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Isa Burak Guney*, Zafer Teke**, Kadir Alper Kucuker*, Orcun Yalav***

**Cukurova University, Faculty of Medicine, Department of Nuclear Medicine, Adana, Turkey*
***Cukurova University, Faculty of Medicine, Department of Surgical Oncology, Adana, Turkey*
****Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey*

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AIM: *In patients with colorectal cancer an accurate diagnostic work-up is mandatory in order to perform the most specific treatment. In this study, we aimed to evaluate the accuracy of computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for detection of regional lymph node metastases (RLNMs) and the additional value of PET/CT in the preoperative staging of colorectal cancer.*
MATERIAL AND METHODS: *From June 2015 to May 2018, 72 colorectal cancer patients were preoperatively examined using CT, MRI, and PET/CT. Histopathological examination of regional lymph nodes were performed in 53 patients who underwent colorectal surgery. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) of CT, MRI, and PET/CT for RLNMs, and the additional value of PET/CT in distant metastases were determined.*
RESULTS: *There were 44 male and 28 female in our study. The mean age was 61±11 years. Histopathologically, 27 patients (51%) were negative and 26 patients (49%) were positive for RLNMs. The sensitivity, specificity, PPV, NPV, and ACC of PET/CT were 88.5%, 59.3%, 67.6%, 84.2%, and 73.6%, respectively. PET/CT changed the patient management with diagnostic contribution to the suspicious lesions identified by radiological imaging modalities.*
CONCLUSION: *PET/CT is a useful tool in the evaluation of colorectal cancer, and it allows to metabolically characterize undetermined lesions suspected for recurrence of disease, to perform a complete pre-surgical staging and to identify occult metastatic disease. PET/CT should be considered an essential diagnostic tool in the management of patients with colorectal cancer, especially in the preoperative staging.*

KEY WORDS: Colorectal Cancer, Computed tomography, Magnetic resonance imaging, Positron emission tomography

Introduction

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the world. Approximately 1,8 million patients were newly diagnosed and 881,000 deaths were due to colorectal carcinoma in 2018 [1]. Despite many cutting-edge chemotherapeutical agents and surgical techniques, the 5-year survival rates of colorectal carcinoma are still relatively low. Of all diagnosed colorectal cancer patients, approximately 64.4% may have a 5-year survival, and this rate decreases to 14.2% with metastatic disease [2]. It is well known that 20% of patients have distant metastatic disease at the time of diagnosis [3].
Since total colonoscopy give a chance to visually assess the colorectum and take samples from the suspected

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Correspondence to: Isa Burak Guney, MD, Cukurova University, Faculty of Medicine, Department of Nuclear Medicine, Adana, Turkey (e-mail: isaburak@gmail.com)

areas, it is the first-step diagnostic tool in this group of patients. Although endoscopic ultrasound (EUS) is useful in detecting early stage (T1) and advanced stage (T3, T4) lesions, it is less reliable in detecting peripheral lymph nodes [4]. While allowing morphological assessment, computed tomography (CT) has limitations in tumors which are small-sized and confined to rectal wall, and in normal-shaped regional lymph nodes which may contain microscopic metastases. However, CT has fast scanning time and can show wider areas. Therefore, larger tumors, pathological looking regional lymph nodes and some distant metastatic foci can be demonstrated easily with CT scan. Magnetic resonance imaging (MRI) has a high accuracy in local evaluation, especially to distunguish T3 lesion which consists of muscularis propria invasion or mesorectal fascia invasion (circumferential resection margin) and T4 lesion with visceral peritoneum, adjacent organs or musculature involvement from T1 or T2 lesions. Regional metastatic lymph nodes and liver metastases can also be detected in a detailed manner with MRI [4,5].

^{18}F-2-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) has a critical role in colorectal carcinomas as well as other malignant diseases. ^{18}F-FDG PET is based on the principal that tumor cells have a high metabolic activity and ^{18}F-FDG, which is a glucose analog, accumulates after transporting into cells without entering glycolytic pathways. Then, the areas with high glucose consumption create hyperactive foci due to a high tumor to background ratio. PET systems collect all these data from whole body and convert to 3-D images with CT integration. Integrated PET/CT not only gives metabolic activity of lesion, but also more accurate anatomical information. In colorectal carcinomas, PET/CT has a limited place in local T staging due to low soft tissue spatial resolution but is very effective in correct localization of primary tumor and surgery planning as well as initial detection of distant metastases. After curative treatment, it is also very sensitive in detecting local recurrences and distant metastases together with serum carcinoembrionic antigen (CEA) elevations during follow-up [4-9].

Although the NCCN Clinical Practice Guidelines in Oncology recommend conventional radiological imaging techniques such as CT and MRI for the initial evaluation of colorectal tumors [10,11], the ESMO and SEOM guidelines for colorectal cancers recommend that PET/CT can be used in conjunction with liver MRI and contrast enhanced CT of the thorax, abdomen and pelvis to assess features at presentation associated with a high risk of metastases, e.g. extensive extramural vascular invasion on MRI or high levels of CEA [12-14].

In this study, we compared three imaging modalities in terms of diagnostic power in patients who were newly diagnosed as either colon or rectal carcinoma and did not receive any treatment before.

Materials and Methods

Patient Profile

Seventy-two patients who were diagnosed pathologically as colorectal carcinoma and referred to our department between June 2015 and May 2018 were included in the study. All patients were referred to our institute for PET/CT imaging for primary staging and had not received any treatment modality before referral. The informed consent was read and signed by all participants. This study was approved by the Institutional Review Board of our institute (IRB No. 05.06.2015/43/14).

Data Processing

All colorectal cancer patients were diagnosed with flexible rectosigmoidoscopic or colonoscopic biopsies. In the preoperative period, PET/CT, CT and/or MRI images of study patients were evaluated. Regional or distant lymph node metastases as well as liver and lung metastases were investigated and noted with all three imaging modalities and the detection rates were compared. Attention was paid for that the time interval between radiological modalites and PET/CT not to exceed two weeks. The histopathological report of surgical specimen was also recorded both to determine the histopathological type of primary tumor and its origin precisely and to check the metastatic status of regional lymph nodes if they had been harvested. The patients who had insufficent medical data in our hospital database were excluded from the study. All metastases detected with three imaging modalities were proven with biopsy or serial radiological imaging.

PET/CT Imaging

PET/CT scans of patients were performed with Biograph™ PET/CT system (Siemens Molecular Imaging, Hoffman Estates, IL, USA) consisting of a PET unit and 6-slice spiral CT in our department. The patients were required to fast at least 6 hours before the scan, and blood glucose level was measured to confirm that the level was < 180 mg/dL before the ^{18}F-FDG injection. After a 7-12 milliCurie of ^{18}F-FDG injection, the patients were rested in a comfortable and quiet place with appropriate temperature for approximately 60 minutes. In this period, patients received intravenous hydration, and forced urine extraction provided to prevent urinary system artifact just before the scanning. In addition, oral opaque material was given to patients for CT imaging from 06:00 a.m. until the ^{18}F-FDG injection. Whole body PET/CT images were obtained approximately 60 minutes after ^{18}F-FDG injection, between the skull base and the mid-thigh region. The patients were

in the supine position with normal breathing rate during acquisition. All images were reconstructed with an increase rate of 2.4 mm and a cross-sectional thickness of 5 mm. PET emission time was adapted to the patient's weight; <60 kg: 2 minutes, 60-80 kg: 2.6 minutes, 80 kg: 3 minutes bed position. The given activity, time of administration and patient's weight were used to calculate the maximum standardized uptake value (SUVmax).

Image Interpretation

Radiographic lymph node involvement was defined when the longest lymph node diameter was > 1.0 cm or 0.7-1.0 cm in size with round shape, heterogeneity, eccentricity, hilar thinning, calcification, central necrosis, or perinodal infiltration [15]. If the longest lymph node diameter was <1.0 cm and the configuration was normal, lymph node was accepted suspicious.
All images were evaluated by 2 nuclear medicine physicians in 3 sections (axial, coronal and sagittal) and in 3-D projection (maximum intensity projection, MIP). The SUVmax value of focus was calculated according to dense ^{18}F-FDG uptake. When the measured SUVmax value exceeded 2.5, the lymph node was considered positive. Regional lymph nodes, which showed increased uptake and whose SUVmax value was <2.5 were accepted as suspicious focus. Regional and distant metastatic foci were evaluated with all three modalities and included in the study. The lesions which were accepted as positive with imaging methods were proved with biopsy or serial radiological or nuclear medicine imaging.

Statistical Analysis

We calculated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for CT, MRI, PET/CT and combinations of the 3 modalities. The level of agreement between the CT, MRI and PET/CT was evaluated using Cohen's kappa. Statistical analysis was carried out using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Based on the results of analyses, the p value < 0.05 was considered to be statistically significant.

Results

A total of 72 patients who were newly diagnosed as colorectal carcinoma and did not receive any treatment before diagnostic imaging were included in the study. Table I shows the demographical and pathological characteristics of the patients. There were 44 male and 28 female patients. The mean age was 61±11 years.
Adenocarcinoma was diagnosed in 68 patients, mucinous variant of adenocarcinoma in 3 (2 in rectum and 1 in descending colon) and rectal neuroendocrine carcinoma in 1. Most of the primary tumors were in rectum (41 patients; 56,9%) followed by rectosigmoid junction (10 patients; 13,9%) and ascending colon (8 patients; 11,1%), respectively. The mean SUVmax value of primary tumor in 66 patients whose tumor was able to be discriminated visually in PET/CT was 18,71±9,02. All patients had PET/CT images as well as CT and/or MRI images. Fifty-three patients had pathological report of surgical specimen after total resection of primary tumor. Nineteen patients had biopsy result and were followed up without surgical operation during data collection and referred to systemic therapy due to metastatic disease.

Table I - *Clinicopathologic characteristics for the 72 patients under study*

Patient and Tumor Characteristics	(n, %)
Number of patients	72
Gender	
Male	44 (61.1%)
Female	28 (38.9%)
Age (year) (mean) (SD)	61±11
Histopathology of tumor	
Adenocarcinoma	68 (94.4%)
Mucinous adenocarcinoma	3 (4.1%)
Neuroendocrine tumor	1 (1.4%)
Tumor localization	
Rectum	41 (56.9%)
Rectosigmoid junction	10 (13.9%)
Sigmoid colon	5 (6.9%)
Descending colon	4 (5.6%)
Transverse colon	2 (2.8%)
Ascending colon	8 (11.1%)
Appendix	1 (1.4%)
Cecum	1 (1.4%)
Harvested metastatic regional lymph nodes	
Yes	27 (27/53; 51%)
No	26 (26/53; 49%)

SD: Standard Deviation

Lymph Node Evaluation

In CT, MRI and PET/CT, mesocolic/mesorectal lymph nodes, which were located along the lymph drainage routes of primary tumor, were evaluated. Regional lymph nodes were harvested during surgery in 53 patients and metastatic lymph nodes were detected in 27 patients. Table II gives diagnostic rates of three imaging modalities in patients with histopathologically proven regional lymph nodes. PET/CT revealed positive or suspicious regional lymph nodes in 53 of 72 patients. In the subgroup of patients with proven metastatic lymph nodes, sensitivity, spesificity and accuracy rates of PET/CT were 88,5%, 59.3% and 73,6%, respectively. Table III summarizes the diagnostic abilities of CT, MRI, and PET/CT in the evaluation of regional lymph node metastasis.

TABLE II - *Detection rates of regional lymph node metastasis for the 72 patients under study*

Regional lymph node metastasis	Negative(n, %)	Suspicious(n, %)	Positive(n, %)	Total number of patients(n, %)
^{18}F-FDG PET/CT	26 (36.1%)	12 (16.7%)	34 (47.2%)	72 (100%)
CT	19 (35.8%)	8 (15.1%)	26 (49.1%)	53 (100%)
MRI	13 (28.9%)	8 (17.8%)	24 (53.3%)	45 (100%)

^{18}F-FDG PET/CT: ^{18}F-2-fluoro-2-deoxyglucose Positron Emission Tomography/ Computed Tomography
CT: Computed Tomography
MRI: Magnetic Resonance Imaging

TABLE III - *Detection rates of reginal lymph node metastasis by three imaging modalities for the 53 patients whose regional lymph nodes were harvested during surgery*

	CT	MR	PET/CT	≥1+	≥2+	3+	CT & MRI	CT & PET/CT	MRI & PET/CT	
LN	+	−	+	−	+	−	+	−	+	−
+	−	+	−	+	−	+	−			
+	16	3	15	1	23	3	24	3	23	4
8	0	8	0	16	2	15	1			
-	9	12	10	9	11	16	14	13	11	
16	5	8	6	7	9	12	10	9		
Total	25	15	25	10	34	19	38	16	34	
20	13	8	14	7	25	14	25	10		
Sensitivity (%)	84.2	93.8	88.5	88,9	85.2	100.0	100.0	88.9	93.8	
Specificity (%)	57.1	47.4	59.3	48,1	59.3	61.5	53.8	57.1	47.4	
PPV (%)	64.0	60.0	67.6	63,2	67.6	61.5	57.1	64.0	60.0	
NPV (%)	80.0	90.0	84.2	81,3	80.0	100.0	100.0	85.7	90.0	
ACC (%)	70.0	68.6	73.6	68,5	72.2	76.2	71.4	71.8	68.6	

CT=computed tomography; MRI= magnetic resonance imaging; PET/CT=^{18}F-2-fluoro-2-deoxyglucose positron emission tomography/computed tomography; ≥1+=regional lymph node metastasis was suspected based on the results of more than one test; ≥2+= regional lymph node metastasis was suspected based on the results of more than two tests; 3+= regional lymph node metastasis was suspected based on the results of all 3 tests; PPV=positive predictive value; NPV=negative predictive value; ACC=accuracy.

Of 53 patients who had abdominal CT images, 34 patients were reported as positive or suspicious and nineteen patients were reported as negative on CT scans. Two patients were reported as suspicious on CT, but negative on PET/CT. The lesions of these two patients were very small for metabolical evaluation and did not show any increased FDG uptake significantly. The sensitivity, specificity and accuracy rates of CT were 84,2%, 57,1% and 70,0%, respectively, and were similar to those that were found for PET/CT of patients with harvested regional lymph nodes. There were a moderate agreement between CT and PET/CT when the histopathologic result was positive (κ value: 0,769) and a high level of agreement between CT and PET/CT when the histopathologic result was negative (κ value: 0,901). At this point, one patient was inconsistent between the results of both imaging methods, depending on whether the histopathologic result was positive or negative. However, the remaining patients had the same results in both imaging methods. PET/CT gave only one more accurate result than CT when the histopathologic result was either positive or negative.

Of 45 patients who had abdomino-pelvic MRI images, 32 patients were reported as positive or suspicious for regional lymph node metastasis. There were two incompatible patients for these two imaging modalities. One of the patients was reported as suspicious on MRI and the other one as positive, but both patients were reported as negative on PET/CT. Histopathologic results of these two patients were reported as negative. The lesions were subcentimetric in these two patients. In addition, 27 patients were reported as suspicious or positive on both PET/CT and MRI, and 10 patients were reported as negative. According to the histopathologic results, the sensitivity, specificity and accuracy rates of MRI were 93,8%, 47,4% and 68,6%, respectively. MRI revealed slightly higher sensitivity and lower specificity rates, but almost similar accuracy rate in comparison to other imaging modalities with regard to regional lymph nodes. When the histopathologic result was positive, there was an excellent agreement between MRI and PET/CT (κ value: 1,0). That is, when the histopathologic result was positive, both imaging methods yielded the same result. However, both imaging modalities were negative

in one patient, although the histopathologic result was positive. Therefore, 93.75% of the results of both MRI and PET/CT (in 15 of 16 patients) were consistent with the histopathologic results. When the histopathologic result was negative, the agreement decreased slightly (κ value: 0.791). The percentage of patients that both imaging methods reported as negative at the same time was 47.37% (in 9 of 19 patients). Consistent with the results presented at Table III, PET/CT was better at detecting the negative result than MRI. That is, PET/CT was superior to MRI in specificity.

Fifty-three patients had histopathologic reports of total excision materials. In 27 patients (51%) who were reported as suspicious or positive in imaging modalities, metastases were detected in the mesocolic/mesorectal lymph nodes histopathologically. In 14 patients (26.4%), neither suspicious/positive foci were detected, nor regional metastatic lymph nodes were reported by any imaging modalites. Results of 17 patients showed differences between imaging modalities and histopathologic reports. In 14 patients (26.4%), histopathologic reports were negative in contrast to all three imaging modalities. Additionally, despite negative results in CT, MRI or PET/CT, histopathologic examinations reported positive regional metastatic lymph nodes in 3 patients (5.6%).

Liver and Lung Evaluation

Histopathologically or radiologically proven metastatic liver lesions were detected with PET/CT in 16 of 72 patients. The mean SUVmax value of metastatic liver lesions was 13,33±6,93. MRI demonstrated liver lesions in 9 of 36 patients who had upper abdominal MRI images. Thirteen metastatic liver lesions detected by CT, including 4 suspicious and 9 positive in 53 patients. Three of 4 suspicious lesions excluded with PET/CT, and one of these suspicious lesions ruled out with additional MRI images. Positive CT results of other 9 patients were parallel to the other imaging modalities (Table IV).

None of the patients had thoracal MRI images. Two patients were reported as suspicious and six patients were reported as positive for lung metastasis on chest CT scans of 8 patients. The proven metastatic lung lesions were detected by PET/CT in 7 patients. The mean SUVmax value of lung lesions was 3,85±2,21. Two out of 8 patients were reported as suspicious on chest CT scans. However, PET/CT detected metabolic activity in one of them (SUVmax: 2.42). The other showed no increase in metabolic activity suggesting that the lesion was benign. A brain metastasis was also detected with PET/CT in one of the patients with lung metastasis (Table V).

Patient Management

Four patients whose liver lesions were reported as suspicious by CT were proved to be negative by PET/CT or MRI images. We considered that the disease was limited to the colorectum in these four patients according to PET/CT or MRI images. Thus, unnecessary locoregional therapies or surgical procedures for suspicious liver lesions were avoided thanks to these imaging modalities. Although liver metastasis was excluded by PET/CT in one of 4 patients, the disease stage did not change because of histopathologically proven metastatic pulmonary nodules. Distant metastasis was detected in 19 patients by PET/CT. Seven patients had lung metastasis, 14 patients had liver metastasis, and 2 patients had both

Table IV - *Detection rates of liver lesions for the 72 patients under study*

Liver metastasis	Negative (n, %)	Suspicious (n, %)	Positive (n, %)	Total number of patients (n, %)
^{18}F-FDG PET/CT	56 (77.8%)	0	16 (22.2%)	72 (100%)
CT	38 (74.5%)	4 (7.8%)	9 (17.6%)	51 (100%)
MRI	28 (75.7%)	0	9 (24.3%)	37 (100%)

^{18}F-FDG PET/CT: ^{18}F-2-fluoro-2-deoxyglucose Positron Emission Tomography/Computed Tomography
CT: Computed Tomography
MRI: Magnetic Resonance Imaging

Table V - *Detection rates of lung lesions for the 72 patients under study*

Lung metastasis	Negative (n, %)	Suspicious (n, %)	Positive (n, %)	Total number of patients (n, %)
^{18}F-FDG PET/CT	64 (88.9%)	0	8(11.1%)	72 (100%)
CT	64 (88.9%)	2 (2.8%)	6 (8.3%)	72 (100%)

^{18}F-FDG PET/CT: ^{18}F-2-fluoro-2-deoxyglucose Positron Emission Tomography/Computed Tomography
CT: Computed Tomography

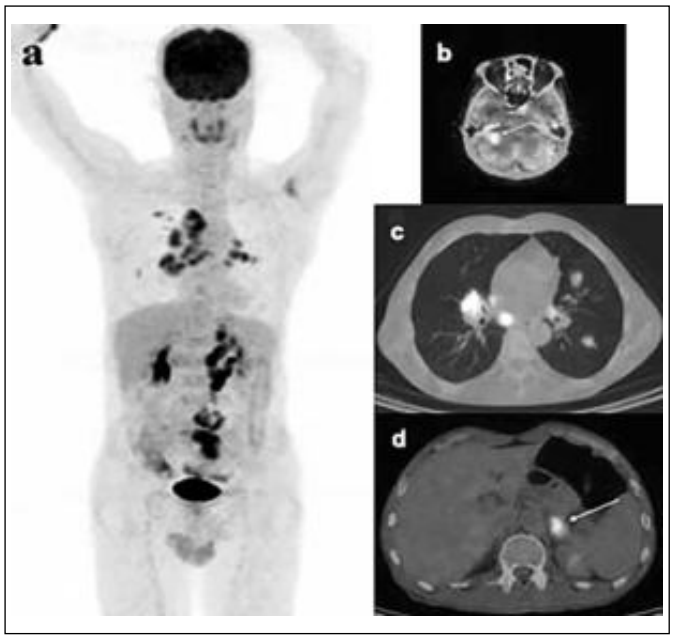

Fig. 1: ^{18}F-FDG PET/CT of a 64-year-old man with rectosigmoid colon adenocarcinoma. A) Maximum intensity projection (MIP) whole body image and axial fusion images of B) brain, C) thorax, and D) abdomen showing high ^{18}F-FDG uptake in metastatic lesions in brain, lung, mediastinal lymph nodes and left adrenal gland.

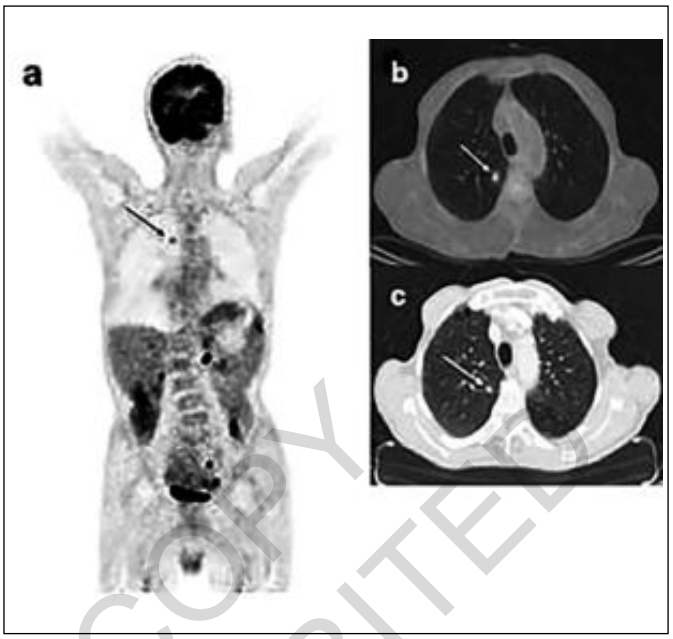

Fig. 2: ^{18}F-FDG PET/CT images of an 84-year-old man with sigmoid colon adenocarcinoma. A) Coronal whole body image and B) axial fusion image showing high ^{18}F-FDG uptake in milimetric nodulary lung lesion. C) Axial contrast-enhanced chest CT image was reported as suspicious.

lung and liver metastases. In addition to lung metastasis, brain and adrenal metastases were also detected by PET/CT in one patient (Fig. 1). Since 5 of 19 patients had fewer than three liver metastases, primary colorectal tumor was removed and liver metastasectomy was performed in the same session. In one patient whose milimetric solitary lung lesion was reported as suspicious by chest CT scan, a high ^{18}F-FDG uptake in PET/CT images revealed it to be a metastasis (Fig. 2). Then, both primary colorectal tumor and lung metastasis were able to be removed thanks to PET/CT. Histopathologic examination confirmed the lung lesion to be a metastasis of adenocarcinoma. The data of remaining 8 patients could not be accessed in the database of our hospital.

Discussion

Radiological imaging modalities have a crucial role in colorectal cancers for the detection of both regional lymph node and distant organ metastases as well as the determination of disease stage. Regional and whole body findings obtained by imaging modalities can change the clinical stage and management of a patient with colorectal cancer.

The NCCN Clinical Practice Guidelines in Oncology put emphasis on a randomized study of patients with resectable metachronous metastases that evaluated the role of PET/CT in the workup of potential curable disease [16]. The panel reported that PET/CT changed surgical management in 8% of patients. For example, resection was not performed for 2.7% of patients because additional metastatic disease was discovered (bone, peritoneum/omentum, abdominal nodes). Moreover, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. In our study, PET/CT detected a brain metastasis in 1 patient because it performed full-body imaging. Therefore, we recommend the use of PET/CT in the primary staging of colorectal cancers so that the patient can be staged correctly in the preoperative period.

An abdomino-pelvic CT scan is widely used for primary tumor, regional lymph nodes and distant metastases in the preoperative staging of colorectal cancers. However, MRI is superior to CT scan in evaluating the spread of tumor to the surrounding tissues. PET/CT gives information about metabolic activity of suspected lesions detected by other morphological diagnostic methods due to high glucose use of malignant tissues [4,5,17,18]. Engelmann *et al.* compared the whole body PET/CT and CT of 66 colon cancer patients in staging tumors, lymph nodes and other metastases, and PET/CT showed higher accuracy in T4 tumors, metastatic disease and lung lesions compared to CT images [19]. Moreover, PET/CT excluded falsely reported positive liver and lung lesions in 31 patients. Bianchi *et al.* staged 29 rectal carcinoma patients preoperatively with EUS and body coil MRI [20]. They concluded that EUS was more accurate (79.3%) in deter-

ming bowel wall penetration of the tumor, while MRI was more accurate (72.4%) in the evaluation of lymph node involvement. However, Bayrak *et al.* reviewed the data of 156 patients who underwent colorectal surgery, and compared preoperative modalities, including colonoscopy, CT, MRI, and FDG-PET/CT, to correctly identify the location of distal colorectal tumors [21]. They reported that no preoperative assessment modalities provided excellent accuracy for tumors of the sigmoid colon, rectosigmoid junction, or rectum. In our study, MRI had the highest sensitivity rate (93.8%) in detecting regional lymph node metastasis. However, specificity and accuracy rates (47.4% and 68.6%, respectively) of MRI were lower than the other two imaging methods. PET/CT had the highest specificity and accuracy rates (59.3% and 73.6%, respectively) compared to MRI and CT.

Hepatic metastases from colorectal cancers are very common, and almost one in four patients has liver metastasis at the time of diagnosis [22]. However, patients with liver metastases have also a chance of curative surgical resection. In patients who underwent liver metastasectomy, the 5-year survival reaches up to 30% [23,24]. Therefore, accurate detection of liver metastases affects directly the management of patient. Both radiological imaging methods (CT and MRI) and nuclear medicine imaging modalities (PET/CT) have high detection rates and performance in liver lesions [25]. In their meta-analysis of a large group of patients, Bipat *et al.* found that the most effective method on a patient basis was PET, but they did not see any significant difference in comparison to other modalities on a lesion basis [26]. Oh *et al.* showed in 108 patients that contrast-enhanced MRI was superior compared to PET/CT only in lesions less than 2 cm [27]. In our study, the lesion detection rates of PET/CT and MRI were similar in terms of the detection of liver metastasis on a patient basis (22.2% *vs.* 24.3%, respectively), whereas the lesion detection rate of CT was found to be lower (17.6%). Four patients (7.8%) reported as suspicious on CT scans showed no metastasis according to PET/CT or MRI findings.

Neoadjuvant chemotheraphy for node-positive colon cancer remains of great interest to researchers. The theoretical benefits of neoadjuvant chemotheraphy include the reduction of micrometastatic disease and tumor shedding during surgery, and the use of tumor response to neoadjuvant chemotherapy to guide further adjuvant therapies if needed after surgery. Metastasectomy can only be performed especially for limited metastatic disease of liver, lung and peritoneum. On the other hand, systemic chemotherapy is administered to the patients with diffuse disease. However, radiation therapy is delivered to the patients with locally invasive cancers. In a study comparing the PET, contrast-enhanced CT (ceCT) and integrated PET/ceCT results of liver metastases in the preoperative period after neoadjuvant chemotherapy, the diagnostic power was increased by combining PET and ceCT and the sensitivity of PET, ceCT and integrated PET/ceCT were 38.2%, 91.3% and 94.78%, respectively [28]. In a study in which the effect of CT, MRI and PET/CT on the treatment approach was investigated in the restaging process after neoadjuvant therapy, PET/CT was found to be the most effective imaging modality in the treatment planning of 199 rectal carcinoma patients [29]. In our study, distant metastases were detected in 19 patients who were accepted as stage IV disease. Seven patients had lung metastasis, 14 patients had liver metastasis, and 2 patients had both lung and liver metastases. PET/CT guided the surgeon in removing the primary colorectal tumor with metastasectomy in the same session in 6 patients. Five of these 6 patients had fewer than three liver metastases and one patient had a solitary pulmonary metastasis. In our study, only 5 patients received neoadjuvant chemotherapy, and the control PET/CT after neoadjuvant chemotherapy showed that 3 patients became operable. In 18 patients, although there was no distant metastasis, due to the local advanced stage of the disease, these patients were first treated with chemoradiotherapy, and then they received surgery. This group included both patients with T3 tumor and patients with locoregional lymph node metastasis.

Mucinous colorectal carcinomas are more aggressive than non-mucinous tumors, and local invasion, lymph node involvement and peritoneal implantation rates are higher [30]. In addition, low cell morphology of mucinous carcinomas leads to low ^{18}F-FDG uptake and it makes PET/CT evaluation challenging [31]. On the contrary, Dos Anjos *et al.* did not find significant differences in SUVmax and SUVmean values in mucinous and non-mucinous groups in their study with 73 patients, but the mean metabolic tumor volume and total lesion glycolysis values were found to be statistically higher in mucinous patients [32]. In our study, three patients had mucinous adenocarcinoma and two were located in rectum, one in the left colon. The SUVmax values of these lesions were 15.16, 6.0 and 14.52, respectively. Contrary to known, two of them were close to the mean SUVmax value of the patient group. But, the third lesion was one of the primary lesions that showing the lowest ^{18}F-FDG uptake.

The partial volume effect, which causes the underestimation of radioactivity concentration in structures with less than two to three times the spatial resolution of PET (4-5 mm), is the cause of the low sensitivity of ^{18}F-FDG PET/CT in the diagnosis of lymph node metastasis [33-35]. Therefore, lower optimal SUV_{max} cut-off values were determined for the evaluation of small lymph nodes than for the large lymph nodes. Several techniques have been developed to calibrate the partial volume effect. In addition, many studies revealed significant improvement in the diagnostic performance of ^{18}F-FDG PET/CT for the determination of small lesions after partial volume correction [36,37]. These methods are generally too complex to be clinically applicable, and most require additional equipment or applications.

Both CT and MRI have been used to evaluate regional lymph node metastasis in rectal cancer by evaluating the size and shape of lymph node [38,39]. Many studies have revealed the limitations of using size criteria alone for lymph node staging in rectal cancer. Approximately 60% of metastatic lymph nodes are <5 mm in diameter [40]. Therefore, evaluating the shape of lymph node can also be useful in diagnosis. In most metastatic lymph nodes, the loss of fatty hilum and kidney bean-shaped structure can be detected. A recent meta-analysis study including 12 CT studies reported that the pooled sensitivity and specificity of CT for lymph node metastasis were 71% and 67%, respectively [41]. Another meta-analysis study including 21 MRI studies reported that the pooled sensitivity and specificity of MRI for lymph node metastasis were 77 and 71%, respectively [42]. For a quantitative approach to the diagnosis of lymph node metastasis on ^{18}F-FDG PET/CT images, a fixed cut-off value of SUVmax of 2.5 has been commonly used to diagnose metastatic lymph nodes [38, 43]. Brush *et al.* found that the sensitivity (38% to 65%) of ^{18}F-FDG PET/CT in the diagnosis of lymph node metastasis was low compared to those of CT and MRI [44]. However, in the present study, ^{18}F-FDG PET/CT using a fixed SUV_{max} cut-off value of 2.5 showed higher sensitivity (88,5%) and lower specificity (59.3%). The reason why our rates differ from those in the literature may be due to heterogeneities in studies because of differences in preferred protocol, experience of nuclear medicine and radiology specialists, approach to image interpretation, and methodologic quality, and to the fact that we did not include the lymph nodes that we considered as suspicious into the group of lymph nodes that we considered as positive. Further studies comparing the diagnostic value of ^{18}F-FDG PET/CT, CT, and MRI in the same patient population may provide important information in selecting diagnostic modalities for preoperative staging of colorectal cancer.

Study Limitations

There were some limitations of our study. Firstly, our study group had a small number of patients. In our hospital, PET/CT is not routinely used for preoperative staging of colorectal carcinoma. There were also a limited number of eligible patients whose data were sufficient for our study. Secondly, we had a heterogenous patient population which included different types of tumor pathology and tumor localizations. We had to reach some results without separating them due to the small number of patients. Thirdly, despite all patients had PET/CT images, some patients had only CT images, MRI images or both. While some patients were able to be compared with three imaging modalities, others could be compared between PET/CT and existing radiological methods.

Conclusion

In conclusion, there was no superiority among imaging modalities in evaluating regional lymph nodes of colorectal carcinoma. Structural imaging methods, including CT and conventional MRI, show the strong abilities to describe the location, size, shape, and texture of lymph nodes, but do not reliably distinguish between benign and malignant lymph nodes. PET/CT was able to give the metabolic status of lesions that morphologically suspicious, and had a very critical function in upstaging or downstaging of the disease, and especially in the evaluation of distant metastases. Owing to the fact that PET/CT allows the assessment of wider areas with faster acquisition time and presents information about the metabolic activity, we are in the opinion that PET/CT is very useful option in primary staging of colorectal carcinoma.

Riassunto

Nei pazienti con carcinoma del colon-retto è necessario un accurato lavoro diagnostico per eseguire il trattamento più specifico. In questo studio, abbiamo mirato a valutare l'accuratezza della tomografia computerizzata (CT), imaging a risonanza magnetica (MRI) e ^{18}F-fluorodeoxyglucose PET/CT per il rilevamento di metastasi linfonodali regionali (RLNM) e il valore aggiuntivo di PET/CT nella stadiazione preoperatoria del carcinoma del colon-retto.

Tra giugno 2015 e maggio 2018 sono stati esaminati prima dell'intervento 72 pazienti con carcinoma del colon-retto mediante TC, risonanza magnetica e PET/CT.

L'esame istopatologico dei linfonodi regionali è stato eseguito in 53 pazienti sottoposti a chirurgia colorettale. Sono stati determinati la sensibilità, la specificità, il valore predittivo positivo (PPV), il valore predittivo negativo (NPV) e l'accuratezza (ACC) di CT, MRI e PET/CT per RLNM e il valore aggiuntivo di PET/CT in metastasi a distanza. La casistica esaminata comprendeva 44 uomini e 28 donne, dell'età media di 61 ± 11 anni. Istopatologicamente, 27 pazienti (51%) sono risultati negativi e 26 pazienti (49%) positivi per RLNM. La sensibilità, specificità, PPV, NPV e ACC di PET / CT erano rispettivamente dell'88,5%, del 59,3%, del 67,6%, dell'84,2% e del 73,6%. La PET/TC ha cambiato la gestione del paziente con il contributo diagnostico alle lesioni sospette identificate dalle modalità di imaging radiologico.

Concludiamo che PET/CT è uno strumento utile nella valutazione del carcinoma del colon-retto e consente di caratterizzare metabolicamente lesioni indeterminate sospette di recidiva della malattia, e per eseguire una stadiazione pre-chirurgica completa per identificazione delle metastasi occulte. La PET / CT deve essere considerata uno strumento diagnostico essenziale nella gestione dei pazienti con carcinoma del colon-retto, in particolare per una stadiazione preoperatoria.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA Cancer J Clin, 2018; 68: 394-424. https://seer.cancer.gov/csr/1975_2016/ (Access date: 04/15/2019)

2. Siegel RL, Miller KD, Jemal A: *Cancer statistics*. CA Cancer J Clin, 2016; 66: 7-30.

3. Heo SH, Kim JW, Shin SS, Jeong YY, Kang HK: *Multimodal imaging evaluation in staging of rectal cancer*. World J Gastroenterol, 2014; 20: 4244-55.

4. Raman SP, Chen Y, Fishman EK: *Evolution of imaging in rectal cancer: multimodality imaging with MDCT, MRI, and PET*. J Gastrointest Oncol, 2015; 6:172-84.

5. Rosenbaum SJ, Stergar H, Antoch G, Veit P, Bockisch A, Kühl H: *Staging and follow-up of gastrointestinal tumors with PET/CT*. Abdom Imaging, 2006; 31: 25-35.

6. Delbeke D, Martin WH: *FDG PET and PET/CT for colorectal cancer*. Methods Mol Biol, 2011; 727: 77-103.

7. Engledow AH, Bond-Smith GE, Francis D, Pakzad F, Bomanji J, Groves A, et al.: *The incremental value of dual modality PET/CT imaging over PET imaging alone in advanced colorectal cancer*. Indian J Surg, 2009; 71: 63-8.

8. Flamen P, Hoekstra OS, Homans F, Van Cutsem E, Maes A, Stroobants S, et al.: *Unexplained rising carcinoembryonic antigen (CEA) in the postoperative surveillance of colorectal cancer: The utility of positron emission tomography (PET)*. Eur J Cancer, 2001; 37: 862-69.

9. Benson AB 3rd, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, et al.: *Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology*. J Natl Compr Canc Netw, 2017; 15: 370-98.

10. Benson AB, Venook AP, Cederquist L, Cederquist L, Chen YJ, Ciombor KK, et al.: *Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology*. J Natl Compr Canc Netw, 2018; 16: 874-901.

11. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, et al.: *Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol, 2013; 24: 64-72.

12. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al: *Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol, 2018; 29: 263.

13. Aranda E, Aparicio J, Alonso V, Garcia-Albeniz X, Garcia-Alfonso P, Salazar R, et al.: *SEOM clinical guidelines for diagnosis and treatment of metastatic colorectal cancer 2015*. Clin Transl Oncol, 2015; 17: 972-81.

14. Choi AH, Nelson RA, Schoellhammer HF, Cho W, Ko M, Arrington A, et al.: *Accuracy of computed tomography in nodal staging of colon cancer patients*. World J Gastrointest Surg, 2015; 7: 116-22.

15. Moulton CA, Gu CS, Law CH, Tandan VR, Hart R, Quan D, et al.: *Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial*. JAMA 2014; 311: 1863-69.

16. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD: *Diagnostic accuracy of computed tomography for colon cancer staging: A systematic review*. Scan J Gastroenterol, 2011; 46: 887-94.

17. Chan K, Welch S, Walker-Dilks C, Raifu A; Ontario provincial Gastrointestinal Disease Site Group: *Evidence-based guideline recommendations on the use of positron emission tomography imaging in colorectal cancer*. Clin Oncol (R Coll Radiol), 2012; 24: 232-49.

18. Engelmann BE, Loft A, Kjær A, Nielsen HJ, Berthelsen AK, Binderup T, et al.: *Positron emission tomography/computed tomography for optimized colon cancer staging and follow up*. Scan J Gastroenterol, 2014; 49: 191-201.

19. Bianchi P, Ceriani C, Palmisano A, Pompili G, Passoni GR, Rottoli M, et al.: *A prospective comparison of endorectal ultrasound and pelvic magnetic resonance in the preoperative staging of rectal cancer*. Ann Ital Chir, 2006; 77: 41-6.

20. Bayrak S, Kinaci E, Ozakay A, Bektas CT, Yardimci AH, Arslan E, et al.: *Preoperative localization of distal colorectal tumours*. Ann Ital Chir, 2016; 87: 595-600.

21. Bengmark S, Hafström L: *The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy*. Cancer, 1969; 23: 198-202.

22. Shah SA, Bromberg R, Coates A, Rempel E, Simunovic M, Gallinger S: *Survival after liver resection for metastatic colorectal carcinoma in a large population*. J Am Coll Surg, 2007; 205: 676-83.

23. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M: *Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies*. Br J Cancer, 2006; 94: 982–99.

24. Ong KO, Leen E: *Radiological staging of colorectal liver metastases*. Surg Oncol, 2007; 16: 7-14.

25. Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, et al.: *Colorectal liver metastases: CT, MR imaging, and PET for diagnosis. Meta-analysis*. Radiology, 2005; 237: 123-31.

26. Oh JW, Oh SN, Choi JI, Choi MH, Yoo IeR, Lee MA, et al.: *Does the Gadoxetic Acid-Enhanced Liver MRI Impact on the Treatment of Patients with Colorectal Cancer? Comparison Study with ^{18}F-FDG PET/CT*. Biomed Res Int, 2016; 2016: 8412071.

27. García Vicente AM, Domínguez Ferreras E, Sánchez Pérez V, Poblete García VM, Villa Guzmán JC, Jiménez Aragón F, et al.: *Response assessment of colorectal liver metastases with contrast enhanced CT/^{18}F-FDG PET*. Eur J Radiol, 2013; 82: 255-61.

28. Schneider DA, Akhurst TJ, Ngan SY, Warrier SK, Michael M, Lynch AC, et al.: *Relative value of restaging MRI, CT, and FDG-PET scan after preoperative chemoradiation for rectal cancer*. Dis Colon Rectum, 2016; 59: 179-86.

29. Okuno M, Ikehara T, Nagayama M, Kato Y, Yui S, Umeyama K: *Mucinous colorectal carcinoma: clinical pathology and prognosis*. Am Surg, 1988; 54: 681-5.

30. Berger KL, Nicholson SA, Dehdashti F, Siegel BA: *FDG PET evaluation of mucinous neoplasms: Correlation of FDG uptake with histopathologic features*. AJR Am J Roentgenol, 2000; 174: 1005-8.

31. Dos Anjos DA, Habr-Gama A, Vailati BB, Rossi CB, Coturel AE, Perez RO, et al.: *^{18}F-FDG uptake by rectal cancer is similar in*

mucinous and nonmucinous histological subtypes. Ann Nucl Med, 2016; 30: 513-7.

32. Rahmim A, Qi J, Sossi V: *Resolution modeling in PET imaging: theory, practice, benefits, and pitfalls*. Med Phys, 2013; 40: 064301.

33. Soret M, Bacharach SL, Buvat I: *Partial-volume effect in PET tumor imaging*. J Nucl Med, 2007; 48: 932-45.

34. Steinert HC, Hauser M, Allemann F, Engel H, Berthold T, von Schulthess GK, et al.: *Non-small cell lung cancer: nodal staging with FDG PET versus CT with correlative lymph node mapping and sampling*. Radiology, 1997; 202: 441-46.

35. Boussion N, Cheze Le Rest C, Hatt M, Visvikis D: *Incorporation of wavelet-based denoising in iterative deconvolution for partial volume correction in whole-body PET imaging*. Eur J Nucl Med Mol Imaging, 2009; 36: 1064-75.

36. Bettinardi V, Castiglioni I, De Bernardi E, Gilardi MC: *PET quantification: strategies for partial volume correction*. Clin Transl Imaging, 2014; 2: 199-218.

37. Tateishi U, Maeda T, Morimoto T, Miyake M, Arai Y, Kim EE: *Non-enhanced CT versus contrast-enhanced CT in integrated PET/CT studies for nodal staging of rectal cancer*. Eur J Nucl Med Mol Imaging, 2007; 34: 1627-34.

38. Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J: *Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging - A meta-analysis.* Radiology, 2004; 232: 773-83.

39. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al.: *Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison*. Radiology, 2003; 227: 371-77.

40. Nerad E, Lahaye MJ, Maas M, Nelemans P, Bakers FC, Beets GL, et al.: *Diagnostic accuracy of ct for local staging of colon cancer: A systematic review and meta-analysis*. AJR Am J Roentgenol, 2016; 207: 984-95.

41. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al.: *Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis*. Ann Surg Oncol, 2012; 19: 2212-23.

42. Tsunoda Y, Ito M, Fujii H, Kuwano H, Saito N: *Preoperative diagnosis of lymph node metastases of colorectal cancer by FDG-PET/CT*. Jpn J Clin Oncol, 2008; 38: 347-53.

43. Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, et al.: *The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: A systematic review and economic evaluation*. Health Technol Assess, 2011; 15:1-192.