RESEARCH ARTICLE

Value of FDG PET/Contrast-Enhanced CT in Initial Staging of Colorectal Cancer - Comparison with Contrast-Enhanced CT

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Abstract

Background: FDG PET/CT is at an equivocal stage to recommend for staging of colorectal cancer as compared to contrast-enhanced CT (ceCT). This study was intended to evaluate the value of FDG PET/ceCT in colorectal cancer staging as compared to ceCT alone. Materials and Methods: PET/ceCT was performed for 61 colorectal cancer patients who were prospectively enrolled in the study. Three patients were excluded due to loss to follow-up. PET/ceCT findings and ceCT results alone were read separately. The treatment planning was then determined by tumor board consensus. The criteria for T staging were determined by the findings of ceCT. Nodal positive by PET/ceCT imaging was determined by visual analysis of FDG uptake greater than regional background blood pool activity. The diagnostic accuracy of T and N staging was determined only in patients who received surgery without any neoadjuvant treatment. Results: Of 58 patients, there were 40 with colon cancers including sigmoid cancers and 18 with rectal cancers. PET/ceCT in pre-operative staging detected bone metastasis and metastatic inguinal lymph nodes (M1a) that were undepicted on CT in 2 patients (3%), clearly defined 19 equivocal lesions on ceCT in 18 patients (31%) and excluded 6 metastatic lesions diagnosed by ceCT in 6 patients (10%). These resulted in alteration of management plan in 15 out of the 58 cases (26%) i.e. changing from chemotherapy to surgery (4), changing extent of surgery (9) and avoidance of futile surgery (2). Forty four patients underwent surgery within 45 days after PET/CT. The diagnostic accuracy for N staging with PET/ceCT and ceCT alone was 66% and 48% with false positive rates of 24% (6/25) and 76% (19/25) and false negative rates of 47% (9/19) and 21% (4/19), respectively. All of the false negative lymph nodes from PET/ceCT were less than a centimeter in size and located in peri-lesional regions. The diagnostic accuracy for T staging was 82%. The sensitivity of the peri-lesional fat stranding sign in determining T3 stage was 94% and the specificity was 54%. Conclusions: Our study suggested promising roles of PET/ceCT in initial staging of colorectal cancer with better diagnostic accuracy facilitating management planning.

Keywords: Colorectal cancer - pre-operative - staging - PET/CT - contrast-enhanced CT

Asian Pac J Cancer Prev, **17 (8)**, 4071-4075

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer related-deaths and the 4th most common malignancy in the United States and worldwide(Siegel et al., 2014). Fluorine-18 (18F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET) computed tomography (CT) [18F-FDG PET/CT] is one of the most commonly used modalities in many aspects of oncologic imaging such as diagnosis, staging, re-staging, monitoring and evaluation after treatment. In CRC, FDG PET/CT is recommended with strong evidence during the period following therapy to detect recurrent disease in case of rising CEA level with sensitivity as high as 80% and very high negative predictive value of 95%. Also, in evaluation of presacral masses post treatment, FDG PET/CT has high diagnostic accuracy in distinguishing between benign post treatment change and local recurrence, which has an impact on clinical management (Shin et al., 2008; Chowdhury et al., 2010).

In clinical staging, there is limited data to support the use of FDG PET/CT in routine staging in patients diagnosed with primary colorectal cancer. Mostly PET/CT is recommended in case of equivocal CT findings that may alter management plan. Accurate staging is highly essential in determining treatment strategy, especially in curative intent, and also in giving disease prognosis and outcome. Curative treatment of CRC involves

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surgical resection of primary tumor, intervention to limited metastatic disease, adjuvant chemotherapy and neoadjuvant chemoradiation in rectal cancer. The pre-operative imaging has 3 primary applications: a) identify metastatic site to avoid futile surgery; b) guide extensive surgery to include metastatectomy; and c) identify T3 (tumor invades through muscularis propria into pericolorectal tissue), T4 (tumor invade adherent organ structure or visceral peritoneum) and N positive diseases in rectal cancer that requires neoadjuvant chemoradiation before surgery.

The NCCN guideline recommends contrast-enhanced chest, abdomen and pelvic CT as an appropriate imaging work-up for initial staging of CRC. PET/CT does not supplant CT and should be used in selected cases to evaluate an equivocal finding or potentially surgically curable metastatic disease. The level of evidence is in category 2A; based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. However, most of the limited published literatures on PET/CT used non-contrast enhance in CT part and were based on retrospective design and heterogenous approach. The use of PET/contrast-enhanced CT instead of CT alone potentially improves the accuracy of pre-operative staging and serves as a one-stop service. The FDG PET/contrast-enhanced CT will possibly correct 3 known problems of CT alone or PET/non-contrast CT: a) suspicious lesion on PET/CT scan which is not considered to be malignant with contrast-enhanced CT; b) equivocal lesions seen on CT which is not considered as malignant on PET; c) early detection of metastasis before anatomical abnormality. Also, contrast-enhanced PET/CT mitigates the downside of non-contrast PET/CT by providing detailed anatomical information which is essential for surgical planning.

The aim of this prospective study was to solely evaluate the value of PET/contrast-enhanced CT as compared to contrast-enhanced CT in pre-operative staging of colorectal cancer patient and its effect to strategic treatment planning.

Materials and Methods

Patients

The study was approved by Chulabhorn Institutional Review Board and all participants gave a written informed consent. Sixty-one patients with histopathological proven colorectal cancer and had not received treatment were prospectively enrolled in this study between July 2011 to July 2014. All patients underwent FDG PET/contrast-enhanced CT then the treatment plan was decided by tumor board consensus per standard treatment guideline.

FDG PET/CT imaging

Patients fasted for 6 hours before undergoing FDG PET/CT using a Siemens/Biograph 16 scanner in 3D mode. Plasma glucose level was measured to ensure that it was less than 180 mg/dL before intravenous injection of 5 MBq/kg of FDG. Ninety minutes after FDG administration, a whole body emission PET scan was performed including 6-8 bed positions (3-min acquisition time per bed position), covered from vertex to proximal thigh. Non-contrast-enhanced CT with 120-keV, 120-mAs, 5-mm collimation and pitch of 0.75 was performed for attenuation correction. Contrast-enhanced CT was undertaken following the administration of contrast media via oral, rectal and intravenous routes.

Image interpretation, treatment determination and data analysis

PET/ceCT results were analyzed by two independent experienced nuclear medicine physicians. In congruent results were reviewed and finalized by consensus. Contrast-enhanced CT parts were analyzed by experienced radiologist to represent the results of solely ceCT. These two groups of readers did not know the results of the other. Staging was performed according to the 7th edition of the American Joint Committee on Cancer staging system. The treatment plan was then decided by tumor board consensus per standard treatment guideline.

Regarding the impact on treatment decision, the T staging was categorized to T1/2, T3 or T4 and was determined by the findings in contrast-enhanced CT. T3 stage was identified by evidence of perilesional fat stranding and T4 by losing intervening fat plane with adjacent structure. N staging was categorized into two groups: with or without regional lymph node metastasis. The criteria for N positive was visual analysis of FDG uptake in lymph node of any size that greater than regional background blood pool activity. The criteria for N positive on ceCT was determined if a cluster of at least three nodes was present, independent of their size, or if fewer than three lymph nodes were present, with at least one of them measuring at least 1 cm in long axis(Filippone et al., 2004). The diagnostic accuracy of T and N staging was determined only in patients who received surgery without any neoadjuvant treatment.

Distance metastasis was defined by visual analysis regarding areas of non-physiologically increased uptake that is inarguably compatible with malignant lesion. Then the treatment plan was decided by multidisciplinary team in tumor board consensus using standard treatment guideline.

Alteration of management plan was defined by any treatment beyond surgical resection of primary tumor

Table 1. Patient Characteristics

Patient characteristic	Number (%)
Sex	
Male	29 (47.5%)
Female	32 (52.5%)
Age (years)	
Average	62
Range	35 - 78
Tumor location	
Cecum	3 (5%)
Ascending colon	11 (18%)
Transverse colon	3 (5%)
Descending colon	3 (5%)
Sigmoid colon	18 (30%)
Rectosigmoid colon	4 (6%)
Rectum	19 (31%)
Total	61

Table 2. PET/CT Staging Correlations with Tumour Characteristics

	All patients (n = 58)		Surgery without neoadjuvant Rx (n = 44)		
	ceCT staging	PET/ceCT staging	ceCT staging	PET/ceCT staging	Pathological staging
T					
T1-2	13	24	10	19	14
T3	42	31	33	24	29
T4	3	3	1	1	1
N					
N0	3	17	10	16	19
N positive	46	41	34	28	25
M	18 (8)	12 (1)	10 (7)	5	5
M1a: one organ/site	9 (7)	6 (1)	6 (6)	3	3
Liver	6 (2)	4	5 (2)	3	3
Bone	-	1	-	-	-
Non regional lymph node	3 (5)	1 (1)	1 (4)	(1)	-
M1b: Multiple organs/sites or peritoneum					
Sites of metastasis					
Liver	13 (2)	9	9 (2)	5	5
Lung	6 (1)	2	3	1	1
Bone	1	2	-	-	-
Non regional lymph node	8 (12)	4	3 (10)	1	1
2nd primary lung cancer	1	1	-	-	-

Numbers in parenthesis () represent the number of equivocal lesions

Table 3. Diagnostic Performance of PET/ceCT and ceCT in T and N Staging

	Sensitivity	Specificity	Accuracy	PPV	NPV
T3	94%	54%	82%	83%	78%
N positive					
ceCT	79%	24%	48%	44%	60%
PET/ceCT	53%	76%	66%	63%	68%

ceCT = contrast-enhanced CT

and regional lymph node i.e. extent of surgery to include distant metastatectomy, neoadjuvant treatment with chemotherapy and/or radiation therapy and non-surgical palliative treatment.

Histopathological diagnosis was used as a reference standard for T and N staging. Therefore, the diagnostic accuracy of T and N staging was calculated only in patients who received surgery without any neoadjuvant treatment.

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of FDG PET/contrast-enhanced CT in the assessment of T and N staging were calculated. A P-value of ≤ 0.05 was considered as being statistically significant in any applicable value.

Results

A total of 61 patients were included. The patient characteristics were shown in table 1. Three patients were then excluded due to lost follow-up after PET/CT scan.

PET/ceCT findings and treatment after scan

Of 58 patients, there were 40 colon cancers including sigmoid cancers and 18 rectal cancers. PET/ceCT in pre-operative staging detected bone metastasis and metastatic inguinal lymph node (M1a) that undepicted on CT in 2 patients (3%) [Figure 1], clearly defined 19 equivocal lesions on ceCT in 18 patients (31%) and excluded 6 metastatic lesions diagnosed by ceCT in 6 patients (10%) (Figure 2).

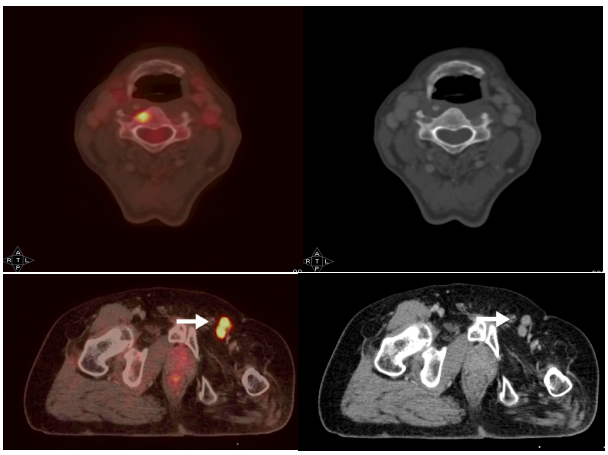

Figure 1. PET/ceCT and ceCT Images of Two Patients with Bone Metastasis and Left Inguinal Lymph Node Metastasis False Negative on ceCT (arrow).

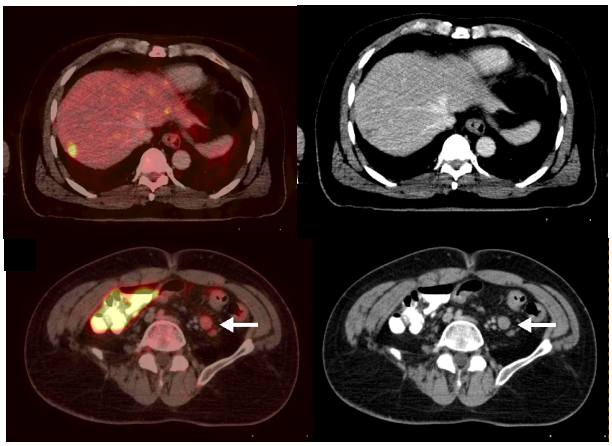

Figure 2. PET/ceCT and ceCT Images of Two Patients with Equivocal Liver Metastasis and False Positive Mesenteric Node Metastasis on ceCT (arrow).

Details of PET/contrast-enhanced CT staging and ceCT staging (see Table 2).

The diagnostic accuracy for T staging was 82%. The sensitivity of the peri-lesional fat stranding sign in determining T3 stage was 94% (29/31) and the specificity was 54% (7/13). The diagnostic accuracy for N staging of PET/ceCT and ceCT alone was 66% and 48% with false positive rate of 24% (6/25) and 76% (19/25) and false negative rate of 47% (9/19) and 21% (4/19), respectively. Diagnostic accuracy of PET/contrast-enhanced CT in identifying T3 stage and locoregional nodal metastases were shown in table 3.

Forty four patients received surgery without any neoadjuvant treatment within 45 days after PET/CT scan (average 27 days; range 14 – 45 days). Twenty-one out of 44 patients received adjuvant chemotherapy (n =18) or concurrent chemoradiation (n = 3). Neoadjuvant treatments were given in 9 patients. Four patients; two for each, received palliative chemotherapy and palliative chemotherapy with radiation therapy.

In total, PET/contrast-enhanced CT altered the management plans in 15 out of the 58 patients (26%) including the change from chemotherapy to surgery in 4 patients, changing extension of surgery in 9 patients and avoid futile surgery in 2 patients.

Discussion

The prognosis of CRC is related to initial staging and ability to have curative surgery. The key findings that would change the management plan include detection of metastasis and whether it is resectable, identification of T3 and T4 stage, and identification of regional nodal metastasis in rectal cancer. PET/CT was reported superior to CT in detecting extrahepatic metastases with sensitivity of 89% *vs* 64%, respectively (Selzner et al., 2004). For hepatic metastasis, PET/CT also provided better detection than CT especially in PET/contrast-enhanced CT (Shin et al., 2008; Niekel et al., 2010). PET/contrast-enhanced CT (PET/ceCT) is an attractive one-stop imaging protocol in oncologic management because it should correct the three major drawbacks of non-contrast PET/CT or contrast-enhanced CT alone: 1) Early detected metastatic disease before CT abnormality or subtle CT findings; 2) Identified suspicious lesions on PET/non-contrast CT but is not considered to be malignant with contrast-enhanced CT and 3) Identified equivocal metastatic lesions on CT that are not considered as malignant on PET. In our study, the benefit of PET/ceCT mainly helped in area of indeterminate metastatic lesions on CT (31%) especially liver metastasis and non-regional lymph node metastasis which mostly resulting in down-staging. In contrast to bone metastasis which PET/ceCT detected more metastasis than ceCT and resulting in up-staging. The NCCN guideline recommends PET/CT in selected cases to evaluate an equivocal CT finding or potentially surgically curable metastatic disease. This statement is concordance with our findings.

According to previous reports, FDG PET/CT alters the management plan in 3.2-50% in CRC staging (Kantorova et al., 2003; Park et al., 2006; Llamas-Elvira et al., 2007; Cipe et al., 2013; Petersen et al., 2014). However, the previous published data were PET alone or non-contrast PET/CT. Peterson et al, recently reported the retrospective study on impact of FDG PET/contrast-enhanced CT on CRC staging and treatment compared to previous conventional imagings (Petersen et al., 2014). They found that the use of FDG PET/CT changed the treatment plan in a total of 30% of the cases, which is not different from 26% in our study.

There was recently published a multicenter randomized clinical trial to evaluate the effect of pre-operative PET/CT versus no PET/CT on surgical management of liver metastasis and also overall survival (Moulton et al., 2014). Non-contrast PET/CT was compared with complete baseline contrast-enhanced CT of the chest, abdomen and pelvis in post colectomy patients with potentially resectable synchronous or subsequent liver metastasis. The investigators found that surgeons would change the surgical plan in 8.7% and canceled in 2.7% based on PET/CT findings. The median follow-up of 3 years showed no difference in overall survival between the groups. The major difference from our study was that we aimed to evaluate the value of contrast-enhanced PET/CT in the clinical setting of initial stage before colectomy and any treatment without previous CT. We enrolled newly diagnosed CRC patients without baseline imaging to avoid selective bias of patients in late stage with known, suspected or equivocal metastasis from conventional imaging. Our study found that PET/contrast-enhanced CT resulted in an improvement in staging in 44% of the patients, as compared to contrast-enhanced CT alone (images were retrieved from one PET/CT protocol per patient). The improved staging affected the treatment plans in 26% which change the surgical plan in 15.5% and canceled in 3.4% of the cases.

Some might argue that the benefit of PET/ceCT is not overcome the benefit of PET/non-contrast CT but increased risk of side effect from contrast media. We have not analyzed our data on this point so far. However, there is a main drawback of PET/non-contrast CT; the limitation in anatomical details especially in determining T4 and vascular anatomy which is crucial for surgical planning. Hence, if PET/non-contrast CT is performed for initial staging, the surgeons almost always need subsequent contrast-enhanced CT study which resulting in increased the total radiation dose to the patient and prolong the time to start surgery. In case of patients who already have contrast-enhanced CT, the PET/non-contrast CT alone might be sufficed for evaluation of equivocal lesion.

The strategy of contrast-enhanced CT first then PET/non-contrast CT when there is equivocal lesion versus only PET/ceCT for one-stop service for initial staging in CRC need further randomized clinical trial in comparative cost-effectiveness design to clearly address this issue. The limitation of our study is the lack of data on cost-effectiveness and overall survival.

Previous report of contrast-enhanced MDCT colonography in overall accuracy of T staging was 83% and N staging was 80% (Filippone et al., 2004) which is comparable to our study of 82% on T stage and 66% on N stage from PET/contrast-enhanced CT. However, in our

study the diagnosis accuracy of contrast-enhanced CT in detecting regional lymph node metastasis is only 48%. In recent study from Liao et al. (2014), there was correlation between pathological findings and parameters derived from FDG PET/CT such as metabolic tumor volume and threshold in patients with rectal cancer. This implies the potential improvement of FDG PET/CT in yielding more accurate T staging result in the future. Shin et al. reviewed that PET/CT showed sensitivity of 43% and specificity of 80% for regional nodal metastasis(Shin et al., 2008) which is close to our study of 53% and 76%, respectively.

To the best of our knowledge, our study is the first to prospectively address the diagnostic performance of PET/contrast-enhanced CT in determining the finding for T and N stage that impacts the change in surgical treatment plan. Our reference standard was only histopathology from the patient without any adjuvant treatment with prospective design; therefore avoiding the error from clinical or serial imaging follow-up and selective bias in advanced disease with equivocal CT finding then undergoing PET/CT. The limitation of our study was that positive PET/CT lesions (T3, N positive) in 9 rectal cancer patients was excluded from diagnostic performance analysis because the patients were conferred to received neoadjuvant chemoradiation before surgery as per the standard treatment guideline and tumor board consensus.

In conclusions, our study suggested that in initial staging of colorectal cancer, PET/contrast-enhanced CT can play a promising role as a one-stop service imaging in yielding a more accurate staging which subsequently alters the management plan. Further study on cost-effective analysis and outcome on survival will endorse this role of PET/ceCT as compared to ceCT.

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