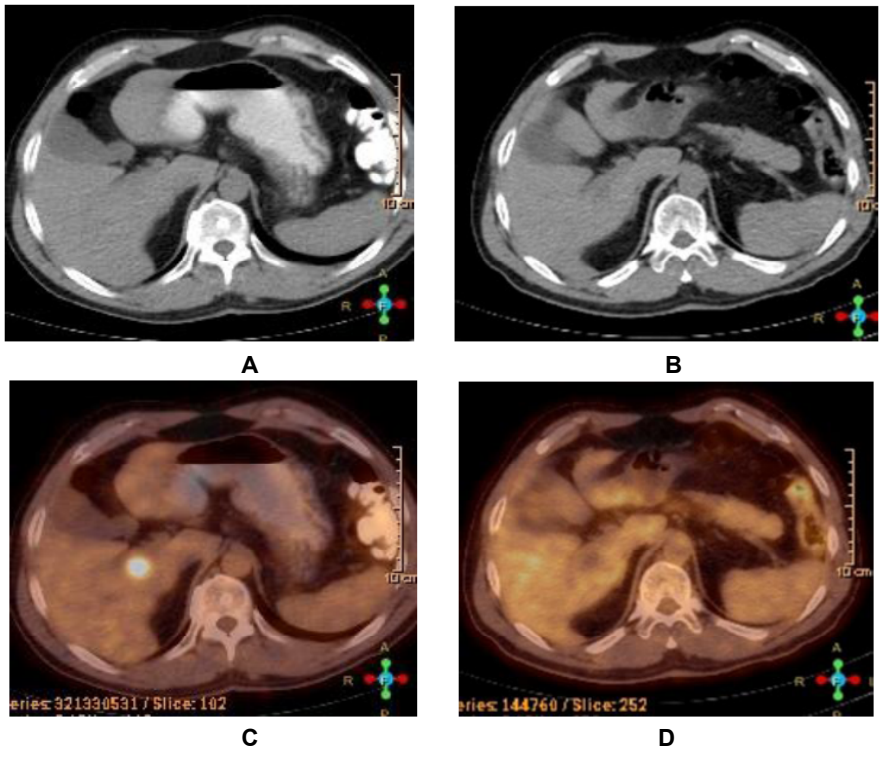

Figure 2A-D: The pre-treatment (**A,C**) and post-treatment (**B,D**) PET-CT scans of the colon cancer patient that had liver metastasis before the treatment.

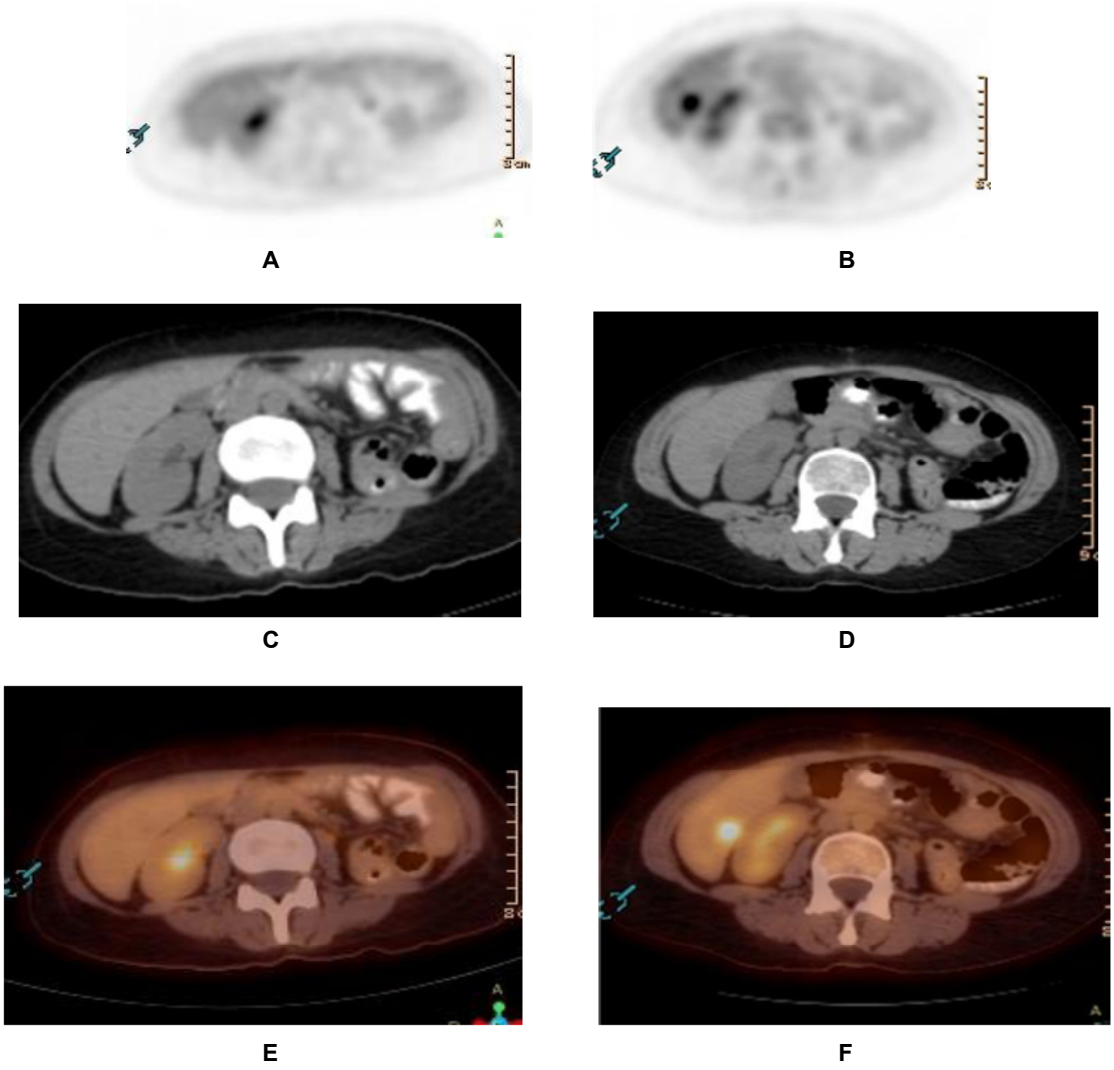

Figure 3A-F: The pre-treatment (**A, C, E**) and post-treatment PET-CT scans of a colon cancer patient that had developed a new metastatic lesion in the liver after the treatment (**B, D, F**).

When the patients' extrahepatic metastases were evaluated, the basal PET-CT showed abdominopelvic (peritoneum, lymph nodes, mesenteric) metastases in 14 patients (63.6%), while the post-treatment PET-CT showed abdominopelvic metastases in 15 patients (68.2%). Moreover, the basal and post-treatment PET-CT showed that 9 patients (40.9%) had metastases in the lungs (Figure **4A-F**), while 5 patients (22.7%) had bone metastasis (Figure **5A-D**).

Seven patients (31.8%) had metabolic response (complete response, partial response) to the treatment and 15 patients (68.2%) did not have any response to the treatment (stable disease, progressive disease). There was no significant difference between genders, histopathological grade and localization of primary tumor in terms of response to the treatment ($p = 0.519$ and $p = 0.783$, $p = 0.867$). Additionally, we did not find any significant difference between the presence of liver metastases at the time of initial diagnosis and the presence of regional lymph node metastases in terms of response to treatment ($p = 0.655$, $p = 0.746$).

The presence, mean SUVmax and metastatic lesion size of liver metastases before and after treatment were evaluated, and no significant difference was detected ($p = 1.00$, $p = 0.473$, $p = 0.220$). The presence of lung, extrahepatic abdominopelvic and bone metastases before and after the treatment and mean SUVmax values were compared and there was no significant difference ($p = 1.00$, $p = 0.129$, $p = 1.00$, $p = 0.244$ and $p = 1.00$, $p = 0.241$).

Lastly, those who survived had a significantly higher response to treatment than those who did not survive ($p = 0.008$), (Table **3**).

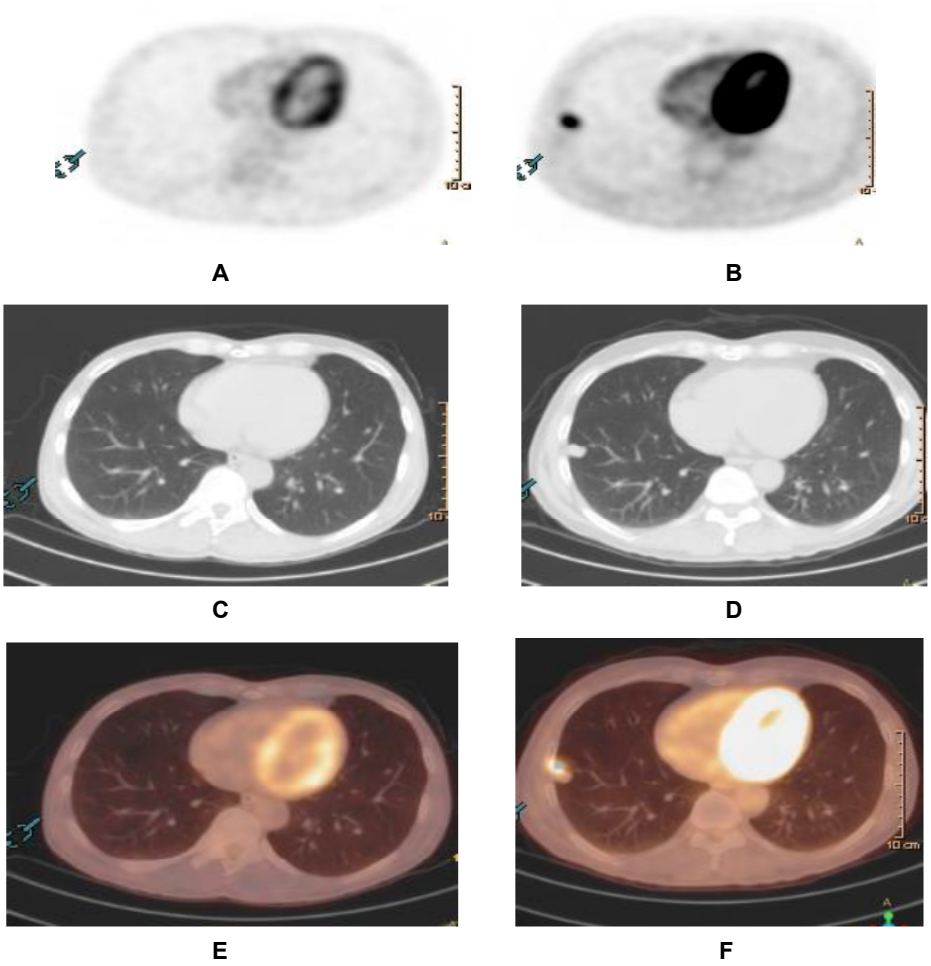

Figure 4A-F: The pre-treatment (**A, C, E**) and post-treatment PET-CT scans of a colon cancer patient that had developed a new metastatic lesion in the lung after the treatment (**B, D, F**).

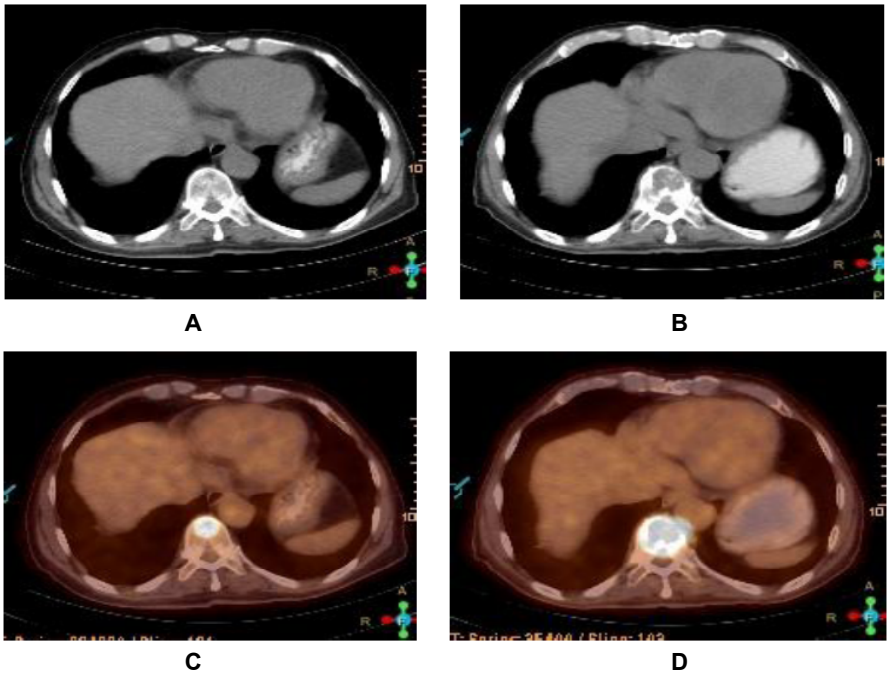

Figure 5A-D: The PET-CT scans of post-treatment (**B, D**) progression in a rectal cancer patient that had bone metastasis before the treatment (**A, C**).

Table 3: The Evaluation of Survived and Deceased Patients in Terms of Response to Treatment

	Survived	Deceased	(N)	P Value
Responded to treatment	7 (100%)	0 (0%)	7 (31.8%)	0.008
Did not respond to treatment	6 (40%)	9 (60%)	15 (68.2%)	
(N)	13 (59.1%)	9 (40.9%)	22 (100%)	

DISCUSSION

The goals of oncologic imaging are lesion detection, lesion characterization, evaluation of the extent of the neoplasm, staging for malignant lesions, and assessment of the therapeutic response. FDG-PET is most helpful to monitor patients with advanced-stage colorectal carcinoma that is associated with a poor prognosis [12].

Lubezky *et al*. evaluated FDG-PET and CT's effectiveness and limitations in re-staging of patients with hepatic colorectal metastases following neoadjuvant chemotherapy. They also compared the outcomes of operations and the pathological findings of the patients. They divided the patients into two groups: the first group consisted of patients who received neoadjuvant chemotherapy, while the second group consisted of patients who underwent a direct resection. The FDG-PET and CT's sensitivity in detecting colorectal metastases was found to be significantly higher in the first group compared to the second group. In patients that received bevacizumab in addition to chemotherapy, the PET and CT's sensitivity in assessment of treatment response was significantly lower compared to those who underwent hepatic resection [13].

Kabbinavar *et al*. compared metastatic colorectal cancer patients treated with a regimen containing fluorouracil, leucovarine and bevacizumab to patients treated with a regimen containing fluorouracil, leucovarine and placebo. They reported the survival in the bevacizumab group was significantly better than placebo group [14]. Zoratto *et al*. also evaluated the efficacy of bevacizumab in the treatment of colorectal cancer patients, and reported that bevacizumab in combination with chemotherapy extended the life expectancy of metastatic colorectal cancer patients from 5 months to 2 years [15]. In a different study, Rossi *et al*. determined that colorectal cancer patients with only hepatic metastases responded better to combined chemotherapy and bevacizumab treatment than patients with extrahepatic metastases or multiple metastases. They also determined that 41.7% of patients had stable disease, 39.8% had partial response to treatment, 3.7% had a complete response to treatment and 14.8% had progressive disease [16]. The results of our study were similar to their study, with 31.8% of patients responded to treatment, while 68.2% of patients did not respond to the treatment. According to the results of our study, mean SUVmax values of liver, abdominopelvic, lung and bone metastases were significantly decreased in patients who responded to chemotherapy and bevacizumab treatment, on the other hand those values were increased the patients who did not respond to the treatment.

Bertolini *et al*. evaluated the effectiveness of FOLFOX6 and bevacizumab treatment in a study with 21 colorectal cancer patients with liver metastases that were not fully resectable. They reported seeing complete response to treatment in 3 patients, partial response in 9 patients, while 1 patient had died due to toxicity. Sixteen of 21 patients were evaluated with PET-CT, and response to treatment was observed in 11 patients (68.75%) with no response to treatment in 5 patients (31.25%) [17].Their treatment response results were different from ours (31.8%).In the same study, Bertolini *et al*. evaluated the PET-CT scans of 16 patients and determined that the mean SUVmax values of liver metastasis before treatment was ≥8.0, while the post-treatment mean SUVmax value was 5.2 [17]. In our study, the evaluation of PET-CT scans showed that the mean SUVmax of liver metastases before treatment was 7.66, while post-treatment mean SUVmax value was 8.80. Unlike Bertolini's study, in our study the mean SUVmax values of post-treatment liver metastatic lesions increased. However, this increase was not statistically significant. In our study, we also compared the mean SUVmax values of hepatic, extrahepatic, abdominopelvic, lung, and bone metastatic foci before and after treatment in all patients. However, we did not find any significant difference between the pre-treatment and post-treatment SUVmax values. We think that the bevacizumab's low treatment response rate (31.8%) and the increase of the SUVmax values of patients with progressing disease might have increased the mean

SUVmax values. The patients were divided into two groups based on response to treatment, and box plot graphs were drawn to evaluate pre-treatment and post-treatment SUVmax values. SUVmax values significantly decreased in patients who responded to treatment, and increased in patients who did not respond to treatment. These results were consistent with the Wahl *et al*. study. Wahl *et al*. compared solid tumors using RECIST and PERCIST criteria, and determined that assessing treatment response with metabolic response criteria yields more reliable results compared to anatomical assessment based on changes in size alone [18].

In a case study by Funaioli *et al*., a patient treated with bevacizumab was determined to have regression based on CT evaluation. However, re-evaluation with PET-CT showed a new metastatic lymph node, and thus the patient's diagnosis was changed to a progressive disease. The results of this study point out that in metastatic colorectal cancer patients taking bevacizumab, response to treatment cannot be determined by anatomic evaluation with CT alone [19]. In our study, before treatment the number of metastatic lesions in the liver was 39, while that number after treatment increased to 45. Moreover, the average size of metastatic lesions in the liver prior to treatment was 3.88 cm, and after treatment the average size of lesions increased to 5.58 cm. SUVmax values before and after the treatment were 7.66 and 8.80, respectively.

Klinger *et al*. conducted a histological evaluation of the effect of bevacizumab treatment in patients with colorectal cancer and liver metastases. Patients were treated with XELOX/FOLFOX, and the study determined that bevacizumab was effective in significantly reducing the tumor growth and prolonging progression-free survival [20]. In our study, all of the 7 patients (31.8%) that respond to therapy survived until the end of the study, while 9 out of 15 patients that did not respond to treatment have died at the end of the study. This relationship between survival and treatment was found to be statistically significant.

A study Cerfolio *et al*. retrospectively evaluated 315 patients with non-small cell lung cancer and measured their SUVmax values with PET imaging. The investigators evaluated all suspicious nodal and systemic localizations by biopsy and lymphadenectomy resections. Authors stated that in patients with early-stage non-small cell lung cancer, SUVmax value was a stronger independent predictor of recurrence and survival than Classification of Malignant Tumors (TNM) staging [21].

In our study we determined the pre-treatment and post-treatment mean SUVmax value of hepatic, extrahepatic abdominopelvic, lung and bone metastatic foci in all the patients. The pre-treatment and post-treatment SUVmax values were 7.66 and 8.80 for hepatic, 11.19 and 13.97 for extrahepatic abdominopelvic, 4.22 and 6.39 for lung, and 8.90 and 13.48 for bone metastases, respectively. When considering that 68.2% of patients did not respond to treatment, these results highlight an increase in the post-treatment SUVmax values and support other studies in the literature.

In our study, we determined that one of the most important aspects of FDG-PET's superiority over the conventional methods was its ability to detect distant extrahepatic metastases. The majority of extrahepatic metastases detected by FDG-PET were located in the lungs (40.9%), followed by extrahepatic abdominopelvic (peritoneum, mesentery, lymph nodes) (63.6%) and bone metastases (22.7%). Similarly, Lai *et al*. used FDG-PET to detect extrahepatic metastases that could not be detected by conventional methods in patients with metastatic colorectal cancer [22]. Moreover, Delbeke *et al*. also used FGD-PET and reported detecting all extrahepatic metastases with 100% sensitivity in patients with metastatic colorectal cancer [23].

CONCLUSION

PET-CT can distinguish the metabolic response to bevacizumab accompanied by chemotherapy before any anatomical changes can occur, and also has the ability to detect extrahepatic distant metastases. Therefore, we believe that PET-CT is a better approach for the evaluation of response to bevacizumab therapy in patients with metastatic colorectal cancer.

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