

RESEARCH ARTICLE

Accuracy of FDG-PET/CT for Detection of Incidental Pre-Malignant and Malignant Colonic Lesions - Correlation with Colonoscopic and Histopathologic Findings

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Abstract

Purpose: We evaluated all PET/CTs acquired for patients without a primary diagnosis of colorectal cancer, and compared results for those who had subsequent colonoscopy within 6 months, to assess the accuracy of FDG PET/CT for detection of incidental pre-malignant polyps and malignant colon cancers. **Materials and Methods:** Medical records of 9,545 patients who underwent F-18 FDG PET/CT studies over 3.5 years were retrospectively reviewed. Due to pre-existing diagnosis of colorectal cancer, 818 patients were excluded. Of the remainder, 157 patients had colonoscopy within 6 months (79 males; mean age 61). We divided the colon into 4 regions and compared PET/CT results for each region with colonoscopy and histopathologic findings. True positive lesions included colorectal cancer, villous adenoma, tubulovillous adenoma, tubular adenoma and serrated hyperplastic polyp/hyperplastic polyposis. **Results:** Of 157 patients, 44 had incidental colonic uptake on PET/CT (28%). Of those, 25 had true positive (TP) uptake, yielding a 48% positive predictive value (PPV); 9% (4/44) were adenocarcinoma. There were 23 false positive (FP) lesions of which 4 were hyperplastic polyp, one was juvenile polyp and 7 were explained by diverticulitis. Fifty eight patients had false negative PET scans but colonoscopy revealed true pre-malignant and malignant pathology, yielding 23% sensitivity. The specificity, negative predictive value (NPV) and accuracy were 96%, 90% and 87%, respectively. The average SUVmax values of TP, FP and FN lesions were 7.25, 6.11 and 2.76, respectively. There were no significant difference between SUVmax of TP lesions and FP lesions ($p>0.95$) but significantly higher than in FN lesions ($p<0.001$). The average size (by histopathology and colonoscopy) of TP lesions was 18.1 mm, statistically different from that of FN lesions which was 5.9 mm ($p<0.001$). Fifty-one percent of FN lesions were smaller than 5 mm (29/57) and 88% smaller than 10 mm (50/57). **Conclusions:** The high positive predictive value of incidental focal colonic FDG uptake of 48% for colonic neoplasia suggests that colonoscopy follow-up is warranted with this finding. We observed a low sensitivity of standardly acquired FDG-PET/CT for detecting small polyps, especially those less than 5 mm. Clinician and radiologists should be aware of the high PPV of focal colonic uptake reflecting pre-malignant and malignant lesions, and the need for appropriate follow up.

Keywords: PET/CT - screening - colon cancer - pre-malignant - incidental findings

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Introduction

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. As the usage frequency increases, many previously unknown normal variations, physiologic uptakes and incidental findings have been revealed. One of the frequent incidental findings is an abnormal intense focal uptake in the colon (Sone et al., 2014). As mentioned

in previous literatures (Lee et al., 2009; Peng et al., 2011; Purandare et al., 2012; Rainis et al., 2014; Seivert et al., 2014; Fuertes et al., 2015; Keyzer et al., 2015; Simsek et al., 2015; van Hoeij et al., 2015), the FDG-avid incidental colonic uptake in comparison to subsequent colonoscopic results yielded 40-84% of true pathologic lesions, including colon cancers, premalignant lesions, polyps, infections and inflammatory processes. This finding has led to the alteration of therapeutic management by 91% (Salazar et al., 2011). However, under this approach in which only colonoscopic results of positive FDG uptake are available, false negative is poorly defined and true

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negative cannot be evaluated. As such, establishing the complete diagnostic value of FDG- PET/CT in significant incidental colonic pathology will help inform radiologists on how effective FDG-PET/CT is as a tool for detection of significant colonic lesions while reading for other indication of primary cancer or for screening purposes. Moreover, although FDG PET/CT is well validated for staging and recurrence detection of colorectal cancer, indication of this modality for screening of precancerous and cancerous lesions has not been well-established thus far.

In WHO world cancer report 2014, colorectal cancer is the 3rd most common malignancy and the 4th leading cause of cancer related-deaths worldwide (Stewart and Wild, 2014). Early detection and screening is a key to concur this cancer. Researchers have also found that endoscopic or surgical removal of precancerous lesion as adenomas reduces the morbidity and mortality of colorectal cancer patients (Salazar Andia et al., 2011).

In order to elucidate the utility of PET/CT in detection of incidental pre-malignant and malignant colon cancer with provided complete diagnostic values, we compared all PET/CT results with colonoscopic results in patients who had subsequent colonoscopy within 6 months.

Materials and Methods

Patients

The study was approved by Massachusetts General Hospital (MGH) institutional Review Board. Medical records of all patients who underwent 18F-FDG PET/CT studies at MGH due to any oncologic indication over the course of 3.5 years (July 2005 - December 2008) were retrospectively reviewed. Patients with a pre-existing diagnosis of colorectal cancer were excluded from this study (total 818 patients: 735 had colorectal cancer, 50 had anal cancer, 24 had cancer in the small intestine, and 9 had cancer of the appendix). Of 8,727 PET/CT studies, 157 patients had followed colonoscopy within 6 months (79 males; mean age 61).

PET/CT imaging protocol

All scans were performed by using a BIOGRAPH 64 Hi-Rez scanner (Siemens) PET/CT. Patients were instructed to fast for at least 4-6 hours and blood glucose level was measured to ensure that it was less than 200 mg/dL before radiotracer injection. Sixty minutes after intravenous injection of 18F-FDG per standard MGH protocol (555-925 MBq; BMI base dose), a whole body emission PET scan was performed, using a dual-slice lutetium oxyorthosilicate (LSO) PET scanner, including 6-8 bed positions (3-min acquisition time per bed position), covered from base of skull to upper 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 also performed for diagnosis. The reconstructed images were reviewed in transverse, sagittal and coronal plane, using a dedicated PET/CT fusion workstation with built-in software (syngo TrueD; Siemens Medical Solutions).

Image interpretation and data analysis

FDG-PET/CT was analyzed visually by nuclear medicine specialist, unaware of clinical history and the results from original PET/CT report, other modalities, colonoscopy and histopathology. An abnormal uptake was defined as any focus of increased uptake greater than the surrounding background blood pool activity and/or hepatic activity. Uptake in the lesions was semi- quantitatively analyzed for maximal standard uptake values (SUVmax). Locations of abnormal FDG foci were documented in 4 colonic segments: cecum/ascending colon, transverse colon, descending colon, and rectosigmoid colon. The PET/CT results were evaluated per lesion-based segmental analysis and considered to be true positive (TP), true negative (TN), false positive (FP) and false negative (FN) by following criteria;

TP – a location of a focal FDG uptake corresponded to that of pre-malignant/malignant lesion found by colonoscopy.

TN – a negative PET/CT correlated with a negative colonoscopy.

FP – there was a focal FDG uptake without a correlative finding by colonoscopy.

FN – no focal FDG uptake seen by PET/CT at a given location, yet pathology was observed at that location by colonoscopy.

Pre-malignant lesions included villous adenoma, tubulovillous adenoma, tubular adenoma and serrated hyperplastic polyp/hyperplastic polyposis. Even though the adenomatous polyp or serrated hyperplastic polyps are benign, but it is proved to have malignant potential and it is a standard medical practice to remove them when found. Therefore, we considered them to be true positive lesions. Non-serrated hyperplastic polyp, Infection and inflammation e.g. diverticulitis were considered as negative lesions.

If patient had more than one lesion in a given segment, the largest lesion, as determined by histopathology, was used for any subsequent analysis. Lesion sizes were determined by histopathologic results. In case those histopathologic results were not applicable, colonoscopic results were used. After comparison between the PET/CT and colonoscopic results, PET/CT images were retrospectively evaluated again in false negative lesions in order to determine SUVmax if applicable. In false positive patients, their medical records were reviewed for any diagnosis of colon disease after initial negative colonoscopy.

Statistical analysis was analyzed with SPSS version 16.0 for Windows (SPSS Inc, Chicago, Illinois). All statistical tests were two-sided Mann-Whitney U test and P value < 0.05 was considered indicative of a statistically significant difference.

Results

The baseline characteristic of 157 patients who had FDG-PET/CT scan followed by colonoscopy within 6 months and their primary cancers were provided in Table 1.

Of 157 patients, 44 patients had incidental colonic

uptake on PET/CT (28%). Of those, 25 patients had true positive, resulting in 48% PPV. Nine percent (4/44) were adenocarcinoma. There were 23 false positive lesions of which 4 were hyperplastic polyp, one was juvenile polyp and 7 were explained by diverticulitis. Fifty eight patients had negative scan but colonoscopy revealed true pre-malignant and malignant pathology (Table 2). This yielded 73% false negative rate and 23% sensitivity. The specificity, NPV and accuracy per colonic

segment analysis were 96%, 90% and 87%, respectively. Histopathologic results of the true colonic pathology were provided in Table 3.

Of 44 lymphoma patients in this study, three (6.8%) revealed colonic involvement by colonoscopy with diffuse large B cell type in pathological reports. Of those, two were depicted by PET/CT. Because the B cell lymphoma does not fit the criteria for primary colonic carcinoma, they (2 TP, 1 FN) were excluded from subsequent size and SUV analysis.

The average size of true positive lesions was 18.1 mm and statistically difference from that of false negative lesions which was 5.9 mm (P=0.00). Fifty-one percent of false negative lesions were not more than 5 mm (29/57) and 88% were not more than 10 mm (50/57) in size while those of true positive lesions were only 11% (2/19) and 21% (4/19), respectively (Figure 1).

The average SUVmax of true positive, false positive and false negative lesions were 7.25, 6.11 and 2.76, respectively (Figure 2). There were no statistically significant difference between SUVmax of true positive

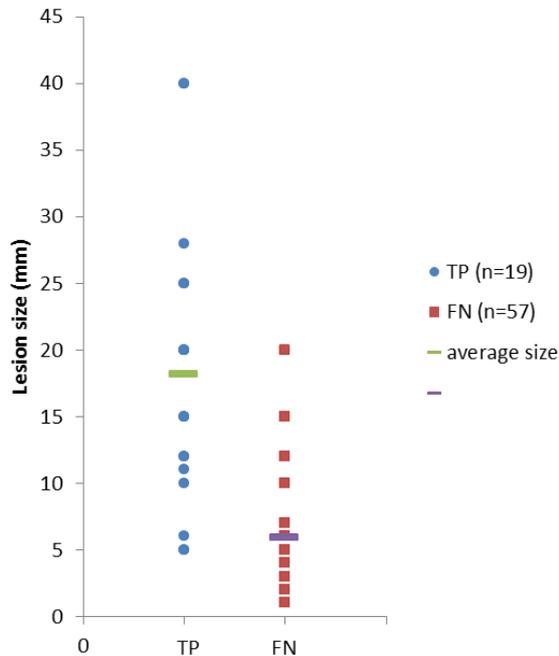


Figure 1. Lesion Size by Histopathology and Colonoscopy

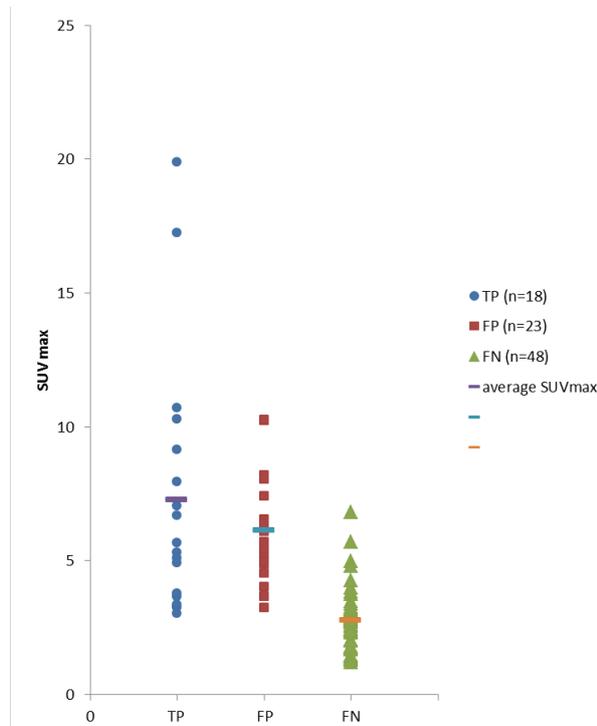


Figure 2. SUVmax of Lesions Categorized by Diagnostic Results. Three lymphomas were excluded from this analysis

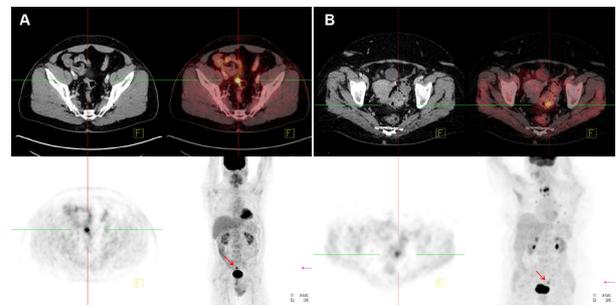


Figure 3. Transaxial PET, CT, Fusion Image and MIP. (A) A true positive lesion with SUVmax of 6.22. The pathology revealed a 16-mm tubulovillous adenoma with high grade dysplasia. (B) A false positive lesion with SUVmax of 5.7 but negative colonoscopy

Table 1. The Baseline Characteristic of the Patients and their Primary Cancers

	Number (%)
Age (mean ± SD)	61 ± 13.6 years
Male	79 (50.32%)
Time interval between PET and colonoscopy (mean ± SD)	67 ± 54 days
Primary cancer type	
Lymphoma	44 (28%)
Unknown primary	32 (20%)
Gynecologic	23 (15%)
Lung	19 (12%)
Abdominal solid organ	13 (8%)
Head and neck	9 (6%)
Gastrointestinal (non-colorectal)	7 (4%)
Melanoma	5 (3%)
Other	5 (3%)

Table 2. 2x2 Table Comparison of FDG-PET/CT and Endoscopic Results per Colonic Segmental Analysis

	Colonoscopy		Total
	Positive	Negative	
FDG positive	21	23	44
FDG negative	58	526	584
Total	79	549	628

Table 3. Histopathologic Findings by Group

Histopathology	True positive lesions	False negative lesions
Adenocarcinoma	4 (20%)	1 (2%)
Villous adenoma	1 (5%)	0
Tubulovillous adenoma	6 (30%)	5 (9%)
Tubular adenoma	7 (35%)	50 (88%)
Lymphoma	2 (10%)	1 (2%)

Table 4. The P-value among Each Pathological Group

	Tubular adenoma	Tubulovillous adenoma	Villous adenoma
Tubular adenoma			
Tubulovillous adenoma	0.27		
Villous adenoma	0.10	0.34	
Adenocarcinoma	0.00	0.16	0.48

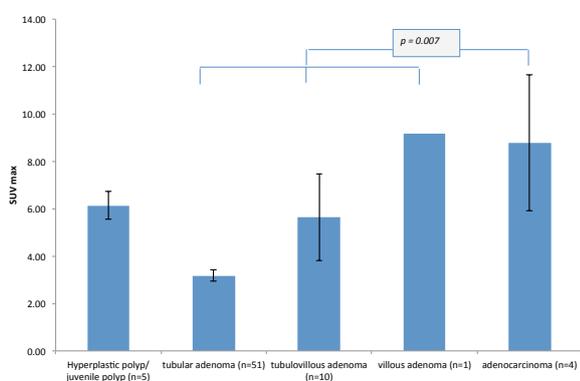


Figure 4. SUVmax of Lesions by Pathology

lesions and that of false positive lesions (P=0.969). Examples of true positive and false positive lesion are provide in Figure 3. Note that SUV of 9 false negative lesions could not be determined because they were not detectable on PET/CT and SUV of one true positive lesion could not be determined due to technical problems.

The SUV were significantly higher in true positive group than in false negative group (P=0.00). The difference in SUV between colon cancer and premalignant lesions reached statistical significance (P=0.007) (Figure 4). However, SUV cannot differentiate between adenocarcinoma and tubulovillous/villous adenoma (P=0.157 and 0.480, respectively). The P-value among each group was shown in Table 4.

Discussion

PPV of 48% for precancerous and cancerous lesions and cancer detection rate of 9% suggested that the focal FDG uptake in colon, found on PET/CT, should lead to recommendation for colonoscopy. The PPV value in our study is approximately the same as that of previously published literatures (Lee et al., 2009; Weston et al., 2010; Peng et al., 2011; van Hoeij et al., 2015). Although 23 sites of focal FDG uptake with recommendation and follow-up led to negative findings by colonoscopy, it is in the best interests of the patient to screen and resect early focal lesions to prevent progression from adenomatous

polyp to colonic adenocarcinoma. Of these 23 patients, 7 cases could be explained by diverticulitis. A positive signal in the absence of any apparent abnormality by colonoscopy for the remaining cases could have many causes, including smooth muscle and mucosal activity, inflammation, intraluminal fecal content, swallowed secretion, or microbial uptake (Rosenbaum et al., 2006; Prabhakar et al., 2007). Interestingly, the difference between SUV of true positive and that of false positive lesions were not statistically significant (Gutman et al., 2005). These findings imply that, for non-specific PET tracer such as FDG, using SUV to differentiate between cancer and infection, inflammation and/or physiologic uptake by using SUV still has been the major limitations and pitfalls. Moreover, we found that

SUV cannot differentiate pathology among each group. Even though the difference between the SUV of pre-malignant and malignant lesions was statistically significance, we cannot draw the same conclusion between each of pre-malignant subgroup and malignant lesion. These validate the importance of colonoscopic confirmation in FDG-avid lesions regardless of SUV (Keyzer et al., 2015; Na et al., 2015; van Hoeij et al., 2015).

In this study, the sensitivity of PET/CT was 27%. The missed lesions included colon cancer, lymphoma, advanced and non-advanced adenoma. Almost 90% of the false negative lesions were smaller than 10 mm and half of them were smaller than 5 mm, which were statistically different from the average size of the true positive group. This reflects the limited sensitivity of the imaging modality itself. Previous studies also showed that the detection rate of polyp by FDG- PET increased with adenoma size and grade of dysplasia (Friedland et al., 2005; van Kouwen et al., 2005; Nakajo et al., 2009).

For the detection of colonic pre-cancerous and cancerous lesions, our study showed the sensitivity of 27% while the study done by Weston et al (Weston et al., 2010), showed the sensitivity of 53% for detection of significant colonic pathology including both cancer and benign pathology and 72% for colon cancer and adenomas which were 10 mm or more in size. They also found that the mean size of colon cancers missed by PET/CT was larger than that of cancers detected by PET/CT. The difference could be explained by three primary reasons. First, we used visual analysis by comparing lesion uptake with regional background blood pool activity and liver activity while Weston et al used SUVmax > 3.5 as a cut point for positive PET findings which can be easily affected by many factors especially a variable bowel uptake. Second, we did not exclude tumor less than 10 mm in order to outline the limitation of PET/CT that radiologists and clinicians should be aware of. Lastly, we focused on the detection of pre-malignant and malignant colon cancer lesions and only considered a focal FDG uptake to be positive by PET. The segmental or diffuse uptake was not included in our criteria of PET positive lesion given that many literatures showed that these characteristics were more specific to infection, inflammatory process or physiologic uptake other than malignant pathology (Tatlidil et al., 2002; Prabhakar et al., 2007). Our inclusion criteria were also

different from a prospective study by Kouwen et al (van Kouwen et al., 2005), which used PET instead of PET/CT and included patients who were suspected of having adenoma from barium enema and sigmoidoscopy. For our study, we included patients without known or suspected colon lesions.

Because of a small number of patients who had negative colonoscopy and also performed PET/CT could result in an artificially low NPV as observed in study of Kouwen et al (45%)(van Kouwen et al., 2005). We tried to solve this problem by analyzing per colonic segment instead of per patient. We believe that this gave a better estimate of negative power of FDG-PET/CT. The ideal study should have all patients without known colonic disease undergo FDG-PET/CT, followed by colonoscopy. However, this is very difficult to perform. Hence, we believe that this study design provides a more complete picture of FDG-PET/CT performance in detecting incidental colonic pre-cancerous and cancerous lesions than earlier literatures. The diagnostic value from our study can also provide better perspective of FDG-PET/CT utility and can serve as a reference value for colon cancer screening indication.

Limitations of this study are attributed by a retrospective analysis in single institution. In conclusion, we observed a high false negative rate of FDG-PET/CT in detecting colonic precancerous and cancerous lesions and showed that this imaging modality had limited sensitivity in small-sized polyps and not suitable for screening. For incidental FDG-avid colonic lesions, the high likelihood of precancerous and cancerous pathology warrants further colonoscopy for this finding.

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