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Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the postoperative clinical management of patients with colorectal cancer

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Abstract

Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the postoperative clinical management of patients with colorectal cancer

Objective: Colorectal cancer (CRC) is a well-known, surgically curable type of cancer if detected early. Survival rate increase depends on the early detection of the recurrent lesions. In this present study, we aimed to emphasize the value of the F-18 FDG PET/CT imaging modality to evaluate the postoperative treatment response of patients with CRC, based on our clinical experience.
Method: Between January 2016 and January 2020, 168 colorectal cancer patients underwent F-18 FDG PET/CT to evaluate residue/recurrence cancer in our institution. Patients enrolled in this study were operated on for primary colon tumors. Before and after systemic therapy, all patients underwent pre and post-treatment F-18 FDG PET/CT to assess treatment response. The images were analyzed retrospectively.
Results: Patients were classified according to primary tumor localization. Of 168 patients, the primary tumor localized in the ascending colon (n=55), the descending colon (n=33), the transverse colon (n=14), the rectosigmoid (n=61), and the caecum in the other five patients. Recurrence of primary tumor site was detected in 57 patients; 33 of them were male (57.9%) and 24 female (42.1%). The mean SUVmax of the local recurrent lesion was 8.97 ± 3.42 g/ml. In addition, from the ascending colon group, two patients had new foci of tumoral lesions (1.20%).
Conclusion: Resection of the colonic segments with tumor, if possible, is the first step in the treatment of patients with colorectal cancer. After the curative operation, recurrence can be seen in approximately 40% of patients within the first two years. Early detection of recurrence improves the survival rate.
Keywords: Colorectal Cancer, Fluorodeoxyglucose Positron Emission Tomography, Treatment Response

Öz

Kolorektal kanseri olan hastaların ameliyat sonrası klinik yönetiminde fluorine-18 fluorodeoxyglucose pozitron emisyon tomografisi/bilgisayarlı tomografi'nin tanısal önemi

Amaç: Kolorektal kanser, erken tespitinde cerrahi kür sağlanabilen yaygın bir kanser türüdür. Bu kanser tipinde tedaviye yanıtın erken belirlenmesi yaşam süresini olumlu etkilemektedir. Çalışmamızda kolorektal kanseri olan hastaların, ameliyat sonrasındaki klinik yönetimlerinde F-18 FDG PET/BT'nin tanısal önemini değerlendirmeyi amaçladık.
Gereç ve Yöntem: Haziran 2016 ve Ocak 2020 tarihleri arasında 168 hasta kolorektal kanser yönetimi amacıyla bölümümüze yönlendirilmiştir. Bu hastaların hepsi primer kolon tümörleri için ameliyat edilmişlerdi. Sistemik tedavi öncesinde ve sonrasında tedavi yanıtının değerlendirilmesi amacıyla bazal ve ardışık F-18 FDG PET/BT incelemesi yapılmıştır. F-18 FDG PET/BT taramaları sırasıyla analiz edilmiştir.
Bulgular: Hastalar primer tümör lokalizasyonlarına göre gruplandırıldı. Toplam 168 hastanın 55'inde sağ kolonda, 33'ünde sol kolonda, 14'ünde transvers kolonda, 61'inde rektosigmoid kolonda ve 5'inde çekumda primer tümör saptandı. Lokal rekürrens 57 hastada saptanmış olup 33'ü erkek (%57.9) ve 24'ü (%42.1) kadındı. Lokal rekürrense ait ortalama SUVmaks 8.97±3.42 g/ml olarak saptandı. Ek olarak çıkan kolon grubunda 2 hastada (%1.20) yeni tümöral odak gözlendi.
Sonuç: Kolorektal kanserli hastalarda, yapılabiliyorsa kolon rezeksiyonu tedavide ilk aşamadır. Küratif cerrahi sonrası ilk iki yıl içinde, hastaların yaklaşık %40'ında rekürrens görülebilmektedir. Rekürrensin erken tespiti, hastaların yaşam süresini iyileştirmektedir.
Anahtar Kelimeler: Kolorektal Kanser, Fluorodeoksiglukoz Pozitron Emisyon Tomografisi, Tedavi Yanıtı

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INTRODUCTION

Colorectal cancers (CRC) are frequently seen in malignancy types in our country and worldwide. Reported recurrence rates for CRC are up to 40% (1–3). The detection of the response to different treatment modalities improves the survival rate. Computed tomography (CT) magnetic resonance imaging (MRI) is the radiologic imaging modality for detecting recurrence along with the fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/CT (F-18 FDG PET/CT) (1).

Patients' clinical follow-up is usually performed with carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) levels. Elevated CEA and CA 19-9 levels are usually detected at the time of CRC diagnosis. These markers have been used as monitoring markers for disease recurrence in clinical routine.

Due to the cost-effectiveness, the F-18 FDG PET/CT is not recommended for primary staging of colon cancer (4). Radiologic modalities like abdominal or thoracal CT are useful for appropriate initial staging of the CRC and recurrence; however, they can only provide morphologic data (5). Multiphase contrast-enhanced CT should be performed to identify the tumor site, lymphadenopathies, and distant metastasis. Also, liver metastases smaller than 1 cm can be detected with a liver MRI (6).

Positron emission tomography (PET) is a molecular imaging modality. Malignant lesions can be detected by their metabolic activities (2). F-18 FDG PET/CT is an imaging procedure based on anatomical and metabolic information simultaneously of the whole body. F-18 FDG PET/CT plays an important role in primary staging of colorectal cancers as well as restaging and detecting treatment response. Multiple studies demonstrated the value of the, F-18 FDG PET/CT in the diagnosis of CRC recurrent lesions in the post treatment period (7-9). The detection of recurrent CRC with F-18 FDG PET/CT has a higher sensitivity than conventional radiologic imaging (3). F-18 FDG PET/CT can define recurrent CRC due to increased tissue metabolism before the appearance of morphological changes

In the present study, we aimed to determine the clinical value of F-18 FDG PET/CT in the treatment response of CRC patients.

METHOD

Patients

This present study is based on our clinical experience. We aimed to describe the clinical value of whole-body F-18 FDG PET/CT in the treatment response of CRC patients after primary surgery.

Between January 2016 and January 2020, 168 patients were referred to our department to manage CRC. All of these patients had an operation for primary tumors of the colon. Before and after systemic therapy, all patients underwent F-18 FDG PET/CT for treatment response assessment.

All of the patients' diagnosis of CRC was confirmed by pathology. F-18 FDG PET/CT was performed on all patients 6-8 weeks after resection. And at least once after postoperative treatment modalities. The patients did not require this imaging modality until two weeks after chemotherapy (CTR) and three months after radiotherapy.

The recurrent or metastatic lesions were confirmed by pathology together with or without repeated imaging.

F-18 FDG PET/CT scans

All patients are required for a minimum of six hours of fasting before F-18 FDG PET/CT scanning (GE Healthcare, Buckinghamshire, UK). Before imaging, all patients' blood glucose levels were <200 mg/dl. F-18 FDG was administered intravenously at an automatically calculated dose of 5.5 MBq/kg body weight. 45 to 60 minutes after administration of radiotracer due to uptake period, F-18 FDG PET/CT scanning was started.

In the F-18 FDG PET/CT system, CT acquisition was performed using a 512×512 matrix size (pixel size, 1 mm). Slice thickness was 4 mm, and bed position was 2 min per. A slice thickness of 1.5 mm and 128×128-pixel matrix was used for two-dimensional (2D) PET acquisition. Attenuation correction was applied based on CT in the PET images. The images were reconstructed by the iterative ordered subset expectation maximization (OSEM) at two iterations and eight subsets. For reconstruction of PET images, attenuation correction was used. Fused images were reviewed in maximum intensity projections and axial, coronal, sagittal planes.

Two experienced nuclear medicine specialists informed the patients' clinical history and reported all images.

18F-FDG PET/CT findings were thought 'positive' if FDG uptake of the suspicious lesions were higher than surrounding vascular, metabolic activity. For suspected lesions, maximum standardized uptake values (SUV_{max}) were calculated.

Statistical Analysis

SPSS software package version 19.0 (SPSS Inc, Chicago, IL, USA) was executed for statistical analysis. The 18F-FDG PET/CT predictive values in defining CRC recurrence, treatment response, and metastatic lesions were compared at different treatment periods about localization of the primary tumor, age, and gender. $P < 0.05$ was thought statistically significant.

RESULTS

F-18 FDG PET/CT images of the participants (n=168) were retrospectively analyzed. The patients' mean age was 64 years (64.05±11.6); 62.5% (n=105) were male and 37.5% (n=63) female.

The patients were classified according to primary tumor localization; 61 in the rectosigmoid, 55 in the ascending, 33 in the descending, 14 in the transverse colon, and 5 in the caecum.

The mean follow-up time in patients without recurrence (66.1% of the study population, n=111) was 4.21±3.65 years. The local recurrent or distant metastatic lesion was detected in 33.9% of participants (n=57). After primary surgery, the mean recurrence time was 3.6±2.9 years.

Detected local recurrence rates by the 18F-FDG PET-CT among the regional recurrences (rectosigmoid, descending, transverse, ascending colon and caecum respectively) are 18,03%, 42,4%, 50%, 40%, and 60%. After treatment, 18F-FDG PET-CT identified local recurrence in 11 participants (6.5%) in the rectosigmoid colon, 14 (8.3%) in the descending colon, 7 (4.2%) in the transverse colon, 22 (13.1%) in the ascending colon, and 3 (1.8%) in the caecum. (Table 1)

Table1. Local recurrence according to localization.

Localization	Local recurrence					
	Tumor +		Tumor -		Total	
	n	%	n	%	n	%
Rectosigmoid colon	11	6.50	50	29.80	61	36.3
Descending colon	14	8.30	19	11.30	33	19.6
Transverse colon	7	4.20	7	4.20	14	8.3
Ascending colon	22	13.10	33	19.60	55	32.7
Caecum	3	1.80	2	1.20	5	3.0
Total	57	33.90	111	66.10	168	100

All lesions were reviewed for their metabolic activity. Local recurrence was detected in 57 patients; 33 were male (57.9%), and 24 were female (42.1%). The mean SUV_{max} of local recurrence was 8.9±3.4 g/ml. In addition, from the ascending colon group, two patients had new tumor foci.

Metastatic lung lesions were seen in 34 (20%) patients (22 male, 12 female). 13 (7.7%) of these were in the rectosigmoid colon, 5 (3%) in the descending colon, 4 (2.4%) in the transverse colon, 12 (7.1%) in the ascending colon. The mean SUV_{max} of lung lesions was 6.0±2.7 g/ml (Table 2).

Table 2: Lung metastasis according to localization.

Localization	Lung Metastasis					
	Positive		Negative		Total	
	n	%	n	%	n	%
Rectosigmoid colon	13	7.70	48	28.60	61	36.3
Descending colon	5	3.00	28	16.70	33	19.6
Transverse colon	4	2.40	10	6.0	14	8.3
Ascending colon	12	7.10	43	25.6	55	32.7
Caecum	0	0	5	3.0	5	3.0
Total	34	20.20	134	79.8	168	100

Hepatic metastasis was seen in 59 (35.1%) patients (36 male, 23 female). 27 of them (16.1%) were in the rectosigmoid colon, 9 (%5.4) in the descending colon, 6 (3.6%) in the transverse colon, 15 (8.9%) in the ascending colon, and 2 (1.2%) in the caecum. The mean SUV_{max} of hepatic lesions was 10.70±6.40 g/ml.

Metastasis with rare localization such as the brain was detected in 1 patient from the ascending colon group. In addition, bone metastasis was detected in 8 patients (4.8%); 5 were in the rectosigmoid (3%), 1 in the transverse colon (0.6%), and 2 in the ascending colon. All of these had lung metastasis as well. The mean SUV_{max} of metastatic bone lesions was 8.67±3.35 g/ml (Table 3).

Table 3: Bone metastasis according to localization.

Localization	Bone Metastasis			
	Positive		Negative	
	n	%	n	%
Rectosigmoid colon	5	3.00	56	33.30
Transverse colon	1	0.60	13	7.70
Ascending colon	2	1.20	53	31.50
Total	8	4.80	160	95.20

All 34 patients with lung metastasis received CTR, except one undergoing resection and 6 receiving additional radiotherapy (RT). In addition, a lung lesion was detected in 1 patient in the transverse colon group, which turned out to be a primary lung tumor. The patient also had adrenal gland metastasis and received immunotherapy in addition to CTR. Eight patients had bone metastasis confirmed by histopathology and received RT together with CTR. Hepatic metastasis was seen in 59 patients. Fourteen of them had a

solitary lesion and underwent resection, whereas 17 received Yttrium-90 ablation therapy and 6 RF ablation therapies. Twenty-two patients did not have other therapy in addition to systemic CTR.

One patient in the transverse colon group had splenic metastasis, and one in the rectosigmoid group had to descend axillary lymph nodes and breast lumps. In the latter, second primary breast cancer was histopathologically confirmed.

DISCUSSION

Colonic tumoral resection is the first line in treatment in CRC. Recurrence can present in approximately 40% of patients within the first two years after colon resection. The patient's survival rate improves due to early detection of the recurrence. The anatomical location of the primary CRC affects the recurrence and metastasis. O'Connor et al. reported that recurrence occurs within the first two years after resection. Local recurrence is common in patients with rectal cancer (4). In our study group, a higher local recurrence rate was seen in the ascending colon group. However, liver or lung metastatic lesions detection rate was higher in the rectosigmoid group. The recurrence rate in our study population was 33.9%, which was lower than the rate of 71% reported by Mittal et al. in CRC patients (5). In the present study, the meantime to local recurrence or metastasis after surgical resection was 3.66±2.98 years. The patients' mean follow-up time was 4.21±3.65 years. Early detection of local recurrence at an operable stage leads to improved survival following the resection of recurrence (5).

Our investigation showed that rectosigmoid cancer had a 45.7% higher risk for liver and 38% of lung metastasis, suggesting that liver and lung imaging should be included in clinical follow-up. Most colorectal cancers drain to the portal vein, hence prompting hematogenous spread to the liver (10,11). Several studies so far have reported an increased risk of lung metastasis in rectal cancers, which is similar to the results of the present investigation. However, the risk for the ascending colon group was close to the rectosigmoid group in our study population. The anatomical localization of the primary tumor is not the sole determinant for diverse metastatic patterns, as other factors do contribute to site-specific metastases (11). PET scans can yield metabolic information about the pulmonary nodule and exclude the presence of other sites of metastasis so that patients can benefit from adjuvant therapy after surgery.

Pfannschmidt et al. (12) mentioned that a low number of lung metastases (<4) could qualify for metastasectomy. Cho et al. (13) emphasized that the recurrence is dependent on the number of metastases after pulmonary metastasectomy for CRC. They also stated that patients with ≤3 pulmonary metastases can have surgical treatment. In our study population, the patients with lung metastasis had multiple lesions, except one patient who had a resection for the lung lesion.

The hybrid imaging modality of PET/CT has been increasingly performed to identify recurrence cancer (2). F-18 FDG is used in PET/CT imaging as a common agent. F-18 FDG accumulates in malignant lesions because of the increased glucose consumption rate. According to an increased glucose consumption rate of malignant lesions, metabolic functions can be determined at the molecular level (2). Luboldt et al. reported that colorectal mass was correctly detected with F-18 FDG PET/CT and the SUV_{max} was ≥5g/ml (14). In the present study, the mean SUV_{max} of pathologically proven recurrent lesion in the primary tumor site was 8.9 g/ml. The mean SUV_{max} of lung lesions was 6 g/ml hepatic lesions 10.7 g/ml, and metastatic bone lesions 8.6 g/ml.

Borasio et al. (15) reported that false-negative cases were all mucinous adenocarcinoma, so this pathological type of adenocarcinoma can be the main reason for false-negative scans. In this present study, 57 participants showed recurrence in the operation site. They were diagnosed as true-positive by F-18 FDG PET/CT. Thirty-six patients' diagnoses were false-positive confirmed by colonoscopy biopsy. They were performed a third round of F-18 FDG PET/CT imaging within three months and showed decreased uptake in anastomotic regions. All the patients had adenocarcinoma and received different kinds of treatment by their F-18 FDG PET/CT reports.

Infrequent sites of metastases have an increasing incidence (16). In our study population, bone and brain metastases were more likely to occur in the setting of lung metastases. Bone metastasis is significantly correlated with the location of colorectal cancer. The prognosis is poor, particularly the patients with bone metastasis from colorectal cancer. A significant prognostic factor in this regard is the number of extraosseous metastatic organs (17,18).

Nevertheless, F-18 FDG PET/CT can define bone metastasis early (19). F-18 FDG PET/CT shows the malignant infiltration of bone marrow (19). Eight patients in our study population had multiple bone metastases; one of these was solitary spinal metastasis. Bone metastasis in CRC is rare, but our investigation could not establish the prognostic impact because of synchronous lung and hepatic metastasis.

Limitations

The present study has some limitations. First, the patients who received neoadjuvant radiotherapy or CTR were not excluded even though these therapies may interfere with F-18 FDG uptake leading to possible false-negative results. Second, the participants' staging F-18 FDG PET/CT imaging data were not included, meaning that primary malignant

colorectal lesion sizes, loco-regional lymph node metastases, and surgical procedures that may affect the recurrence rate were not noted. Our study focused on the implications of metastatic colorectal cancer localization.

CONCLUSION

F-18 FDG PET/CT can correctly define the cancer recurrence in patients with CRC, promising considerable support for clinicians in patient management.

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Health Sciences University, Non Invasive Research Ethics Committee for this study with date 28/01/2020 and number 46418926, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: A.Ç., Design: H.A.A.E., Data Collection or Processing:A.U., Analysis or Interpretation: E.A., Literature Search: A.Ç., Writing: A.Ç.

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