Differentiation of Incidental Intestinal Activities at PET/CT Examinations with a New Sign: Peristaltic Segment Sign

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Purpose

With the present study, we aimed to put forward gastrointestinal system-originated physiological uptakes, which are frequently encountered on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) examinations and are likely to cause mistakes during evaluations, via certain signs other than the maximum standardized uptake value (SUVmax) measurement, which has low sensitivity for the discrimination of malignant versus benign for infection-inflammation-neoplasia.

Increased 18F-FDG uptake, however, besides being present in malignant lesions, is present in benign, inflammatory, or granulomatous processes and in sites of normal, physiologic tracer biodistribution (1-8). These physiologic or benign sites of 18F-FDG uptake may be falsely attributed to a cancerous etiology, and increased tracer activity in malignant lesions may be erroneously interpreted as unrelated to cancer (7,8). 18F-FDG is excreted in part through the gastrointestinal tract (GIT), with uptake in the distal esophagus, stomach, small intestine, and large intestine representing normal patterns of tracer distribution (7,8). Diffuse increased 18F-FDG uptake in the GIT can be defined as physiologic and unrelated to the malignant process with relatively high certainty. A focal, well-circumscribed intraabdominal area of increased 18F-FDG uptake may, however, be interpreted as equivocal or suggestive of malignancy with an unclear location (7,8).

This study was initiated by a series of cases in which focal intraabdominal 18F-FDG uptake that had been localized by PET/CT to the GIT, which had no previously known morphologic lesions, was proven on follow-up to be of malignant or premalignant etiology. The purpose of the present study was to evaluate the frequency of incidental focal sites of increased 18F-FDG uptake in the GIT.

It is difficult to interpret PET images in the absence of correlative anatomical images. FDG uptake may occur in some anatomic localization even without malignancy (1-3). Such uptakes are named as physiological uptakes. FDG uptake traces can be localized by the anatomical information obtained from correlative CT sections. Such discriminations can be made more definitely by multimodality advanced evaluations or biopsies, particularly in the oncologic cases. However, FDG uptake is not only associated with neoplastic diseases, it also represents the fields with increased glucose uptake whatever the reason is. Although PET images alone have low sensitivity, the anatomical configurations on which the functional foci are superposed can be identified with PET/CT. Physiological uptakes in the brain, myocardium, muscular tissues, pharyngeal mucosal surfaces and palatine tonsils can be recognized due to their various characteristics defined in the literature (1, 2). However, activity uptakes in the intestinal traces are more heterogeneous and require more information for discrimination.

Previous large-scale studies showed no significant difference between FDG uptake rates in terms of SUVmax values of underlying malignant, premalignant and benign...
lesions in the focal uptakes occurred in unexpected localizations in GIS (4). Intense focal uptakes in the intestinal traces are seen by 1.3-3% among the cases that undergo PET/CT (4-6). These uptakes may be physiological or may occur due to the inflammatory, benign, premalignant or malignant lesions as well. Physiological uptakes are those occur due to peristaltism and originate from the wall composed of smooth muscle, whereas non-peristaltic uptakes may originate particularly from the reactive uptake in the mural lymphatic tissue that spread over the ceacum and ileum traces (4, 6-8).

This analysis included PET studies showing a single site of focally increased abdominal 18F-FDG uptake that was more intense than liver uptake and was localized by fused PET/CT to the GIT. The patients had no previous malignant involvement and no clinical or imaging suspicion of abnormalities in the same areas. Different from the previous studies (9, 10), in the present study, we additionally aimed to investigate the efficacy of a special sign so-called "intestinal peristaltism sign" in discriminating physiological uptake from malignancy in the focal intestinal uptakes on PET/CT imaging.
Methods and Materials

The gastrointestinal system traces of 823 patients (577 males and 246 females), who had undergone FDG-PET/CT examination because of malignancy in a special health center, were reviewed. The mean age of the cases was 49 years (ranged from 11 to 89 years). Distribution of the tumor types among cases was as follows; 396 pulmonary tumor, 135 lymphoma (Hodgkin disease, NHL), 84 colorectal carcinoma, 37 laryngeal tumor, 27 nasopharyngeal tumor, 23 cervical tumor, 13 ovarian tumor, 9 esophageal tumor, 8 melanoma, 6 soft tissue sarcoma, 5 urine bladder tumor, 4 endometrial tumor, 4 non-pulmonary carcinoid tumor, 4 breast tumor, 2 small intestine tumor, and 66 cases reported to have malignant level FDG uptake. On the images of these cases, the foci that FDG uptake has been identified and the reported intestinal foci were retrospectively evaluated. Reviews were performed retrospectively, being aware of the diagnoses of the cases, on multi-display workstations with multi-planar reformatting focusing on the gastrointestinal system that display abnormal uptake on minimum intensity projection. After reviewing the images and reports of all patients, the cases with localized activation in the stomach, duodenum, jejunum, ileum and colon traces were recorded to be included in the study.

Focal activities shorter than a segment (any of cardia, fundus, corpus, antrum and duodenum) in the stomach and duodenum, non-longitudinal, non-linear focal uptakes in the jejunum and ileum, and focal uptakes limited to maximum one of the ceacum, ascendant colon, hepatic flexure, transverse colon, splenic flexure, descendent colon, sigmoid colon, and rectum segments in the colon were considered available for the localized activity and included in the study. Long segmental uptakes, point or linear uptakes, and the activities that did not show superposition with the intestinal wall on CT fusion images were not included in the study. The field with increased FDG activity was taken into consideration if it was in a more intense nature than the liver and if the SUVmax value was higher than 2.5 units.

The "peristaltism sign" was considered positive in the presence of a sign that was determined to occur during the procedure in the segment or in the proximal or distal part of the segment that show activity, which has been expanded with air and had gradually changing calibration (Figure 1). Absence of a collapsed segment between this special peristaltic segment and the focus with activity was required, and it was targeted that the sign should comprise peristaltism that was associated with the lesion.

Standard protocol that was applied to all cases investigated for malignancy:

- Oral contrast (1000 ml diluted oral contrast 12 hours before the procedure and 500 ml one hour before the procedure)
- Intravenous 13-15 mCi 18-FDG 40-60 minutes before the procedure
- Resting under normal conditions one hour before the examination (rest rooms)
• CT: cranio-caudal, with a section thickness of 3.75 cm, 1.75 pitch, 10 mm collimation, 120 peak kV, and 100-120 mA.
• PET: caudo-cranial 2D

System:

• PET device fused with 16-detector CT (Discovery ST PET/16 slice CT fusion system HPOWER 60; General Electric Medical Systems, Milwaukee, WI)
• A section thickness of 3.75 mm, 2D-PET
• Multi-display workstations: MPR, MIP, PET/CT fused images could be simultaneously evaluated.

Presence or absence of the sign was investigated within the uptake trace in the gastrointestinal systems of 59 cases. Localized intestinal foci showing an uptake more intense than the liver and with a SUVmax #2.5 were included in the study. Endoscopic evaluation (n=47) and endoscopic biopsy (42 of 47 cases) data of the cases with gastric-duodenal-colon uptakes (n=47), exploratory laparotomy data of a case diagnosed with small intestine lymphoma, transabdominal biopsy data of a similar case, and enteroclysis data of a case with Chron's disease-associated small intestine uptake were available.

In the cases with intestinal loop showing peristaltism sign on CT sections; presence of malignancy on the localization with determined activity, despite the presence of FDG uptake morphology consistent with the sign, was considered false positive; whereas, presence of underlying malignancy, despite the presence of peristaltism sign on the localization with FDG uptake, was considered false negative; if FDG uptake and typical peristaltism sign and benignity are together, it was considered true positive; and the cases with FDG uptake and malignancy but without sign were considered true negative. Related data were used to identify the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy value for this special sign.

Figure 1. a) Partial expansion by gas in the proximal and distal aspects of the collapsed sigmoidal segment (arrows) b) Uptake is seen in this segment on PET/CT fusion section (positive peristaltism sign), physiological uptake c) Sigmoid colon is seen collapsed without being expanded by gas (arrows) d) Focal uptake at rectosigmoid junction, occurred without the presence of remarkable peristaltism sign (rectal adenocarcinoma).
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Results

In the present study, non-diffuse FDG uptake was detected on the localizations consistent with loop traces in 59 of 823 cases. Such uptakes have been reported under the name of "variative, inflammatory, reactive, physiological, incidental, or artefactual" in 43 cases and further evaluation via oral, rectal, or oral+rectal CT has been recommended on the PET/CT reports. PET/CT reports of the remaining 16 cases were in favor of malignancy and further evaluation has been recommended by biopsy. In this group with a SUVmax value higher than 2.5 (n=16), the diagnosis of mass has been reported in the first plan if accompanied by wall thickening; whereas, further evaluation has been recommended in the cases that pathological wall thickening have not accompanied focal FDG uptake on CT sections (n=43).

In this system, in which the uptake is evaluated according to the FDG uptake and wall thickening when the focal intestinal involvement has been accompanied by wall thickening, the sensitivity was found 33%, specificity was found 65%, PPV was found 69%, NPV was found 46%, and accuracy was found 47% (Table 1).

In the present study, gastrointestinal uptake was determined in 59 (7.2%) of 823 reviewed cases. Stomach (n=19, 2.3%), small intestine (n=12, 1.5%), and colon (n=28, 3.4%) represented the focal uptake-related segments in varying rates (Table 2). In fact, malignancy was detected in only 16 cases, whereas the activity in the remaining 43 cases was recorded as benign (Table 2).

When the data in the table (Table 3) formed by testing according to the presence or absence of the special peristaltism sign was used; the sensitivity, specificity, PPV, NPV, and accuracy of the sign in discriminating malignant from benign intestinal uptake by itself were found (68%), (80%), (82%), (65%), and (73%) respectively.
Fig. 0: Figure 1. a) Partial expansion by gas in the proximal and distal aspects of the collapsed sigmoidal segment (arrows) b) Uptake is seen in this segment on PET/CT fusion section (positive peristaltism sign), physiological uptake c) Sigmoid colon is seen collapsed without being expanded by gas (arrows) d) Focal uptake at rectosigmoid junction, occurred without the presence of remarkable peristaltism sign (rectal adenocarcinoma).

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**Fig. 0:** Table 1. Data obtained from the evaluation by conventional method

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**Fig. 0:** Table 2. Distribution of the findings in the gastrointestinal system according to the criteria defined in the methodology

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Fig. 0: Table 3. Number of cases having the special sign (peristaltism sign), which has been used in the discrimination of malignant vs. benign uptakes

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Conclusion

In many studies, it has been reported that PET/CT imaging provides useful data in detecting malign diseases and in the discrimination of malignant vs. benign lesions (7, 9). It is known that uptakes with high SUVmax values and morphology that sometimes mimic malignancies are likely to occur in various localizations in the body (2-6). Gastrointestinal system is one of the localizations in which local incidental uptakes are frequently detected (4, 6, 10). There are many literatures about the physiological incidental focal uptake patterns in the stomach, duodenum, jejenum, ileum and colon (9, 11). Although, it has been reported that the majority of underlying causes of focal gastric and small intestinal uptakes are associated with benign physiological activities, further evaluation is required in colonic focal uptakes (4-6, 11). Because, colonoscopies of the cases with incidental, focal colonic FDG activity revealed organic pathologies (mucosal abnormalities, adenoma, or carcinoma) in various rates ranging from 71% to 95% (4-6).

In the present study, an underlying malignant-premalignant lesion was detected in colonic focal uptakes. An interesting finding of the present study is the fact that the lesion was in the colon in eight of 11 false negative cases, that is to say, likelihood of underlying neoplasia was 73% for colon, despite the presence of the sign. However, the likelihood of detecting an underlying organic neoplasia despite the presence of sign was only 37% for the stomach-duodenum-jejenum-ileum all together. Increment in localized peristaltism due to partial obstruction caused by the lesion may be responsible for the focal uptake in the colon and concurrent peristaltism sign. Moreover, as was understood with the present study, detecting focal uptake in the colon should be considered significant and requires further evaluation even the peristaltism sign is positive (5).

In a study evaluating overall incidental focal uptakes of the gastrointestinal system, probability of an organic pathology, which changed the future diagnostic and therapeutic step, has been mentioned in 28% of the cases with intestinal focal uptake detected on PET/CT (5). The rate was a bit higher (a malignancy rate of 57%) in the cases of the present study. We attributed this high rate to the fact that small point and linear uptakes, or inversely, manifest focal-massive uptakes, not the longitudinal segmental uptakes, have been included in the study.

There is information about the efficacy of SUVmax measurements in the differentiation of etiological factors of focal uptake (4, 12), whereas there are also studies emphasizing that discrimination of malignant vs. benign lesions could not be made properly by measuring uptake value alone and that further evaluation is required (13, 14). Moreover, a review, which displayed that there was no statistically significant difference between physiological uptake and incidental uptake occurred due to premalignant-malignant lesions in terms of SUVmax values of incidental uptake in the intestinal trace, has shown that SUVmax has no efficacy in discriminating malignity in a focal incidental uptake (4). The number of the cases with benign lesions that have substantially high SUVmax is not low at all.
Nonetheless, since malignancy detection in the lesions with low SUVmax has not been reported for intestinal system, we considered a SUVmax value of 2.5 as cut-off value for a more specific patient group. On the other hand, many studies emphasized that long segmental uptakes are caused by benign entities (physiological or inflammatory or post RT colitis) (9, 10). Therefore, as was in the present study, future studies have targeted to discriminate malignity via new parameters taking the cases with focal uptakes into consideration (15).

For example, a study reported that dependent intestinal mucosal-mural FDG uptake occurs frequently due to contact with stool and irritation. The same study emphasized that nondependent incidental focal intestinal uptakes are more meaningful and require further evaluation (16). In the present study, discrimination of dependent vs. nondependent has not been used as a criterion. Because, this method might be unable to discriminate the origin of FDG shining area in the presence of uptake in the collapsed small intestine or in colonic loop trace. In order to eliminate luminal or mural pathology of the colon, methods that discriminate the wall from the lumen are required. For this procedure, lumen and the wall can be clearly exposed with rectal contrast enema that would expanse the entire colon. Otherwise, peristaltic segments or the segments with insufficient filling might not be visualized optimally. Since rectal contrast use is not likely during PET/CT imaging, it can be used just in the suspected cases, if required, as the next evaluation step. In the present study, colon opacification was provided with 1000 ml of 1500 ml oral contrast solution prepared using 40 ml nonionic contrast that was drunk a night before the procedure. Stomach and the small intestine were opacified with the same solution drunk an hour before the procedure. Thus, we have screened the specific peristaltism sign based on the PET images fused with CT sections, in which opacification was tried to be provided in the gastrointestinal system, even though complete expansion could not be provided. In some other studies, it has been defended that focal intestinal uptakes require further evaluation due to the probability of representing underlying premalignant small lesions, even in the absence of remarkable massive formation that attract attention on CT sections (5, 17-25). On the other hand, literature information revealed that physiological uptakes might vary within a wide spectrum including focal, multifocal and diffuse uptakes (17-25). Moreover, mostly unifocal uptakes are seen in Barret's esophagus and tubulovillous adenomas, whereas multifocal, segmental or diffuse intestinal uptake is seen in the inflammatory bowel diseases (17-25). With the inspiration of the previous studies that has been indicated need for further assessment and PET/CT-guided tissue sampling in patients with unexpected single areas of focal abnormal 18F-FDG uptake in the GIT. Because most of these incidental foci may represent unexpected GIT-related abnormalities, such as second primary tumors, sites of unusual metastatic spread, or premalignant lesions (9, 10). In the present study, particularly the cases with focal FDG uptake reported in only a single segment were retrospectively included, and SUVmax was considered #2 within a wide spectrum, although it was nonspecific even for large-scale participants.

As was mentioned in the other studies, incidental physiological activities are frequently seen throughout the GIT and occasionally a SUVmax value of 10 is encountered as well (21, 24, 26). In some studies, along with the additional late phase imaging protocols, it
has been reported that, for example, gastric focal uptakes could not be differentiated from
the activities in the same lodge such as pancreatic tile uptake and lymph node uptake
of the splenic medial pole (27).

In the present study, substantially low SUVmax values were included, and since
accompanying peristaltism sign has been investigated as projection, matched sections
were found, superposed, and accordingly, the discrimination of intestinal vs. non-
intestinal could have been made definitely. Since the superposition of the images has
been considered necessary, it can be thought that searching for peristaltism sign, even
though required for the protocol, contributes to the uptake to be localized more clearly
and thus, to the solution of the problem (28, 29). Owing to the fact that there may be
artefactual uptakes throughout the entire GIT, lowering the number of swallowing and
providing colon cleaning with iso-osmotic solution may reduce the frequency of abnormal
activity (30).

Again, focal segmental diffuse uptakes related to quite common non-malignant activities
can be encountered together with the common inflammatory and infectious pathologies
accompany the physiological activities throughout the entire GIT (21, 24, 26). Besides,
many studies have evaluated the incidental uptakes that occurred in the whole abdomen
in general, under the title of abdominal, or throughout the intestinal traces under title
of colorectal, and thereafter elicited the clinical importance of the existent state and the
rates of benign and malignant conditions comparing with the histopathological evaluation
findings (31-34).

In the present study, beyond revealing a rate only comparing with the histopathological
data, we tried to discriminate malign focal FDG uptakes from the benign ones, which
were retrospectively investigated throughout the entire intestinal system and were well
localized, via a special sign benefiting from the multidetector characteristic of the fused
CT system. As was in the literature, in the present study as well, an underlying malignancy
has been detected by such a high rate as 27% at these incidental intestinal uptake
foci. The method that we found discriminated the malignancies more sensitively than
the conventional method (33% vs. 68%) for these uptakes, which were detected while
investigating another primary or suspected malignancy and which might lead to both time,
cost and morale loss.

It is known that intestinal uptakes exist in a wide spectrum including diffuse,
segmental and focal uptake. In general, literature information revealed that endoscopic
correlation is required to eliminate malignancy in case of esophageal uptakes. Because,
histopathological sampling is in question to eliminate premalignant lesion even for the
benign activities, in which uptake occurs at Barret's point (9, 35).

We already have excluded esophagus for the indicator special sign, since an active
peristaltism would not be in question except for nutrition. Many studies emphasized that
PET/CT can be successfully used in detecting gastric malignancies (36-38). To show that
PET/CT is able to detect malignancy was the common characteristic of all these studies.
In the present study, we as well investigated the presence of special peristaltism sign for stomach and duodenum considering the existence of low-grade adenocarcinomas, which are likely to have low SUVmax rates. The present study showed high rates of false negativity (approximately 60%) in the cardia. This was attributed to the point's being the Barret's point, and peristaltism-associated changes' being unable to be visualized on CT sections, despite the presence of premalignant and malignant lesions. Moreover, since neither the cardia nor the distal segment of esophagus could be evaluated in terms of presence or absence of peristaltism because of the same problem, such a high false negativity has been considered as a directive, rather than a handicap, for endoscopy to eliminate the premalignant lesions.

In the small-intestine-related uptakes, the point that the literature has particularly dwelled on is the diagnostic use of activity elevation for the inflammatory bowel diseases and is the pathologies that should be kept in mind in the differential diagnosis of small intestine uptakes (4, 34, 39, 40).

In the present study, the discrimination of malignant vs. benign conditions could be made only via the sign we used in 12 cases that the focal uptakes in the jejunoileal segments have been evaluated, except for a case with FP and another case with FN. Considering the efficacy of the sign used in the present study on the differential diagnosis, further evaluation of a patient that have already exposed to high radiation due to CT and PET by expensive or invasive modalities or by the modalities that include radiation would not be reasonable (41). FDG activity within the colon is typically heterogeneous. There is higher uptake within the cecum and right colon due to the higher concentration of lymphoid tissue in this region (35). Diffuse uptake is usually associated with infectious or inflammatory colitis. Focally increased FDG uptake within the bowel has been described for both malignant and benign processes. PET-CT findings in these cases may be diagnostic, since the CT manifestations of these entities are well described in the literature as appendicitis, diverticulitis or nonspecific uptakes (42, 43). On the other hand, although FDG PET has been shown to be highly sensitive in detecting colorectal cancer, which is one of the most common cancers in the developed countries, it has low specificity because of physiological uptakes as well as inflammatory causes (44, 45). Due to being the focus that intestinal malignancy is frequently seen, the literatures, in which the intestinal FDG uptakes and related mistakes have been widely discussed, concern the colorectal segment (6). Among the present cases, the discrimination of malignant vs. benign could be made in totally 28 focal colonic uptake cases, except for three false positive and six false negative cases, regardless of the frequency of malignant or benign underlying pathologies. Discrimination of malignant vs. benign could be achieved in 19 of 28 cases (seven malignant and twenty-one benign) via the sign without using no other auxiliary method or modality.

In the present study, false positivity rate of the sign we used was more common in the gastrointestinal system, whereas the false negativity rate was higher in the colon, likely due to less peristaltism; we could have not predicted this fact. That is to say, false negativity means sign positive but malignancy positive as well; this might be, in
general, secondary to the increased peristaltism caused by malignancy-related partial obstruction. Moreover, it can be thought that water-soluble iodine-based hyperosmolar contrast agent taken a night before to provide intestinal luminal opacification, which was given according to the protocol of the present study, might have increased the rate of false negativity by inducing increment in peristaltism. Despite such a limitation, the present study have shown once again that such focal uptakes certainly require further evaluation by diagnostic tests in case of absence of a typical underlying pathology (wall thickening, mass, or LAP, etc. in diverticulitis for example), despite presence of increased focal uptake in the colon.

The present study that we performed based on the semi-quantitative values has other limitations as well. First, we determined the SUVmax value arbitrarily. However, it was thought that this value being subjectively more remarkable than the liver and being at least 2.5 units would relatively lower the rate of false positivity ignoring very simple and physiologically mild activities; thus, also the lower rates of false negativity were targeted. The other limitation is the absence of dynamic imaging (early + late phase). The present study was retrospective and the late phase imaging of the patients, except for three, was unavailable. Actually, showing a decrement in focal FDG uptake by late phase imaging may be used as a criterion in the discrimination of malignant vs. benign. Nevertheless, such type of protocols lead to increased degree of exposure in the cases that have already been exposed to both CT- and PET-related high-ionized radiation. A less significant limitation was the uptake images caused by the attenuation difference (pseudouptake) emerged from the iodine content of the oral contrast agents. These artifacts could be easily solved correlating with CT section (46, 47).

Another minor limitation of the present study was inability to statistically evaluate the availability of the sign for each segment due to the limited number of the cases. However, the availability of the sign should be tested in the studies that would be performed on larger series. Herein, the major reasonable limitation was the malignancy’s being likely to show concurrence with peristaltic movements. Nonetheless, since malignancy show transmural expansion and tends to invade neurogenic plexus as well, and thinking that the likelihood of occurrence of peristaltism in this affected segments is low, it can be said that the sign can be used also in such cases (48, 49).

In conclusion; On PET/CT examination, focal FDG uptakes may be in question throughout the entire gastrointestinal system and in the gastric-duodenal-jejunal-ileal trace. In the present study, discrimination of malignancy can be achieved by 33% sensitivity and by 65% specificity when the focal uptake accompanied by pathological wall thickening on CT sections was considered as a criterion; whereas, the sensitivity and specificity have been increased up to 68% and 80% respectively when peristaltism sign was used. In case of detecting focal-segmental FDG uptakes in the gastrointestinal system, even incidental, a with SUVmax exceeding 2.5 but have not been accompanied by peristaltism sign, should certainly be further evaluated by endoscopic tests.


42. Mahfouz T, Miceli MH, Saghaifar F, et al. 18Ffluorodeoxyglucose positron emission tomography contributes to the diagnosis and management of


