Detectability of colorectal neoplasia with fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT)

Short title: Colorectal neoplasia and FDG-PET/CT

Tomoko Hirakawa [a]; Jun Kato [b]; Yoshihiro Okumura [c]; Keisuke Hori [d]; Sakuma Takahashi [a]; Hideyuki Suzuki [a]; Mitsuhiro Akita [a]; Reiji Higashi [a]; Shunsuke Saito [a]; Eisuke Kaji [a]; Toshio Uraoka [e]; Sakiko Hiraoka [a]; Kazuhide Yamamoto [a]

[a] Department of Gastroenterology and Hepatology, [c] Department of Radiology, and [d] Department of Endoscopy , Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

[b] Second Department of Internal Medicine, Wakayama Medical University
811-1 Kimiidera, Wakayama City, Wakayama 641-0012, Japan

[e] Division of Research and Development for Minimally Invasive Treatment, Cancer Center, Keio University School of Medicine
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Address correspondence to Tomoko Hirakawa
Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Tel: +81-86-235-7219 Fax: +81-86-225-5991

E-mail: tomokoh@t.okadai.jp

Abstract

Background

The purpose of this study was to analyze the detectability of colorectal neoplasia with fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT).

Methods

A total of 492 patients who had undergone both PET/CT and colonoscopy were analyzed. After determining findings of PET/CT and colonoscopy independently, the results were compared in each of the six colonic sites of all patients examined. The efficacy of PET/CT was determined using colonoscopic examination as a gold standard.

Results

In all, 270 colorectal lesions 5 mm or more in size, including 70 pathologically confirmed malignant lesions, were found in 172 patients with colonoscopy. The sensitivity and specificity of PET/CT for detecting any of the colorectal lesions were 36% and 98%, respectively. For detecting lesions 11 mm or larger, the sensitivity increased up to 85%, with the specificity remaining consistent (97%). Moreover, the sensitivity for tumors 21 mm or larger was 96% (48/50). Tumors with malignant or high-grade pathology were likely to be positive with PET/CT. Size of 10 mm or smaller (odds ratio, OR; 44.14, 95% confidence interval, CI; 11.44-221.67) and flat morphology (OR; 7.78, 95% CI; 1.79-36.25) were significant factors that were associated with false-negative cases in PET/CT.

Conclusion

Sensitivity of PET/CT for colorectal lesions is acceptable, showing size- and pathology-dependence, suggesting for the most part, that clinically relevant lesions are

detectable with PET/CT. However, it should be cautioned that there are cases with false-negative results, when considering PET/CT for screening purposes.

Keywords: colorectal neoplasia, positron emission tomography, computer tomography, cancer screening, colonoscopy

INTRODUCTION

Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is well accepted in the imaging workup of various malignancies. Accordingly, PET has been shown to detect a wide variety of tumor foci including lymphoma, melanoma, lung cancer and colorectal cancer (CRC). PET is now widely used and has shown high sensitivity in the diagnosis, staging, therapeutic monitoring, and restaging of diverse cancers [1]. Furthermore, combined PET/computed tomography (CT) is superior to PET or CT for localizing metabolically active foci and in readily distinguishing physiological activity from pathological findings [2]. However, PET/CT is occasionally faulted for revealing intense metabolic activity at sites not considered to be related with the malignant process under study, as well as not discovering all clinically relevant neoplastic lesions [3].

As for detecting colorectal neoplasia, colonoscopy has been considered to be the most accurate method. However, colonoscopy is sometimes burdensome for patients because of the requirement of the preparation with laxative use, abdominal fullness due to air insufflation, and possible complication occurring such as perforation. Recently, CT colonography (CTC) has been shown to have sensitivity up to 65% for 5 mm or more lesions, and 90% for 10 mm or more lesions [4]. However, as with colonoscopy CTC also requires a laxative and air insufflation. Although guaiac or immunochemical fecal occult blood tests are commonly used for CRC screening worldwide, the sensitivity of such tests alone are not satisfactory even if performed repeatedly [5-7].

The usefulness of PET or PET/CT, which is non-invasive and requires no particular preparations, for incidental detection of premalignant colonic lesions has been previously reported [8-11]. In addition, several studies have recently reported the detectability of

colorectal neoplasia by PET or PET/CT. However, these studies had problems in evaluating precisely the ability of PET. Principally, a small scale and/or a biased cohort were used [10,12,13], and all patients did not undergo both PET and colonoscopy [11,14-17]. In addition, no large scale studies using PET/CT have been conducted on detecting colorectal lesions according to morphology, pathology, and location. Therefore, the previous studies could not show unambiguous results regarding the usefulness of PET/CT for detecting colorectal lesions. It remains to be determined whether PET/CT can be used as a screening modality for colorectal malignancy and clinically relevant colorectal lesions.

In this study, therefore, we examined the ability of PET/CT to detect colorectal neoplasia in a large cohort using the findings of colonoscopy as a gold standard. All patients of this cohort underwent both PET/CT and colonoscopy within an interval of one year. Using this large cohort, moreover, we determined the sensitivity of PET/CT for colonic neoplasia according to tumor characteristics such as pathology, morphology, and location. In addition, we determined patient and tumor factors contributing to false-negative results with PET/CT, because such cases are problematic in using PET/CT as a screening modality.

PATIENTS AND METHODS

Patients

This was a retrospective study based on chart and image reviews of patients who underwent both PET/CT and colonoscopy within one year. A total of 7,014 patients who were treated at Okayama University Hospital underwent PET/CT at Okayama Diagnostic Imaging Center between April 2006 and January 2010. Of these, 587 patients underwent colonoscopy at Okayama University Hospital in the same year before or after PET/CT. The following patients were excluded from the study: 54 patients who had history of prior colon resection; 32 patients with incomplete colonoscopy; and 9 patients with a serum glucose level of over 150 mg/dl measured at ^{18}F-FDG injection. Thus, 492 patients (306 men; 62%, 186 women; 38%) with a median age of 66 years (range 10-88) were analyzed.

Demographic data, medical history including primary cancer, and indication for PET/CT of the patients were obtained from medical charts. This study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

PET/CT imaging protocol

PET/CT was taken in the recommended standard condition with PET/CT Scanner Biograph LOS/Sensation 16 (Siemens, Munich, Germany) at Okayama Diagnostic Imaging Center. All patients fasted for at least 5 hours before the PET/CT studies. A serum glucose level measured at the time of ^{18}F-FDG injection was confirmed to be less than 150 mg/dl in all patients. ^{18}F-FDG (3.7 MBq/kg body weight) was administered intravenously into the arm and the patient was then seated on a chair to rest for 90 minutes to uptake, while drinking 350 ml of mineral water for hydration. A whole body PET/CT scan from the upper end of the orbit

to the femoral region was performed 90 minutes after the ^{18}F-FDG administration. The patients were in the supine position and their bilateral upper limbs were elevated. The scans consisted of seven to eight bed positions, with 2.4 minutes per position. Urinary tract activities were minimized in most patients by the placement of a Foley catheter before injection of ^{18}F-FDG and by administering furosemide and intravascular fluids after injection of ^{18}F-FDG. PET images were scatter corrected and reconstructed using an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm and with the use of a post-reconstruction Gaussian filter (3 mm full width half maximum). A technical parameter for a 16-detector row helical CT induced a section thickness of 3 mm and was obtained from the base of the skull through the proximal thighs at 140 kV and 12 to 40 milliampere seconds for attenuation collection and diagnosis.

Interpretation

All ^{18}F-FDG PET/CT images were interpreted by two of the authors (T.H. and Y.O.) without the knowledge of the results of colonoscopy. The colon was divided into six segments on PET/CT images: cecum, ascending colon (including hepatic flexure), transverse colon, descending colon (including splenic flexure), sigmoid colon, and rectum. This partition was established to accurately localize the ^{18}F-FDG hotspots, allowing an easier matching with the colonoscopic findings.

Any focal glucose uptake in the colon significantly higher than background was considered abnormal. Physiologic ^{18}F-FDG uptake due to fecal stasis, if present, was distinguished from uptake due to the presence of neoplastic lesions, the former usually being diffuse, and by analyzing the CT images.

Colonoscopy

On the day of the colonoscopy, the patients received a colonic lavage using two liters of a polyethylene glycol-based electrolyte solution for bowel preparation in accordance with the recommended protocol of the manufacturer (Ajinomoto Pharma, Tokyo, Japan). All colonoscopy cases were performed by an experienced endoscopist by using a colonoscope with magnifying function and narrow band imaging (CF-H260AZI, PCF-Q240ZI, EVIS LUCERA, Olympus, Tokyo, Japan). All tumors found at colonoscopy were observed with magnification using dye-spraying and NBI mode. Tumors were then endoscopically diagnosed as malignant lesions (CRC, lymphoma, or metastatic cancer) or nonmalignant polyps (adenoma or hyperplastic) according to the definitions of Kudo et al. and Katagiri et al [18-20]. All tumors which were suspicious of malignancy with magnifying colonoscopy were pathologically examined by using specimens collected with biopsy, polypectomy, or surgical resection. CRC was defined as an invasive cancer with involvement of the submucosal layer of the colorectum, and intramucosal carcinoma was defined as a high-grade adenoma. All polyps that were regarded as non-malignant were not examined pathologically, because a considerable number of patients had more serious disease than colorectal polyps. Endoscopists were blinded to the results of PET/CT if PET/CT was performed prior to colonoscopy.

Colonoscopic findings were determined from colonoscopy reports written by the endoscopists. In addition, all endoscopic images recorded in digital media were reviewed and confirmed by two of the authors (J.K. and S.H.), who were blinded to the results of PET/CT. The location of tumors was determined and recorded by dividing the colon into six segments, as was done with PET/CT. Size of the tumors was determined by measuring extirpated specimens when polypectomy or surgical resection was performed. If tumors were not

resected, the size was estimated with endoscopic images. Macroscopic appearance of colorectal lesions was defined as protruded (pedunculated or sessile) or flat. A flat-type colorectal tumor was endoscopically defined by a height of less than half of its diameter, or histologically defined by thickness of the lesion of less than twice that of the adjacent normal colonic mucosa, with or without depressive areas [21,22].

Comparison of findings between PET/CT and colonoscopy

After determining findings of PET/CT and colonoscopy independently, the results were compared in each of the six colonic sites of all patients examined. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT for colonic lesions were determined relative to colonoscopic findings as a gold standard. Polyps smaller than 5 mm found at colonoscopy were not included in the analysis, because PET/CT was insensitive to lesions smaller than 5 mm in the large intestine. When two or more polyps were found in each colonic site with colonoscopy, polyps of the greatest dimension were compared against their counterparts detected by PET/CT. In analysis by location, the proximal colon was defined as the cecum, ascending colon, and transverse colon, while the distal colon included the descending colon, sigmoid colon and rectum. In case PET/CT was performed after polypectomy during colonoscopy, the resected polyps were not counted.

Statistical analysis

Sensitivity, specificity, PPV, NPV, and accuracy were determined based on the comparison between PET/CT and colonoscopy findings at six colonic sites of all 492 patients. Ninety-five percent confidence intervals (95% CI) were calculated for these estimates. Univariate analyses were performed with the chi-squared test or Fisher's exact test, and a

multivariate analysis was performed with the logistic regression model. A two-sided *P* value of less than 0.05 was accepted as significant. Statistical analysis was conducted using JMP 8 software (SAS Institute, Cary, NC).

RESULTS

Patients and colonoscopic findings

Table 1 summarizes the demographics and colonoscopy results of the 492 patients. In all, 270 colorectal lesions of 5 mm or more in size, including 70 pathologically confirmed malignant lesions, were found in 172 patients by colonoscopy. Among 200 polyps which were considered nonmalignant, 164 (82%) were 10 mm or smaller, 30 (15%) were 11-20 mm, and 6 (3%) were 21 mm or larger. High-grade adenoma or adenoma with villous component were seen in 24 polyps among 79 pathologically examined polyps. Malignant lesions consisted of 57 CRCs, 10 lymphomas, 2 cancers of adjacent organs penetrating to the colorectal lumen, and 1 metastatic tumor. The average size of the malignant lesions was 31 mm (range 6-80).

Diagnostic ability of PET/CT for colorectal lesions

Table 2 shows the sensitivity, specificity, PPV, NPV, and accuracy of PET/CT for colorectal lesions. Positive or negative for PET/CT was determined at six colonic sites in each patient, and compared with the findings of colonoscopy. Hence, the data were obtained based on 2,952 colonic sites of the 492 patients. The median interval between colonoscopy and PET/CT was 14 days (range 0-364).

The results are shown according to tumor size (5 mm or more: n = 270; 11 mm or more: n = 97; and 21 mm or more: n = 50). The sensitivity and specificity for tumors 5 mm or more were 36%, and 98%, respectively. Hence, the sensitivity for tumors with 5-10 mm in size was only 9.2% (16/173). However, the sensitivity for tumors 11 mm or more increased up to 85% (82/97). Moreover, the sensitivity for tumors 21 mm or more was 96% (48/50), suggesting that the sensitivity of PET/CT for colorectal lesions is size-dependent, and that a large part of

clinically relevant polyps (larger than 10 mm) are detectable with PET/CT. The specificity was above 96% for any tumors greater than 5 mm, suggesting that few tumors would be found in the PET/CT negative regions. Endoscopic findings and PET/CT images of one true-positive case and one false-negative case are shown in Figure 1.

Sensitivity of PET/CT for colorectal lesions stratified by pathology

The sensitivity of the PET/CT stratified by pathology is shown in Table 3. The sensitivity to high-grade adenoma and adenoma with villous component was analyzed for 24 pathologically confirmed cases. Although the sensitivity to benign lesions of 5-10 mm was less than 10%, the sensitivity for malignant lesions of similar size was 33%. For 11-20 mm lesions, increased sensitivities were seen in malignant lesions (94%), high-grade or villous (80%), and other polyps (50%), respectively. Although almost all lesions measuring 21 mm or more were detectable with PET/CT regardless of pathology, there were two lesions that were negative in PET/CT. One was a 25 mm flat-type polyp in the cecum, and the other was a 30 mm invasive cancer in the rectum. In the latter case, continuous physiologic ^{18}F-FDG uptake was observed from the descending colon to the rectum.

Sensitivity of PET/CT for colorectal lesions according to location and macroscopic appearance

Next, the sensitivity of PET/CT for colorectal tumors was determined according to tumor location and macroscopic appearance (Table 4). In general, PET/CT was less sensitive to tumors in the proximal colon. In particular, the difference in sensitivity between proximal and distal colon was greater in 11-20 mm tumors (53% vs. 81%, respectively). Macroscopically flat lesions were likely to be negative in PET/CT (the sensitivity to 11-20 mm tumors was 44% in flat vs. 79% in protruded), although the number of flat lesions was

small compared to that of protruded lesions. These results suggest that the detectability of colorectal lesions by PET/CT is different according to tumor location and/or morphology.

Identification of factors that contribute to being false-negative in PET/CT

Differences in sensitivity have been shown of PET/CT for colorectal lesions according to tumor characteristics. In clinical practice, false-negatives in PET/CT studies of clinically relevant lesions would be problematic. Factors that contributed to false-negative results in PET/CT were determined in detecting clinically relevant lesions including malignant lesions, high-grade or villous adenomas, and polyps larger than 10 mm. The parameters used in the multivariate analysis were patient gender and age, and tumor size, location, and macroscopic appearance (Table 5). The results revealed that small size (10 mm or smaller) (odds ratio, OR: 44.14; 95% CI: 11.44-221.67) and flat morphology (OR: 7.78; 95% CI: 1.79-36.25) were significant factors that contributed to false-negatives in PET/CT. Small and/or flat tumors are likely to escape from being detected by PET/CT.

DISCUSSION

In this study, we demonstrated the sensitivity of PET/CT for detecting colorectal lesions in a large cohort, in which approximately 500 patients had undergone both PET/CT and colonoscopy. To the best of our knowledge, this is the largest cohort among studies that have examined the performance of PET/CT for colorectal lesions. Besides using this large cohort, we analyzed the sensitivity of PET/CT according to tumor characteristics such as tumor size, pathology, morphology, and location. In particular, in-depth analysis regarding colonic location was performed by calculating sensitivity for each colonic section. This showed that there was a difference in sensitivity of PET/CT between the proximal and distal colons. Another original and strong facet of this study was the identification of factors contributing to false-negative results in PET/CT. Although PET/CT may have the potential to be used as a screening modality for colorectal neoplasia, data accounting for the pros and cons of the problem are limited. Successful identification of false-negative factors by using this large cohort may clarify the issues on this topic.

We demonstrated the sensitivity of PET/CT for colorectal lesions larger than 10 mm was approximately 85%, which was similar to the results shown in the previous studies [13,23]. Although the size and pathology-dependence (higher in high-grade and villous component, and malignancy) of the sensitivity had also been observed in the previous reports [9,12,13], our large scale study provided sufficient data for confirming the efficacy of PET/CT for detecting clinically relevant colorectal lesions. In contrast to previous reports, we calculated the specificity, PPV, NPV, and accuracy by dividing the total colon into six segments. Because the prevalence of colorectal lesions is relatively low, specificity, NPV, and accuracy were likely to be higher, while PPV tended to be lower than the results of the

previous reports. In clinical settings however, the interpretation of PET/CT images is usually made by dividing the colon as performed in this study, and hence these values may reflect the true performance of PET/CT for colorectal lesions.

Our results indicated that neoplasia in the proximal colon and flat lesions were likely to be false-negative with PET/CT. In particular, flat appearance was an independent factor that contributed to being false-negative in PET/CT. Friedland et al. also reported that PET was insensitive to flat lesions [12]. They reported the sensitivity for flat lesions was 23% in precancerous lesions larger than 10 mm, which was lower than our results (50%, 6/12), possibly because PET alone is less sensitive than PET/CT for colonic lesions [2]. In addition, the difference may be attributed to the fact that almost all (11/13) of the flat lesions they reported were located in the proximal colon, in which polyps are likely to be insensitive to PET.

Although the precise reasons for the insensitivity of PET/CT to flat and/or proximal colonic neoplasia are unknown, the following factors may be involved. First, it may be affected by tumor volume. Because PET reflects metabolic activity of the tumor, sensitivity depends on tumor volume i.e., the number of tumor cells [24]. Flat lesions generally have smaller volumes and consist of smaller numbers of tumor cells than protruded lesions. Therefore, these lesions are insensitive to PET/CT. Second, because flat lesions are likely to be located in the proximal colon, tumor cells of proximal neoplasia may be different in glucose metabolism. Biological differences have been shown between proximal and distal colon cancers: proximal cancers are likely to be microsatellite unstable, hypermethylated, p53-wild, and diploid, while distal cancers tend to be chromosomal unstable, lower methylated, p53-mutated, and aneuploid [25-27]. Therefore, differences in glucose

metabolism may exist between proximal and distal neoplasia. A recent proteome analysis showed that glucose was lower in microsatellite instability high colorectal tumors than in microsatellite stable tumors [28]. In the future, we may be able to evaluate molecular differences in colorectal tumors according to positivity of PET/CT. Moreover, it has been reported that the growth rate of adenomas in the proximal colon is lower than that of adenomas in the distal colon [29]. Lower growth rate is probably correlated with lower rate of cell division, which involves poor glucose metabolism, resulting in poor sensitivity for PET/CT.

We have shown that PET/CT has a reasonable sensitivity for clinically significant colorectal neoplasia. An emerging issue is the possibility of using PET/CT in screening for colorectal neoplasia. Minamimoto et al. reported that the sensitivity of PET and PET/CT for CRC in an asymptomatic population was 90%, on the basis of more than 50,000 cases analyzed in the Japanese Nationwide Survey [30]. Our results were comparable, though admittedly the data were of a lesser scale. The main goal of CRC screening is the detection of advanced neoplasia, and the sensitivity to those lesions was 75% in our study. The percentage is marginally lower than the sensitivity of CTC, which is a similar non-invasive radiology-based method. Previous studies indicated sensitivity of CTC for advanced colorectal neoplasia was 86-90%, and this method was recommended as one of the screening options for CRC by the American Gastroenterological Association [4,31,32]. PET/CT, however, has the advantages of not requiring bowel preparation and the detectability of cancers in other organs. These advantages may facilitate using PET/CT as a preferable screening test for cancers in the whole body including CRC. Although PET/CT is a non-invasive method, exposure to radiation, which may cause cancer development or affect

other health conditions, is a serious problem. Hence, PET/CT is impractical for annual or biannual screening purposes. Determining an optimal interval for CRC screening with PET/CT is a further problem, considering its questions of effectiveness and safety.

In Japan, one session of whole-body PET/CT is provided at approximately $1000, which is higher than the cost of a colonoscopy, and much higher than the cost of a fecal occult blood test. Thus, PET/CT is a very expensive procedure only for the detection of colorectal neoplasia, regardless of its relatively high sensitivity and safety. At the same time, the cost of using PET/CT to detect malignancies in other organs as well as in the colorectum needs to be evaluated. Ultimately, PET/CT for screening use will be subjected to a cost effectiveness analysis.

Our data concurred with previous studies in that colonoscopy should be performed in patients with positive results of PET/CT. However, for screening purposes, negative results of PET/CT do not justify dispensing with colonoscopies, regardless of false-negative patients. Our results, in particular, indicated that small but relevant lesions and flat lesions were likely to be missed by PET/CT. Although PET/CT could be used in whole body cancer screening, it should be noted that it is not perfect at least for CRC. Clinicians should inform patients in PET/CT screening of this limitation. For screening, PET/CT may be more practical when used in combination with a more non-invasive test such as a fecal occult blood test.

It should also be noted that our results do not apply to inflammatory bowel disease (IBD)-related malignancy, because FDG can be incorporated in the intestine with inflammation. In fact, there have been reports regarding the feasibility of evaluating the inflammatory status of IBD with PET/CT [33]. In addition, a large part of dysplasia/cancer observed in ulcerative colitis are flat lesions, which are likely to escape detection with

PET/CT. The detection of IBD-related malignancies with PET/CT remains as an important problem, because no other modalities could definitively detect these lesions.

The limitations of this study include those inherent in any retrospective analysis of a single institution's experience. Secondly, some of the locations detected by PET/CT may be inaccurate, because colonic location was determined with PET positivity by analyzing recorded CT images. However, coronal and sagittal section images of CT were used concurrently. Therefore, any inaccuracy of localization was considered minimal. Third, all polyps that were regarded as non-malignant were not examined pathologically, because a considerable number of patients had more serious disease than colorectal polyps. Therefore, ‘other polyps’ in Table 3 may include some high-grade or villous adenomas, resulting in overestimation of the sensitivity to insignificant lesions. Fourth, since most of the patients in this study harbored a malignancy as an underlying disease, this precludes an accurate estimate of the utility of PET/CT as a screening tool for colorectal neoplasia in an asymptomatic population. In our study, 12% of the patients analyzed had colorectal malignancies, and 28% had colorectal polyps. The high prevalence of target lesions could make our data of sensitivities and specificities different from cases of an asymptomatic population. Fifth, we analyzed patients who had undergone both PET/CT and colonoscopy within a maximum interval of one year, which may be considered a wide range. However, since the actual median interval was 14 days, comparison of the results between the two methodologies was considered reasonable. Finally, although we used findings of colonoscopy as a gold standard, nevertheless, colonoscopy has been shown to be imperfect and can miss relevant polyps [34].

In conclusion, our study found that most of the clinically important colorectal lesions were detectable with PET/CT. However, it should be noted that smaller lesions, and flat

and/or proximal lesions are less sensitive to PET/CT. The interpretation of PET/CT study of a whole body should be performed**,** considering our findings in detection of colonic neoplasia. For use in CRC screening settings, there are still problems to be investigated including radiation exposure, appropriate screening intervals, and the existence of false-negative cases.

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FIGURE LEGENDS

Figure 1

Endoscopic findings and PET/CT results of the representative cases: (a) Protruded polyp, 12 mm in size, in the sigmoid colon with positive PET/CT results. (b) Flat lesion, 10 mm in size, in the cecum with false-negative PET/CT results.