

Original article

Focal Colonic FDG Activity with PET/CT: Guidelines for Recommendation of Colonoscopy

Tianye Liu, Spencer Behr, Sana Khan, Robert Osterhoff¹, Carina Mari Aparici

Departments of Radiology and Biomedical Imaging and ¹Medicine, University of California, San Francisco, California, USA

Abstract

Focal ¹⁸F-fluorodeoxyglucose (FDG) colonic activity can be incidentally seen in positron emission tomography/computed tomography (PET/CT) scans. Its clinical significance is still unclear. The purpose of this study was to assess the significance of focal FDG activity in PET/CT scans by correlating the imaging findings to colonoscopy results, and come up with some guidelines for recommendation of follow-up colonoscopy. A total of 133 patients who underwent both ¹⁸F-FDG PET/CT for different oncological indications and colonoscopy within 3 months were retrospectively studied. Imaging, colonoscopy and pathology results were analyzed. Of the 133 FDG-PET/CT scans, 109/133 (82%) did not show focal colonic FDG activity, and 24/133 (18%) did. Of the 109/133 PET/CTs without focal colonic FDG activity, 109/109 (100%) did not have evidence of colon cancer after colonoscopy and histology. Of the 24/133 PET/CTs with focal colonic FDG activity, 10/24 (42%) had pathologic confirmation of colon cancer and 14/24 (58%) did not have evidence of colon cancer after colonoscopy and histological analysis. Sensitivity was 10/10 (100%), specificity 109/123 (89%), positive predictive value (PPV) 10/24 (42%) and negative predictive value (NPV) 109/109 (100%). Incidental focal ¹⁸FDG activity in PET/CT imaging shows a high sensitivity, specificity and NPV for malignancy, with a not so high PPV of 42%. Although some people would argue that a 42% chance of malignancy justifies colonoscopy, this maybe is not possible in all cases. However, the high sensitivity of the test does not allow these studies to be overlooked. We provide our recommendations as per when to send patients with focal FDG colonic activity to have further characterization with colonoscopy.

Keywords: Colorectal cancer, fluorodeoxyglucose, positron emission tomography

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in the world. Around 60% of cases are diagnosed in developed countries. Globally more than 1 million people develop colorectal cancer every year.^[1] Symptoms depend on the location of the tumor but the common warning signs include worsening constipation, blood in the stool, decrease in stool caliber, loss of appetite and weight. Risk factors include older age, male gender, obesity and smoking.^[2,3] Colonoscopy, the endoscopic examination of the colon, is regarded as the recommended standard for colorectal cancer screening

because it both provides a visual diagnosis and grants the opportunity for biopsy or removal of suspected colorectal cancer lesions.^[4]

Positron emission tomography (PET) is widely used in oncology.^[5,6] Incidental ¹⁸F-fluorodeoxyglucose (FDG) diffuse and focal colon activity of multiple levels of intensity is incidentally seen in the ¹⁸F-FDG-PET/computed tomography (CT) scans. Although diffuse activities are more confidently considered physiological, little information is available for the clinical significance of the focal activities in the colon. We therefore performed a study to assess the significance of incidental focal FDG activity in ¹⁸F-FDG-PET/CT scans in the diagnoses of colorectal cancer by correlating the imaging findings to colonoscopy and pathology results.

Materials and Methods

This study was approved by the Institutional Review Board and the need for informed consent was waived.

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DOI:

10.4103/1450-1147.150524

Address for correspondence:

Mr. Tianye Liu, Department of Radiology and Biomedical Imaging, University of California, San Francisco, California, USA. E-mail: tianye.Liu@ucsf.edu

We performed a retrospective review of patients with ^{18}F -FDG-PET/CT scan and colonoscopy during the last 7 years (2006–2013). Those who had a colonoscopy within 3 months from their ^{18}F -FDG-PET/CT scan were included in the study.

Imaging technique

The ^{18}F -FDG-PET/CT studies were obtained using a discovery 64 slice PET/CT scanner from general electric (GE) with bismuth germanium oxide crystals. The patients were nil per os for 6 h prior to the test. After assessment of glucose levels, the patients with glucose level <140 mg/dL were intravenously administered with 10 mCi (370 MBq) of ^{18}F -FDG. 60 min later, they were taken to the scanner for imaging. A transmission scan (5 mm contiguous axial cuts) was obtained using an integrated multi-slice helical CT from vertex to mid-thighs. The acquisition was obtained with a one-slice overlap at the borders of the field of view to avoid artifacts, using 120 kV, and a 512×512 matrix size. Immediately after, and without moving the patient, an emission scan was obtained in three-dimensional-mode in 7–8 beds at 3 min/bed over the same anatomical regions. The PET emission scan was corrected using segmented attenuation data of the conventional transmission scan. A Gaussian filtering (6.4 mm) was performed for smoothing of images. The PET images were reconstructed with a standard iterative algorithm (ordered subsets expectation maximization, two iterative steps, 24 subsets) using (General Electric) software.

Imaging criteria

Two American Board of Nuclear Medicine (ABNM) certified physicians reviewed the ^{18}F -FDG-PET/CT scans. A scan was considered positive when “focal” FDG activity was identified in the colon and the activity was above the blood pool. A scan was considered negative when no “focal” FDG activity was identified in the colon, or the focal activity was below the blood pool level. The two ABNM certified physicians reviewing the ^{18}F -FDG-PET/CT scans and achieved a consensus in all cases.

Colonoscopy

In preparation for the colonoscopy, the patients' colons were cleansed. They were asked to drink clear liquid and not eat solid food for 3 days. During the colonoscopy examination, the colonoscope was inserted through the anus and gently advanced to the lowest part of the small intestines while the patient was sedated. Abnormal polypoid and flat lesions detected during colonoscopy were biopsied and sent for final pathological analysis.

Pathology

After histological analysis, a lesion submitted after colonoscopy was considered positive for malignancy in

the following cases: Carcinomas, invasive adenomas, metastatic disease, primary malignancies like melanoma, and myeloproliferative processes infiltrating colonic mucosa. Hyperplastic polyps as well as tubulovillous, villous and tubulovillous polyps were not considered positive findings for malignancy.

Results

The retrospective review provided a total of 133 patients (57 males and 76 females) with a mean age of 58 years old (age range 10–87) who underwent both ^{18}F -FDG-PET/CT and colonoscopy within 3 months of the scan. Of these 133 FDG-PET/CT scans, 109/133 (82%) did not show focal colonic FDG activity, and 24/133 (18%) did.

Of the 109/133 PET/CTs without focal colonic FDG activity, all 109 (100%) did not have evidence of colon cancer after colonoscopy and histologic analysis. Of the 24/133 PET/CTs with focal colonic FDG activity, 10/24 (42%) had pathologic confirmation of colon cancer and 14/24 (58%) did not have evidence of colon cancer after colonoscopy and histological analysis.

The statistical analysis demonstrated a sensitivity of 10/10 (100%), specificity 109/123 (89%), positive predictive value (PPV) 10/24 (42%), negative predictive value (NPV) 109/109 (100%) [Tables 1 and 2].

Discussion

In this retrospective study comparing ^{18}F -FDG-PET/CT scans with colonoscopy/histology findings obtained within 3 months of the imaging study, only 18% (24/133) of the scans showed focal FDG activity in the colon. This finding suggests that the pattern of focal FDG activity in the colon (the one that may raise concern for malignancy) is not seen as frequently as the diffuse pattern (18% vs. 82%).

Of the 109 patients without focal FDG activity in the scans, 0/109 patients ended up having evidence of malignancy in the colonoscopy. These results suggest that ^{18}F -FDG-PET/CT has a very high NPV, in our series of 100%, to rule out colon cancer when no focal FDG colonic activity is seen. Therefore, the probability of

Table 1: Comparison of ^{18}F -FDG PET/CT and colonoscopy/histology results

Within 3 months	FDG-PET/CT		Total
	Focal FDG colon	No focal FDG colon	
Colonoscopy and histology (+)	10 (TP)	0 (FN)	10
Colonoscopy and histology (-)	14 (FP)	109 (TN)	123
Total	24	109	133

TP: True positive; FN: False negative; FP: False positive; TN: True negative; FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography

Table 2: Colonoscopy findings

Pathology findings	Lesions	Lesions larger than 2 cm ³	Pathology criteria for malignancy	Focal FDG activity in colon in recent FDG-PET/CT (<3 months)	SUVmax
Normal colonic mucosa	3	0/3	0/3	0/3	-
Mucosal prolapse	1	0/1	0/1	0/1	-
Cytomegalovirus	1	0/1	0/1	0/1	-
Active colitis with rare histiocyte aggregate	1	0/1	0/1	0/1	-
Hyperplastic polyps	3	0/3	0/3	0/3	-
Tubular adenoma	13	0/13	0/13	0/13	-
Tubulovillous adenoma	2	1/2	0/2	1/2	1.6
Poorly differentiated carcinoma	3	0/3	3/3	3/3	7.6, 9.3, 16.3
Invasive adenocarcinoma	4	2/4	4/4	4/4	9.6, 10.4, 15.3, 18.4
Malignant melanoma	1	0/1	1/1	1/1	3.9
Metastatic ovarian carcinoma	1	0/1	1/1	1/1	3.9
AML	1	0/1	1/1	1/1	18.1
Total	34	3	10	10 malignant 1 benign	

Colonoscopy findings in our cohort of patients in relation to histology and imaging. FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography; AML: Acute myeloid leukemia; SUVmax: Maximum standardized uptake value

having cancer in the colon that would have been picked up with colonoscopy in a patient with no focal FDG activity in the colon is remote.

Due to the retrospective nature of the study, some limitations exist. Selection bias, such as those involving not including patients who were not recommended for colonoscopy by their physicians could potentially be present.

In our study, hyperplastic polyps as well as tubulous, villous and tubulovillous polyps were not considered positive findings for malignancy. However, it is well known that the latter lesions are considered premalignant. Villous adenomas are the most likely type of polyp to become cancerous followed by tubulovillous adenomas. Villous adenomas >2 cm have 53% chance of containing cancer and tubulovillous adenomas >2 cm have 46% chance.^[7] In our study, two tubulovillous adenomas were identified in the final pathology. One measured <2 cm and did not show focal FDG activity. The other one measured >2 cm (3.3 cm × 2.1 cm × 1.5 cm) and showed focal high-grade dysplasia in histology. Interestingly, the patient's FDG-PET/CT showed "focal" FDG activity with an maximum standardized uptake value (SUVmax) of 1.6. Although slightly above blood pool (SUVmax 1.2) the FDG activity was clearly associated with an anatomical abnormality. This finding was considered a false positive (FP) in this paper, however it raises the possibility of FDG-PET/CT being able to identify and/or have a role in the characterization of these premalignant lesions, and consider it advantageous to refer these patients for colonoscopy before possible malignant transformation.

Of the 24 patients with focal FDG activity in the colon, only 42% (10/24) had histological confirmation

of malignancy [Figure 1], providing a PPV of 42%. This PPV doesn't justify the need to recommend colonoscopy to every patient with focal FDG activity in the colon. In ~ 58% of the cases, the study would be negative and resources would have been allocated unnecessarily [Figure 2]. However, considering that the sensitivity was 100% (10/10), this is obviously a pattern not to be dismissed. Therefore, a good compromise about when to recommend colonoscopy after visualization of focal FDG activity on PET/CT is required.

The SUVmax values of the 24 focal FDG colonic regions in this study ranged from 1.6 to 18.4. The SUVmax values of the 10 focal FDG colonic regions confirmed to be malignant ranged from 3.9 to 18.4, and the benign lesions from 1.6 to 13.3. Both, benign and malignant lesions in the colon show a very wide range, and seen in [Figure 3], there is significant overlap between SUVmax of benign and malignant lesions in the colon showing focal FDG activity. Therefore SUVmax cannot be used to allow differentiation between these malignant and benign lesions.

In one case [Figure 4], the FDG-PET/CT demonstrated a very intensely hypermetabolic lesion with SUVmax 15.3 in the rectosigmoid associated with marked wall thickening and luminal narrowing that was very suspicious for malignancy. A colonoscopy was recommended and surprisingly, the results of the colonoscopy were negative. In fairness, the patient was not very well prepared for the colonoscopy. However, the report clearly assessed the rectosigmoid as negative for malignancy. 15 days later the patient presented with a paralytic ileus and required surgery. During surgery, a colon cancer in the rectosigmoid colon (corresponding to the FDG-PET/CT images) was identified as the culprit lesion. The finding identified in the PET/CT was considered a true positive for this study since the histology results from the surgical

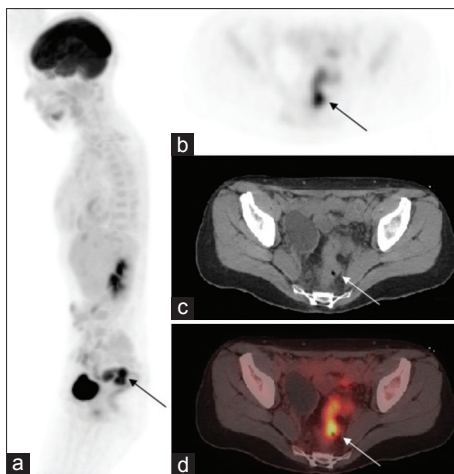


Figure 1: An example of true-positive focal-fluorodeoxyglucose (FDG) colonic activity in a positron emission tomography/computed tomography (PET/CT). (a) FDG-PET/CT maximum intensity projection image showing intensely hypermetabolic wall thickening in the rectosigmoid colon (maximum standardized uptake value 9.6). (b-d) Respectively the (b) FDG images (c) CT images and (d) hybrid images of the malignancy

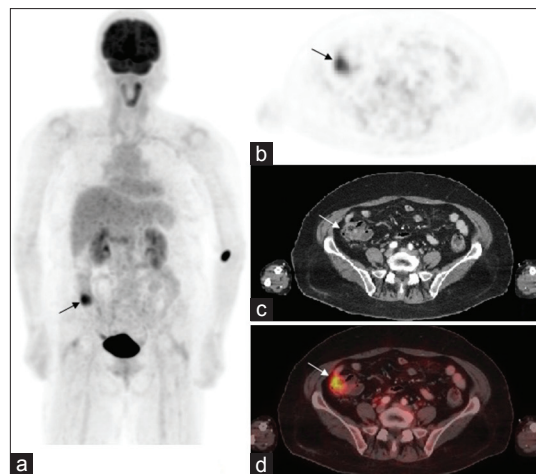


Figure 2: An example of a false-positive focal-fluorodeoxyglucose (FDG) colonic activity in a positron emission tomography/computed tomography (PET/CT) in a patient with history of lymphoma. (a) FDG-PET/CT maximum intensity projection image showing focal FDG activity in the distal cecum (maximum standardized uptake value 7.6). No significant abnormalities were identified in the colonoscopy. (b-d) Respectively the (b) FDG images (c) CT images and (d) hybrid images of this region

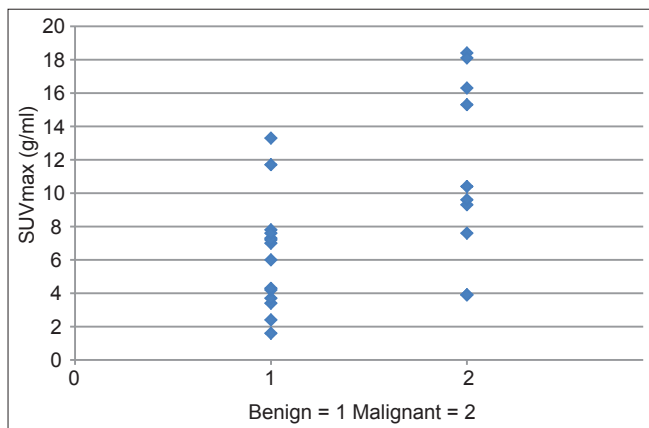


Figure 3: Maximum standardized uptake value comparison between benign and malignant lesions

procedure was obtained within a month from the scan [Table 3]. Colonoscopy, as with all other techniques, can produce false negative results. Therefore, in cases with high suspicion for malignancy in the imaging findings close, even with negative colonoscopy, close attention on follow-up should be recommended.

There is a paucity of studies in the literature assessing the significance of colonic ‘focal’ FDG activity in the PET/CT scans. A retrospective study by Cho *et al.* enrolling 241 patients with FDG-PET/CT performed within 2 weeks of colonoscopy produced similar statistic results. The NPV (95.9%) was very high and similar to that of our study. As with our study, the PPV (51.6%) was the lowest value, though not as low as in our cohort. The low PPVs are consistent with the recognized high frequency of FP results in PET/CT performed for the detection of malignancy in the colon.^[8] Sensitivity and NPV in our study were both

100% and similarly they were high in this study (89.1% and 95.9%, respectively).^[9] A noteworthy difference in the imaging criteria is that our criteria for positive focal FDG was based on the comparison of focal FDG activity with blood pool activity, whereas Cho’s study defined a positive criteria on imaging findings with SUVmax >3.5. As a consequence, our study has more FP cases and lower sensitivity since benign focal areas of FDG activity in colon with SUVmax as low as 1.6 were considered. Of interest, in our study all malignancies showed an SUVmax >3.9. Therefore, a focal SUVmax of 3.5–4 in the colon could be a good SUVmax cut-off for concerning malignancy.

Another retrospective study by Purandare *et al.* enrolling only 32 patients had PPV of 40%, which is very close to our PPV of 42% despite the lower number of patients included in their study.^[10] Another retrospective study by Lee *et al.* with 195 oncology patients assessed concerning focal colonic FDG uptake, but confined only to the left-sided colon, and concluded that ¹⁸F-FDG uptake by oncology patients to the left-sided colon warrant endoscopic verification because a significant portion (145/195) of the patients with focal ¹⁸F-FDG uptake had advanced colonic neoplasm.^[11] Although our study did not show similar findings, it is true that all the confirmed malignancies were identified between the splenic flexure and the anus.

A retrospective study by Rainis *et al.*^[12] with only 56 patients, showed that out of 21 patients with positive focal FDG-PET/CT only 3 showed malignancy while the rest were benign findings. The PPV for malignancy (14%) was lower than that of our study, and the authors conclude that many nonmalignant abnormalities such



Figure 4: Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) demonstrating a intensely hypermetabolic lesion with maximum standardized uptake value 15.3 in the rectosigmoid colon associated with marked wall thickening and luminal narrowing, highly suspicious for malignancy. However, colonoscopy showed negative results. 15 days later the patient presented with a paralytic ileus and required surgery. A colonic mass was identified in the operating room in the location identified by the images. The mass was histologically confirmed to represent rectosigmoid adenocarcinoma. The finding identified in the FDG-PET/CT images was considered a true positive for this study since the histological results from the surgical procedure were obtained within a month from the scan. (a-c) Respectively the (a) FDG images (b) CT images and (c) fused images of the hypermetabolism

Table 3: Imaging findings

SUVmax	Location	CT correlate	Colonoscopy/pathology	Reason test
1.6	Descending colon	2 cm soft tissue mass	Tubulous adenoma	Thyroid cancer
2.4	Cecum	No	Negative	Lymphoma
3.4	Distal sigmoid colon	Diverticulum	Diverticulitis	NSCLC
3.7	Cecum	No	Negative	Lymphoma
3.9	Splenic flexure	1.5 cm×1.2 cm soft tissue density	Metastatic carcinoma	Ovarian cancer
3.9	Anus	No	Malignant melanoma	Melanoma
4.2	Ileum mid quadrant	No	Negative	Lymphoma
4.3	Transverse colon near hepatic flexure	1.5 cm focal concentric wall thickening of transverse colon near hepatic flexure	Negative. 1.3 cm×1.2 cm×0.3 cm colonic mucosa with granulation tissue and scar	Colon and prostate cancer
6.0	Transverse colon	No	Negative	Family history of malignancy
7.0	Descending colon	No	Negative	Lung cancer
7.2	Ascending colon at hepatic flexure	Suggestion of some irregular enhancing soft tissue	Negative	Lymphoma
7.3	Descending colon	No	Negative	Colon cancer
7.6	Rectum	Wall thickening of distal rectum	Poorly differentiated adenocarcinoma	Ano-rectal cancer
7.6	Distal cecum	No	Negative	Lymphoma
7.8	Cecum	No	Negative	Lung cancer
9.3	Rectum	Yes	Poorly differentiated carcinoma	Cirrhosis and blood per rectum
9.6	Recto-sigmoid	Marked wall thickening	Invasive adenocarcinoma	Colon cancer
10.4	Descending colon	Concentric relatively short segment wall thickening of descending colon	Invasive adenocarcinoma	Lymphoma
11.7	Sigmoid colon	No	Negative	Breast cancer
13.3	Descending colon	No	Negative	Colon cancer
15.3	Sigmoid colon	Luminal narrowing of proximal sigmoid secondary to encompassing soft tissue mass	Negative colonoscopy but positive laparoscopic anterior resection after colon obstruction 2 weeks later	Breast and prostate cancer
16.3	Anterior rectum	4.5 cm×3.4 cm	Poorly differentiated carcinoma	Colon cancer
18.1	Rectosigmoid colon	Soft tissue implant	AML infiltrating colonic mucosa	AML
18.4	Sigmoid colon	Apparent enhancement of the sigmoid colon	Invasive adenocarcinoma	Lymphoma

SUVmax ranged from 1.6 to 18.4

The imaging findings in our cohort of patients. The 24 patients with focal colonic ¹⁸F-FDG are presented in ascending order based on SUV. This is related to colonoscopy/histological findings, anatomical findings and reason for the test. CT: Computed tomography; NSCLC: Nonsmall cell lung cancer; AML: Acute myeloid leukemia; SUVmax: Maximum standardized uptake value; FDG: Fluorodeoxyglucose

as polyps and adenomas were found by FDG-PET/CT.^[12] This is not consistent with our findings. Out of 18 polyps identified on colonoscopy in our series (3 hyperplastic, 13 tubular adenomas and 2 tubulovillous adenomas) only one, a 3.3 × 2.1 × 1.5 cm tubulovillous adenoma with focal high-grade dysplasia, showed very mild associated FDG activity.

Both the study by Purandare *et al.* and another similar retrospective study by Putora *et al.* concluded that malignancy could not be ruled out based on SUVmax alone because the differences of SUVmax between the premalignant adenomatous polyps and the malignant lesions was not significant.^[10,13] This is consistent with our observation of the SUVmax in our study. A comparison

between benign and malignant SUVmax values by Roh *et al.* also concluded that SUVmax should not be used as an independent indicator for diagnosing benign and malignant lesions for the same reason. However, the study did note that malignant lesions tend to have higher SUVs and proposed a cut-off value of 4.95 for cases that may be presumed as higher possibility of being malignant.^[14] As discussed above, in our series, 2 confirmed malignancies showed an SUVmax as low as 3.9. Therefore, a more conservative cut-off is required.

Conclusion

Incidental focal colonic FDG activity in ¹⁸F-FDG-PET/CT scans is not a frequent finding, in our series occurring in only 18% of the scans. This pattern of focal colonic FDG activity show a high sensitivity, specificity and NPV for colonic malignancy, but a relatively lower PPV of 42%. Therefore, although a PPV of 42% may be considered justifiable for colonoscopy, it is not recommended to confirm every focus of FDG activity in the colon with a colonoscopy. However, due to its considerably high sensitivity of 100%, it is certainly a pattern not to be dismissed. SUVmax by itself is not a good independent indicator. Therefore, a good compromise to recommend colonoscopy after visualization of focal FDG activity on - PET/CT is required. Our recommendations are: Patients with “focal” FDG activity in the colon and one of the following is recommended to undergo colonoscopy for further assessment: High risk of colon cancer, prior history of colon cancer, concerning associated anatomical changes, focal FDG activity at site of prior anastomosis for cancer (with or without concerning associated anatomical changes), and focal FDG activity in the “same location” seen in a prior FDG-PET/CT scan. Otherwise, incidental focal FDG activity in the colon could be considered an incidental finding and attention on follow-up PET/CT recommended to confirm resolution.

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How to cite this article: Liu T, Behr S, Khan S, Osterhoff R, Aparici CM. Focal Colonic FDG Activity with PET/CT: Guidelines for Recommendation of Colonoscopy. *World J Nucl Med* 2015;14:25-30.

Source of Support: Nil, **Conflict of Interest:** None declared.