

Classification of Physiological ^{18}F -fluorodeoxyglucose Uptake in the Large Intestine: a Preliminary Study

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Varying degrees of physiological uptake of ^{18}F -fluorodeoxyglucose (FDG) are often noted in the large intestine and can be problematic when interpreting positron emission tomography (PET) images. In relation to colorectal tumor detection with FDG PET, we tentatively classified physiological FDG uptake in the large intestine according to its patterns and intensity. Subjects were 144 asymptomatic individuals (109 men, 35 women; mean age 57.5 ± 10.1 years) in our cancer screening program who underwent total colonoscopy within 24 days of FDG PET study and showed no evidence of colonic lesions on colonoscopy. Distinct FDG uptake on FDG PET images was classified into four types: focal, defined as distinctly nodular and visible on at least 4 axial; localized, 2 to 8 cm with $\text{SUV}_{\text{mean}} \geq 4$; diffuse, > 8 cm with $\text{SUV}_{\text{mean}} \geq 4$; and mixed, of more than one type. $\text{SUV}_{\text{means}}$ were examined by placing multiple circular regions of interest of 1 cm in diameter on the axial images. We found 21 distinct FDG uptakes matching our criteria in 20 of 144 subjects (13.9%): focal ($n = 4$), localized ($n = 1$), diffuse ($n = 14$), and mixed ($n = 1$; focal and diffuse). With regard to colorectal tumor detection, 6 subjects (4.2%) with focal or localized type of uptake were considered at risk of false-positive tumor identification, and 15 subjects (10.4%) with diffuse type of uptake were considered at risk of their tumors being missed at the site of FDG uptake. To confirm the feasibility of our criteria, this classification should be tested with a larger number of subjects.

Key words: Positron emission tomography (PET), ^{18}F -fluorodeoxyglucose (FDG), Large intestine, Physiological FDG uptake, Colorectal cancer screening

INTRODUCTION

Colorectal tumors can be detected incidentally on ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) [1-6]. However, varying degrees of physiological FDG uptake is noted in the large intestine [7-9], which occasionally makes it difficult to differentiate between colorectal lesions and physiological uptake when interpreting FDG PET images. Clarifying the pattern and frequency of physiological uptake may help to differentiate the two situations. To evaluate physiological FDG uptake, here we reviewed PET images of subjects confirmed by colonoscopy to have no lesions in the large intestine.

SUBJECTS AND METHODS

Between November 2010 and January 2012, 152 asymptomatic individuals underwent both PET/computed tomography (CT) and total colonoscopy under our cancer screening program. All examinees underwent colonoscopy within 1 to 24 days (5.5 ± 3.5 days) after PET/CT, regardless of the PET/CT findings. Colonoscopy revealed 9 lesions in 8 examinees. The remaining 144 examinees with no colorectal lesion (109 men, 35 women; mean age, 57.5 ± 10.1 years) were the subjects of this study.

PET/CT was performed 60 min after injection of

145-260 MBq FDG (Discovery ST, GE Healthcare). Axial PET images were reconstructed with a 3.75-mm distance between each slice. The PET/CT images were retrospectively reviewed by one of our physicians experienced in PET oncology. The rotating maximal intensity projection images were used to screen for increased FDG uptake in the abdomen. If increased FDG uptake was noted and it was higher than the uptake of the liver, the reviewer proceeded to examine the axial and coronal images. Distinct FDG uptake was then classified into four types depending on the size and intensity of FDG uptake: focal, defined as distinctly nodular and visible on at least 4 axial slices; localized, 2 to 8 cm with a $\text{SUV}_{\text{mean}} \geq 4$; diffuse, more than 8 cm with a $\text{SUV}_{\text{mean}} \geq 4$; and mixed, of more than one type. $\text{SUV}_{\text{means}}$ were examined by placing multiple circular regions of interest of 1 cm in diameter on the axial images, and areas of SUV_{mean} no less than 4 were sought.

All subjects provided written informed consent for the PET/CT study and for use of their personal data for research purposes.

RESULTS

Twenty-one distinct FDG uptakes matching our criteria were recognized in 20 of the 144 subjects (13.9%): focal ($n = 4$), localized ($n = 1$), diffuse ($n = 14$), and

mixed ($n = 1$; focal and diffuse). These 20 subjects consisted of 13 men and 7 women (mean age, 55.9 ± 9.5 years) and the remaining 124 subjects consisted of 96 men and 28 women (57.8 ± 10.3 years). No significant difference was observed in sex or age between the two groups. Representative cases with distinct FDG uptake are shown in Fig. 1 to 4.

With regard to colorectal tumor detection, 6 subjects (4.2%) with focal or localized type of uptake were considered at risk of false-positive tumor identification. Fifteen subjects (10.4%) with diffuse type uptake were considered at risk of their tumors being missed at the site of FDG uptake.

DISCUSSION

Physiological FDG uptake is observed in various organs on FDG PET images. Usually, high FDG uptake is observed in the brain, since the brain depends on glucose as its main source of energy and is the main consumer of glucose [10]. Varying degrees of FDG uptake are observed in the myocardium. The energy metabolism of the myocardium has been investigated and it is proven that β -oxidation of fatty acids and glycolysis is the major pathways of myocardial energy metabolism [11].

FDG uptake also varies in the large intestine, but the energy metabolism in the colonic wall is not fully understood as yet. The intestinal wall consists of mucosal and smooth muscle layers. In these layers in the small intestine of cats, glucose uptake from arterial plasma is approximately the same [12]. Intestinal mucosa receives energy sources from not only the vascular supply but also the luminal supply, and luminal short chain fatty acids are important energy substrates of colonocytes [13]. In the large intestine of mice, a mechanism acts to absorb luminal glucose as an energy source [14]. However, this mechanism does not seem to apply to physiological FDG uptake in the large intestine because intravenously administered ^{14}C -deoxyglucose was found insignificantly in the lumen of the small intestine in cats [12].

There are intriguing reports that metformin, a first-choice oral antihyperglycemic drug for type 2 diabetes mellitus, significantly increased FDG uptake in the colon [15] and that this increased uptake disappeared after cessation [16]. An experiment using rats showed that metformin promoted glucose utilization in the intestinal mucosa [17]. To date, however, the mechanism of glucose metabolism in the large intestine has not been fully elucidated, and the reason for variation in the physiological FDG uptake of the large intestine is unclear. Because PET provides information on the in vivo glucose metabolism in the large intestine, it seems meaningful to classify and document the physiological FDG uptake seen.

Previous reports have used visual evaluation of uptake in the colon compared with that in the liver [7–9, 15, 16] and SUVmax [8, 9, 15, 16]. In this study, physiological uptake was classified into 4 types, namely focal, localized, diffuse, and mixed. Because most small colorectal tumors are polypoid in form and PET is insensitive in detecting small colorectal tumors < 1 cm, focal type uptake is defined as distinctly nodular in appearance and visible on at least 4 axial slices (3.75-mm

distance between each slice). Localized and diffuse types of uptake were tentatively defined as $\text{SUV}_{\text{mean}} \geq 4$ based on previous findings that the SUV_{max} in most colonic neoplasms is ≥ 5 [3], and based on our observation that the SUV_{mean} of the liver is 2.36 ± 0.27 ($n = 30$). Further studies should seek to determine the most appropriate SUV cut-off values.

Until now, standard criteria have not been proposed for physiological uptake in the large intestine. One of the benefits of determining such criteria would be to reduce uncertainty in FDG PET image interpretation. The ideal criteria should attain low false-positive and low false-negative rates in colorectal tumor detection. With the aim of detecting colorectal tumors, Teglia *et al.* [5] retrospectively reviewed focal, well circumscribed colorectal FDG uptakes, which were more intense than adjacent bowel uptake of FDG and equal to or more intense than the liver uptake of FDG. They found focal uptake of FDG in 1.1% of PET/CT cases, and the false-positive rate was 23%. Using our criteria, the false-positive (focal and localized) rate was as low as 4.2%.

In the 15 cases of diffuse uptake in this study, we examined whether or not there were common sites for physiological uptake. Four cases (26.7%) were in the right colon and 11 (73.3%) were in the left colon or rectum. In the right colon, physiological uptake was seen only in the ascending colon. In the left colon or rectum, at least one segment of the sigmoid colon or rectum was included. In other words, diffuse uptake was seen only in the ascending colon (26.7%) or in at least one segment of sigmoid colon or rectum (73.3%).

Carcinomas and adenomas can be detected by incidental colonic activity [1–5, 18]. Originally, our study was begun to determine the feasibility of PET/CT for cancer screening, including colorectal cancer [19]. With our criteria, the false-positive rate of 4.2% is low compared with that of the fecal occult blood test for colorectal cancer screening. In colorectal cancer screening using guaiac-based fecal occult blood tests, positivity was 2.0%, and advanced colorectal neoplasia (cancers and adenoma classified as high or intermediate risk) was detected in 43% of men and 29% of women among the examinees with positive results [20]; thus, the false-positive rate was as high as 57–71%. With our criteria, diffuse uptake was observed in 10.4% of subjects. In such cases, colorectal tumors may be missed at the site of high background activity, resulting in incomplete studies with respect to colorectal cancer screening.

With regard to the sensitivity of PET for detecting colorectal lesions in our asymptomatic subjects, 7 lesions were not recognizable on PET projection images (3 cases of mild colitis or proctitis and 4 colonic polyps of 10 to 14 mm), while 9 lesions were found in 8 of the 152 individuals screened by colonoscopy. A sigmoid colon polyp of 13 mm (SUV_{mean} 4.5) and ulcerative colitis localized in the caecum (SUV_{mean} 6.2) were recognizable on PET images. As a result, the sensitivity of PET for detecting colorectal lesions was as low as 22% (2 of the 9 lesions). The false-negative lesions, however, were either mild inflammation or small polyps. We can assume that PET sensitivity increases in lesions with more severe inflammation or larger size.

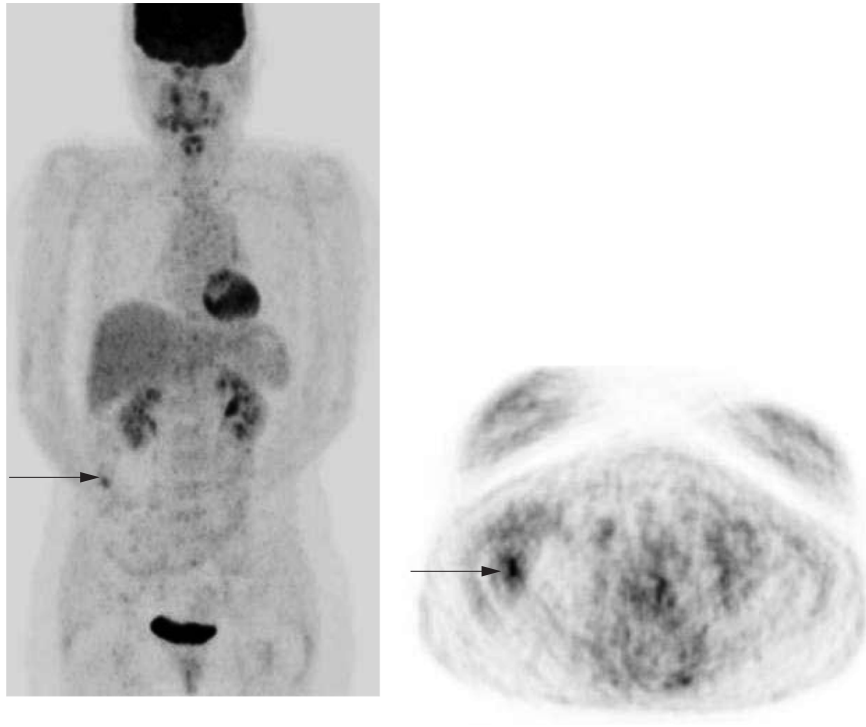


Fig. 1 Focal type, defined as distinctly nodular and visible on at least 4 axial slices (arrows).

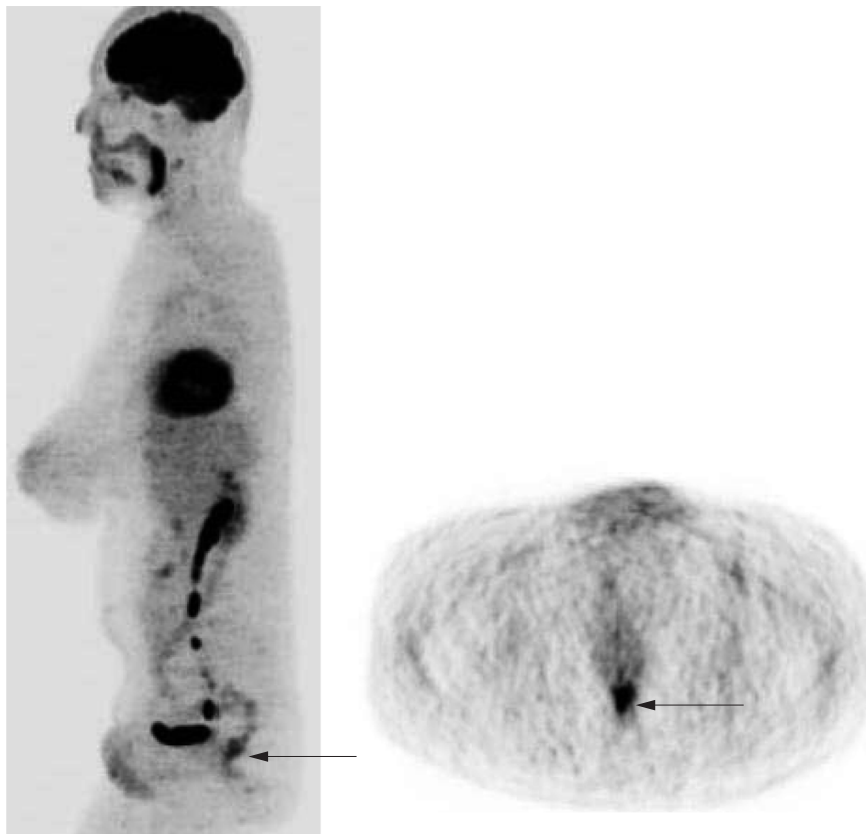


Fig. 2 Localized type, defined as 2 to 8 cm with a SUVmean ≥ 4 (arrows).

We recognize obvious limitations to PET/CT screening of colorectal tumors. Most colorectal carcinomas can be visualized with FDG PET, but PET is insensitive in detecting small colorectal tumors < 1 cm and mucinous adenocarcinomas.

Furthermore, focal and localized physiological uptake results in false-positives, and diffuse uptake with a high background activity gives rise to sites of incomplete study.

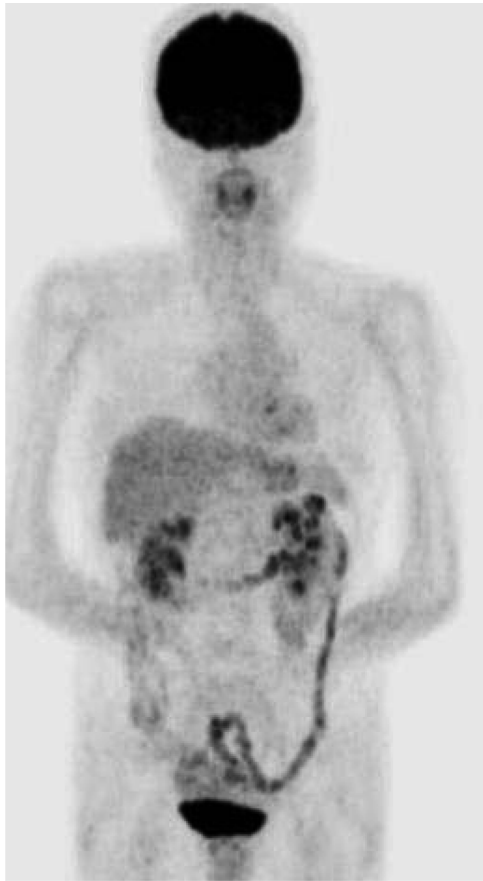


Fig. 3 Diffuse type, defined as more than 8 cm with a SUVmean \geq 4.

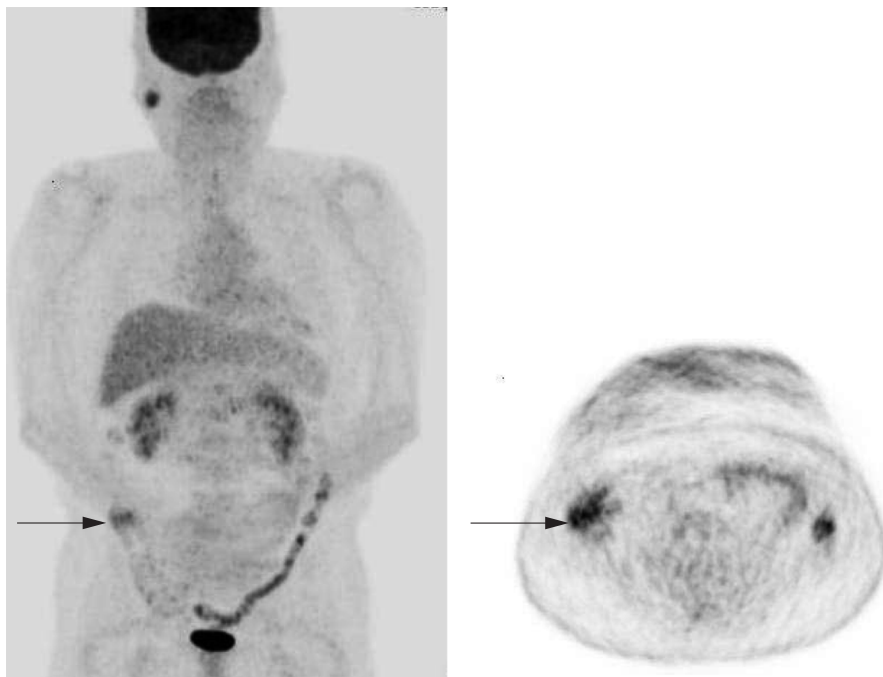


Fig. 4 Mixed type, defined as having both focal (arrow) and diffuse types.

CONCLUSION

We proposed a classification of physiological FDG uptake in the large intestine with respect to colorectal

tumor detection. With our criteria, physiological uptake was observed at an overall rate of 13.9%. The false-positive rate was 4.2%, and in 10.4% of cases with diffuse type uptake, subjects were considered at risk of

their tumors being missed at the site of FDG uptake. To confirm the validity of our classification system, it should be tested in a larger sample.

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