Original Article

PET-CT changes the management and improves outcome in patients with recurrent colorectal cancer

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ABSTRACT

Background: The present study aims to analyze the impact of positron emission tomography/computed tomography (PET/CT) on management change in patients with suspected or proven colorectal cancer recurrence, and to assess the effect of this management change on progression-free survival (PFS) and overall survival (OS).

Materials and Methods: We retrospectively evaluated 122 patients with suspected potentially resectable recurrent colorectal cancer who underwent PET/CT scan. We determined management plans for these patients before and after the PET/CT examination.

Results: While previous conventional imaging studies had revealed solitary metastases, additional sites of disease were determined by PET/CT scan in 52/122 (42%) patients. PET/CT examination results changed the treatment plan to curative intent in 35 (37%) patients. While the median PFS was 22 months (95% CI, 11.2-32.6 months) among the patients planned to receive curative treatment after the PET/CT scan, it was 11 months (95% CI, 8.1-13.9 months) in patients planned to receive curative treatment before the PET/CT examination, and the difference between median PFS durations was statistically significant (HR, 0.51 [95% CI, 0.32 - 0.88], $P = 0.004$). Furthermore, OS was significantly longer in patients planned to receive curative treatment after the PET/CT scan (27 months [95% CI, 22.1-31.9]) compared with those who received curative treatment before the PET/CT scan (21 months [95% CI, 15.6 - 26.4]), and the difference was statistically significant (HR, 0.63 [95% CI, 0.42 - 0.89], $P = 0.045$).

Conclusion: The present study demonstrates the significant impact of PET/CT on the management and outcome in patients with recurrent colorectal cancer.

KEY WORDS: Improved outcome, management change, recurrent colorectal cancer, positron emission tomography/computed tomography scan

INTRODUCTION

Colorectal cancer (CRC) incidence and mortality rates vary markedly around the world. CRC is the second most commonly diagnosed cancer both in males and in females.[1] While cure is achieved in many patients undergoing initial surgery for primary disease, approximately 40% of the patients with stage II and stage III CRC develop recurrent locoregional or metastatic disease.[2] A large proportion of CRC recurrences are mainly localized in a single organ such as pelvis, liver, or lung.[3,4] Surgery provides cure in some patients with localized recurrent disease; Tepper *et al*. reported resection with curative intent in 34% of patients with solitary tumors, and the 5-year overall survival (OS) probability was 27% among these patients while it was found to be 6% in patients who did not undergo surgical resection.[3] In a study reported by Goldenberg *et al*., 20% of the patients underwent salvage surgery with curative intent and the 5-year survival rate was 23% in disease recurrence.[4]

There is no clear consensus on the factors that predict the success of surgery for recurrent pulmonary and hepatic metastases.[5-7] Previously, some large studies demonstrated that multiple hepatic metastases and the presence of additional extra hepatic metastases are poor prognostic factors in patients undergoing liver resection for recurrent disease.[5,6]

18F Fluoro-deoxyglucose (FDG) positron emission tomography (PET) has significantly improved the assessment of the patients with suspected CRC recurrence.[8-12] Several previous studies demonstrated that PET scan provides a comparable sensitivity to computed tomography (CT) scan for the detection of liver disease. Since in most situations, additional metastases undetected by CT scans are detected by PET scans, PET scans may influence the clinical management of the patients.[13-18] Kalff *et al*. indicated that PET scan may influence the management of patients with recurrent colorectal disease. In this study, the planned surgery was abandoned in 60%

of the patients due to the additional PET scan findings.[19] However, apart from a recent study, no previous studies have evaluated the impact of PET on patient outcomes.[20] Scott *et al*. demonstrated the significant impact of PET scan on the management and outcome in patients with suspected recurrent CRC.[20]

In this study our aim was to analyze the impact of PET/CT on management change in patients with suspected or proven CRC recurrence, and to assess the effect of this management change on progression-free survival (PFS) and OS.

MATERIALS AND METHODS

Patients

A total of 122 patients referred to our tertiary oncology centers between January 2003 and December 2011 for a clinically indicated 18F-FDG PET/CT scan evaluation of a suspected or proven potentially resectable recurrence of CRC were retrospectively analyzed.

The FDG PET/CT scans were performed in all patients for a variety of indications: suspicion of distant or local recurrence at diagnostic CT, which was potentially resectable. Patients were not included in the study if they had an additional metastatic disease (except the presence of recurrence at a single site or single organ), poor performance status (Eastern Cooperative Oncology Group [ECOG] >2), inadequate renal or hepatic function, a second primary cancer and chemotherapy or radiotherapy (RT) performed less than 3 weeks before the PET/CT scan, abdominal surgery within 6 weeks prior to PET/CT scan, or blood glucose level higher than 200 mg/dl. Patients who were pregnant at the time of the PET/CT scan were also excluded.

Clinical information such as age at the time of diagnosis, tumor stage, grade, histopathological type, treatment modality (adjuvant, intended and actual), findings on imaging studies, time of the FDG PET/CT scan, recurrence, progression and time of death were obtained from the patients charts. Written informed consent of the patients or their next of kin were obtained prior to the conduct of the study.

Treatment

Eighty-one percent of the patients received adjuvant treatment. In rectum cancer, a chemotherapy regimen based on protracted 5-fluorouracil (5-FU) infusion (225 mg/m^2/day) was used with concurrent preoperative RT. After the surgery, these patients received four cycles of intravenous bolus administration of adjuvant 5-FU (425 mg/m^2/day) on days 1-5 and intravenous bolus administration of leucovorin (20 mg/m^2/day) on days 1-5 every 28 days, as indicated in Mayo regimen. Bolus 5-FU and leucovorin was employed on days 1-4 every 28 days with concurrent postoperative RT in cycle three and four of the planned six cycles of adjuvant chemotherapy. Patients received a median dose of 50.4 Gray (Gy) (range, 45-64 Gy) in 5 weeks. Patients with colon cancer stage II at higher risk of recurrence (pathologic stage T4, grade III, perforation or obstruction at initial presentation and lympho-vascular invasion) received six cycles of adjuvant bolus 5-FU and leucovorin. Patients with stage III colon cancer received oxaliplatin, 5-FU and leucovorin (FOLFOX4 or FOLFOX6).

During the study period, patients with metastatic CRC received systemic first-line chemotherapy consisting of 5-FU, leucovorin, and oxaliplatin; and irinotecan as the second line chemotherapy. Bevacizumab and cetuximab were added to the standard chemotherapy regimen for patients with KRAS wild-type CRC as of 2008. Patients undergoing surgery with curative intent, received chemotherapy for 6 months. Surgery with curative intent was performed in 10 patients with solitary lung metastasis, 19 patients with solitary liver metastasis and 21 patients with single site pelvic tumor recurrence.

Documentation of management plans and outcomes

We analyzed the management plans of the patients before they received the results of the PET/CT scan (intended treatment modality) and the actual management after PET/CT scan, and evaluated whether the management plan would be changed based on PET/CT scan findings. We also divided the patients into two groups as curative treatment arm and palliative treatment arm. Curative treatment was defined as surgical resection after detection of recurrence at a single site or single organ on PET/CT scans. The impact of stratification of patients (into curative versus palliative intent groups based on PET/CT scan) on PFS and OS was analyzed.

Follow-up and evaluation of treatment

The evaluation included clinical examination, complete blood count, serum chemistry tests, serum carcinoembryonic antigen (CEA) level, thoracic and abdominal CT examinations or PET/CT scans (if indicated) and colonoscopy as indicated. Treatment response was evaluated by CT or PET/CT scans (if indicated) every 8 or 12 weeks based on the initiated treatment modality, or whenever clinically requested. The Response Evaluation Criteria in Solid Tumors were used to classify tumor responses. Recurrence or progression was diagnosed on the basis of imaging findings and/or elevated CEA levels. Pathologic confirmation was obtained in selected cases. PFS was defined as the time from treatment modality (after PET/CT scan) baseline to disease progression or death. OS was calculated from the date of initiation of treatment modality (after PET/CT scan) to death due to any cause or the date of loss during the follow-up.

Imaging techniques

Chest and abdominal/pelvic diagnostic CT scans were performed using the MS CT scanner (Siemens Somatom Sensation, 40-slice CT system). Images with 40 × 0.72 mm collimation were obtained. Axial, coronal and sagittal reformations with different thicknesses were acquired using maximum intensity projection (MIP) + multiplanar

reformation (MPR) before and after administration of iomeprol contrast medium 1 ml/kg (60-100 ml) from the xiphoid process to the pubic symphysis with IV administration for early arterial and portal phases for the abdomen and pelvis. For the thorax, axial images with 40 × 0.72 mm collimation and coronal and sagittal reformations using MIP + MPR before and after administration of 1 ml/kg (60-100 ml) iomeprol contrast medium were obtained from the thoracic inlet to the inferior of the surrenal glands.

The median interval between the diagnostic CT and FDG PET/CT scan was 2 weeks (range 1-4 weeks). The patients fasted for at least 6 hours prior to PET/CT imaging and their blood glucose levels were obtained prior to tracer injection. The blood glucose levels of all patients were below 200 mg/dl at the time of FDG injection. Each patient received intravenous 10-15 mCi (370-550 MBq) of FDG as tracer. Following this, the patients rested on a comfortable chair in a silent room for 1 hour to allow FDG biodistribution. For the optimal delineation of bowel structures, 400-600 ml of contrast material diluted to 2.4% (v/v) with water was ingested 1 hour before CT imaging. No urinary bladder catheterization was performed, and no diuretics were administered at this time.

Whole-body imaging was performed 1 hour after radiotracer injection using a Siemens Biograph PET/CT scanner with lutetium orthosilicate (LSO) detectors (Siemens Biograph 6, IL, Chicago, USA). First, low-dose CT was performed with 140 kV, 50 mA, a table speed of 22.5 mm/s and without any specific breath-holding instructions. Scanning from the top of the skull down to the upper thighs was performed in a single step with the patients in the supine position. CT data were used for attenuation correction (5 mm contiguous axial cuts). Immediately afterwards, a PET emission scan was obtained without changing patient's position. Six to eight bed positions were used with an acquisition time of 4 minutes for each bed position. The PET scan was acquired in a three-dimensional mode over the same anatomical regions, starting at the level of the mid-thigh. The PET image data sets were reconstructed iteratively using the CT data for attenuation correction and coregistered images were displayed on a workstation.

Image analysis

The diagnostic CT images were interpreted by an experienced radiologist who had no information about the FDG PET/CT findings. Recurrent viable tumors on diagnostic CT images were identified by the presence of a highly contrast-enhanced, predominantly solid lesion in the pelvic region. Relapses of the disease were also identified as areas of abnormal contrast enhancement in the pelvis, abdomen and thorax. The diagnosis of lymph node involvement of the neoplastic disease on diagnostic CT images was based on morphological criteria. The presence of distant metastases was also evaluated.

All FDG PET/CT images were analyzed by an expert nuclear medicine physician who had no information about the diagnostic CT findings. Attenuation-corrected PET images, CT scans, and coregistered PET/CT images were interpreted using a dedicated image fusion workstation and a final consensus was reached for all patients. Any foci of increased FDG uptake, except for areas of physiologically increased FDG uptake, corresponding to a CT abnormality (tissue or lymph node) were considered positive for recurrent lesions. Suspicious findings on CT were considered negative if they did not correspond to an area of increased FDG uptake. Standardized uptake values (SUV) greater than 3.0 were considered to be indicative of malignant lesions in light of the previous reports.[9,10]

Statistical analysis

Categorical and continuous variables were compared with Chi-square and Mann–Whitney U tests, respectively. The PFS and OS were estimated by using the Kaplan–Meier method and these values were compared between groups by using the maximum likelihood test by the Cox regression model. A $P < 0.05$ was considered significant.

RESULTS

Patient characteristics

In this study, 122 patients were evaluated between January 2003 and November 2011. The median age was 58 years (range: 35-78), and 59% of the patients were male. Primary tumor site was rectum in 39% of the patients and colon in 61% of the patients. The median follow-up duration was 32 months (range: 6.2-52 months). The median interval between the conventional image and PET/CT was 2 weeks (range: 1-4). The characteristics of patients are shown in Table 1.

The Comparison of PET/CT with conventional imaging modalities regarding detection of additional metastatic sites

All 122 patients with suspected potentially resectable recurrence/metastasis of CRC underwent PET/CT scans. A total of 26 (21%) potentially resectable solitary lung metastases, 43 (35%) liver metastases, and 53 (43%) pelvic recurrences were determined by conventional imaging modalities. In 52 of the 122 patients, PET/CT determined other disease sites in addition to those previously demonstrated by the conventional imaging modalities. The sites of metastatic lesions detected by conventional imaging modalities and PET/CT are shown in Table 2 and Figure 1.

Changes in the treatment management plan after the PET/CT examinations

After the PET/CT examination, the management plan was changed in 62 (51%) patients ($P = 0.01$, 95% CI, 41.2-58.6%). We also determined whether the treatment would be given with curative or palliative intent, both after the conventional imaging and PET/CT examination. Treatment with curative intent had been planned in 97 (88%); however, the treatment plan was changed in 35 (37%) of these 97 patients after the PET/CT examination. The difference between conventional imaging

Table 1: Characteristics of 122 patients and resected primary cancers

	n	%	
Median age, years	58		
Range	35-78		
Gender			
Female	49	41	
Male	73	59	
Primary site			
Rectum	47	39	
Colon	75	61	
Histopathology			
Adenocarcinoma	107	88	
Mucinous adenocarcinoma	14	11.2	
Signet ring cell carcinoma	1	0.8	
Tumor differentiation			
Well differentiated	53	43	
Moderately differentiated	36	30	
Poorly differentiated	22	18	
Unknown	11	9	
Clinical stage			
Stage I	5	4	
Stage II	31	24.5	
Stage III	79	67.5	
Stage IV	5	4	
Surgery type			
LAR	46	36.5	
APR	26	21	
Colectomy	50	42.5	
Adjuvant chemotherapy			
Yes	99	81	
No	23	19	
Adjuvant radiotherapy			
Yes	45	36	
No	77	64	
Interval between the diagnosis and recurrence			
Median, range	28 Months	8-72	Months
Interval between conventional imaging and PET/CT			
Median, range	2 Weeks	1-4	Weeks
Time to recurrence CEA level			
>5 ng/dl	49	40	
≤5 ng/dl	44	36	
Unknown	29	24	

CEA=Carcinoembryonic antigen, PET/CT=Positron emission tomography/computed tomography, APR=Abdominoperineal resection, LAR=Lower anterior resection

Table 2: The sites of metastatic lesions detected by conventional imaging modalities and PET/CT

Site	Conventional imaging *n* (%)	PET/CT *n* (%)
Lung	26 (22)	26 (22)
Liver	43 (35)	43 (35)
Pelvis	53 (43)	53 (43)
Adrenal		6 (5)
Retroperitoneum		12 (10)
Bone		9 (7)
Multiple lymph node		14 (11)
Other		11 (9)

PET/CT=Positron emission tomography/computed tomography

and PET/CT was statistically significant in terms of planning a curative treatment ($P = 0.001$, 95% CI, 41-100%). Patients who were treated with curative intent received chemotherapy for 6 months. The intended treatment after conventional imaging and the post-PET/CT treatment plan details are shown in Table 3.

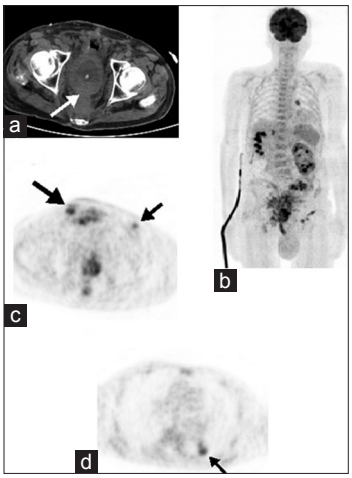

Figure 1: A 77-year-old male patient with history of colon cancer and increasing CEA levels was referred for diagnostic CT and PET/CT imaging for recurrence metastatic disease evaluation. Pelvic CT image showed a recurrence disease in the presacral region (a). When PET/CT imaging was performed for the same patient, recurrence disease was diagnosed. However, multiple metastatic lymph nodes in inguinal region and a metastatic nodule in the left lung were also seen (b MIP). For PET/CT imaging, the patient was injected 440 MBq (11,8 mCi) of F-18 fluoro-deoxyglucose (FDG), and whole body PET images were obtained 60 minutes later using an integrated PET/CT camera, which consisted of a 6-slice CT gantry, integrated with a LSO based fullring PET scanner (Siemens Biograph 6, IL, Chicago, USA). PET/CT images demonstrated multiple metastatic lymph nodes in bilateral inguinal regions (c) and a metastatic lung nodule with intense FDG uptake was also seen (d)

Patient outcomes

We demonstrated the PFS and OS of patients based on conventional imaging and PET/CT, which determined alteration of treatment. Patients were divided into two groups as requiring curative or palliative treatment based on conventional imaging and post-PET/CT imaging. While the median PFS was found to be 22 months (95% CI, 11.2-32.6 months) among the patients planned to receive treatment with curative intent after PET-CT, it was found to be 11 months (95% CI, 8.1-13.9 months) in patients planned to receive treatment with curative intent before the PET/CT examination, and the difference between the median PFS durations was statistically significant (HR, 0.51 [95% CI, 0.32 - 0.88], $P = 0.004$) [Figure 2].

Patients planned to receive curative treatment after PET/CT had a significantly longer OS (27 months [95% CI, 22.1-31.9]) than those treated with curative treatment before PET/CT (21 months [95% CI, 15.6-26.4]), and a significant difference was found between the OS scores (HR, 0.63[95% CI, 0.42-0.89], $P = 0.045$) [Figure 3].

DISCUSSION

The sensitivity and specificity of FDG-PET to detect recurrence in colorectal carcinoma are valuable.[21] A PET scan provides

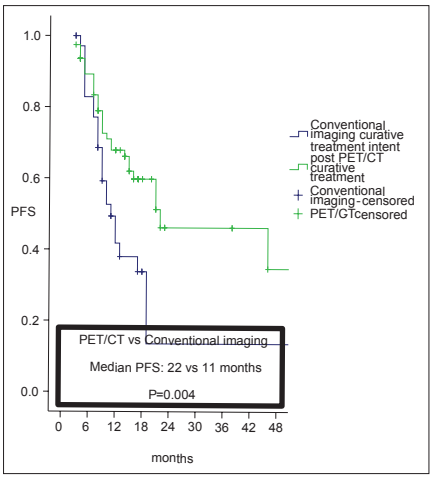

Figure 2: Kaplan–Meier analysis of progression-free survival (PFS) for patients who were treated with curative intent before PET/CT (based on conventional imaging) and after PET/CT

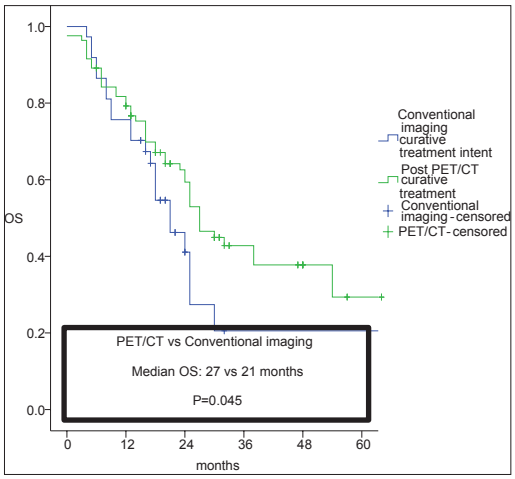

Figure 3: Kaplan–Meier analysis of overall survival (OS) for the patients who were treated with curative intent before PET/CT (based on conventional imaging) and after PET/CT

Table 3: Comparison of intended treatment plans according to conventional imaging and PET/CT imaging

	Conventional imaging *n* (%)	PET/CT treatment imaging altered	
		n (%)	*n* (%)
Surgery	6 (5)	5 (4)	1 (1)
Surgery followed by chemotherapy	80 (66)	33 (27)	47 (39)
Chemoradiotherapy followed by surgery	12 (10)	5 (4)	7 (6)
Chemotherapy followed by surgery	9 (7)	7 (6)	2 (1)
Chemotherapy	15 (12)	12 (10)	3 (2)
Curative intent	97 (88)	62 (51)	35 (37)

PET/CT=Positron emission tomography/computed tomography

comparable sensitivity compared with a CT scan regarding the detection of colorectal liver metastases; however, PET scan provides superior sensitivity for the detection of extrahepatic disease compared with CT, and changes the estimation of disease extent in one-third of patients.[22-24] In a prospective study, Kalff *et al*. reported that the management plan was altered in 56% of the patients as a direct result of unexpected PET findings.[19] Scott *et al*. demonstrated that PET scan detected additional disease sites in 48.4% and 43.9% of the patients who developed single locoregional recurrence and single site distant metastases, respectively.[20]

In our study, PET-CT determined additional disease sites other than those previously demonstrated by conventional imaging in 42% of the patients, and our findings were similar to those of the previous studies.

Regarding the patients with CRC liver metastases, PET is reported to influence the clinical management in 20-50% of the cases, mostly due to detection of additional metastases, which are not detected by CT.[13-18] A recent prospective study reports that PET scan may influence the management of patients with recurrence colorectal disease, and the planned surgical treatment was abandoned in 60% of the patients due to the additional findings on PET scans.[19] Also, another recent prospective study reports that the planned treatment management was changed in 65.6% and 49% of the patients who developed single locoregional recurrence and single site distant metastases, respectively.[20]

In the present study, the treatment plan was changed in 51% of the patients after the PET/CT examination. We also determined that the curative intent of the treatment was changed after the PET/CT examination in 37% of the patients. This finding correlates with the findings of Kall *et al*. and Scott *et al*.[19,20]

However, apart from a recent study, no previous studies have evaluated the impact of PET on patient outcomes.[20] Scott *et al*. demonstrated that the alteration of treatment modality resulting from the additional lesions detected by PET scans was associated with poor PFS compared with the patients with no additional lesions detected by PET in whom the intended treatment was not changed.[20] Nevertheless, the duration of follow-up was short in this study (12 months), and there was no available information indicating whether the PET scan had any impact on OS.

In the present study conducted in patients with suspected or proven CRC recurrence, PFS was significantly longer among the patients planned to receive curative treatment after the PET/CT scans compared with the patients planned to receive treatment with curative intent before PET/CT examination. Furthermore, patients planned to receive curative treatment after the PET/CT had significantly longer OS compared with those planned to receive treatment with curative intent before the PET/CT scan.

The main limitations of this study include biases arising from the retrospective design, analyzing heterogeneous groups of patients who had diverse clinical course of disease such as rectum and

colon cancer, and physician-based treatment decisions without any previously planned and recorded treatment algorithm. Despite all these limitations, this study demonstrates that PET/CT changes modality of treatment and affects survival of patients.

In conclusion, this study determined the significant impact of PET/CT on the management of treatment and outcomes in patients with suspected or proven recurrent CRC.

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