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ORIGINAL ARTICLE

Application of ^{18}F-fluorodeoxyglucose positron emission tomography to detection of proximal lesions of obstructive colorectal cancer

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Abstract
Purpose. In cases of obstructive colorectal cancer (CRC), preoperative diagnosis of the proximal lesion is often difficult when the primary lesion impedes the passage of the endoscope. The aim of this study was to evaluate the usefulness of fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in such cases.
Materials and methods. A total of 52 obstructive CRC patients who underwent preoperative FDG-PET and subsequent surgical resection were retrospectively reviewed. The correlation between characteristics of the proximal lesion and FDG-PET findings was analyzed statistically.
Results. There was a significant correlation between the proximal lesion size and the maximum standardized uptake value ($P = 0.00016$). Abnormal FDG accumulation in the proximal colon indicated the existence of proximal cancer or adenoma with a sensitivity of 50% and a specificity of 100%. There was a significant difference in the distribution of tumor size between the cases with proximal abnormal accumulation and those with no proximal accumulation ($P = 0.00014$). A proximal tumor of ≥ 8 mm can be demonstrated by an accumulation of FDG with a sensitivity of 94.1%.
Conclusion. FDG-PET can estimate the existence of a proximal lesion and its size. Results may contribute to decisions regarding the type of surgery in cases of obstructive CRC.

Key words Fluorodeoxyglucose positron emission tomography (FDG-PET) · Maximum standardized uptake value (SUVmax) · Obstructive colorectal cancer (CRC) · Diagnosis

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Introduction

Colorectal cancer (CRC) is the second most common cause of cancer mortality in developed countries. The prevalence of CRC is increasing owing to changing lifestyles and eating habits.[1] It is well known that patients with primary colorectal lesions may have more than one synchronous lesion in the colon and rectum. Synchronous lesions in a different anatomical segment manifest in about 4.6%–11.0% of cases.[2–4] Preoperative detection of a synchronous lesion is essential as it may change the course of treatment and management of the CRC.

Detection of lesions by optical colonoscopy is regarded as the most sensitive and specific examination for identifying a CRC.[5] However, when optical colonoscopy cannot traverse an obstructive primary lesion, examination for possible proximal synchronous lesions is deterred. Both computed tomography (CT) and magnetic resonance imaging (MRI) provide limited information concerning grade of malignancy for small neoplastic lesions. Positron emission tomography (PET) is a noninvasive technique used for oncological imaging. Currently, fluorine-18-fluorodeoxyglucose (FDG) is the most commonly used tracer in oncology. FDG accumulates in cells that have high glycolytic activity, allowing the detection of neoplastic lesions and differentiation

between benign and malignant cells that cannot be morphologically distinguished.[6] FDG-PET is a useful technique for detecting and investigating the nature of a lesion proximal to an obstructive primary lesion in the colon, which cannot otherwise be observed by an endoscopic fiber. The purpose of this study was to evaluate the diagnostic performance of FDG-PET in the detection of proximal lesions of obstructive CRC.

Materials and methods

Patients and therapeutic strategy

This study retrospectively investigated 87 obstructive CRC patients who underwent preoperative FDG-PET and subsequent radical surgery from October 2003 to March 2010. All patients gave informed consent, and the study protocol was approved by the ethics committee at our hospital. For statistical analyses, 52 cases that met all the following criteria were selected as objects in this study: (1) endoscopy of the proximal region was not possible due to stricture caused by the primary lesion; (2) the obstructive cancers were diagnosed pathologically as adenocarcinoma prior to surgery; (3) the proximal region was evaluated by histopathological and/or follow-up endoscopic examination within 12 months after surgery; (4) the blood glucose level at the time of PET scan did not exceed 200 mg/dl. A high blood glucose level was regarded as an important influence on the accumulation of FDG.[7]

All patients were treated following the standard therapeutic strategy at our institution. In brief, when PET demonstrated an accumulation of FDG in the colon proximal to the primary lesion, inspection and palpation focusing around the location of FDG accumulation were performed during surgery. Proximal lesions were resected if identified. In cases where proximal lesions could not be identified during surgery, follow-up endoscopy was performed. Attempts to detect proximal lesions were made during surgery regardless of the preoperative PET findings.

PET imaging

Patients were required to fast for at least 4 h before imaging. All patients were given FDG at a dose of 5 MBq/kg. The FDG uptake period for all patients was 60 min. PET scanning was performed with the GE Advance NXi PET system (GE Medical Systems, Milwaukee, WI, USA) with a two-dimensional acquisition mode. Image acquisition was started with a set of whole-body emission scans (2 min/bed position) followed by post-injection transmission scans (1 min/bed position). The images were obtained for six or seven bed positions ranging from the head to the upper thigh. Total acquisition time was 18–21 min. The ordered subsets-expectation maximization (OSEM) algorithm (iterations 2, subsets 21) was used. Attenuation correction was included. After acquiring the early-phase image set, the data were reconstructed immediately and reviewed to determine if an additional set of PET scans (delayed-phase imaging) was required. Delayed-phase imaging (120 min after FDG injection) was conducted to exclude artifacts due to physiological FDG uptake and/or to confirm pathological uptake in a questionable lesion. Although the delayed-phase imaging was utilized for clinical purposes, detailed data from those images were not included in the current study.

Because making a decision about whether the FDG uptake was physiological or pathological was crucial and occasionally difficult, the decision was left to a specialist in nuclear medicine. Focal hypermetabolic areas with intensity equal to or exceeding the level of FDG uptake in the liver were judged to be abnormal and were interpreted as intraluminal neoplasia. When a nodular accumulation was depicted on the early phase, the probability that it indicated a tumor was high, and the delayed phase was performed to decrease the number of false positives. When the same or a greater accumulation was demonstrated on the delayed phase, it was judged to be pathological uptake. As longitudinal or diffuse accumulation was considered to be physiological uptake, delayed-phase imaging was not performed in those cases. When physiological uptake interfered with visualization of the suspected location of the tumor, a delayed-phase scan was added after completion of the early-phase acquisition.

The images obtained after early-phase detection were then subjected to semiquantitative analysis by calculating the standardized uptake value (SUV). The SUV was defined as the concentration of FDG in the tissue or lesion and was calculated with the following equation.

$$\text{SUV} = [\text{concentration (MBq/g)}]/[\text{injected dose (MBq)}/\text{patient's body weight (g)}]$$

The SUVmax corresponds to the maximum value of SUV in a region of interest (ROI). The ROI was configured to be a circle drawn on a maximum intensity projection (MIP) image of PET around an area showing the highest FDG accumulation. The size of the circle varied subject to the size of the target or adjacent physiological accumulation. Cases with abnormal FDG accumulation proximal to the primary lesion were considered PET-positive. When no abnormal accumulation of FDG was seen on PET in the proximal intestine, the case was considered PET-negative.

Table 1. Characteristics of patients with FDG accumulation in the proximal region

Patient no.	Primary lesion	Proximal lesion	Proximal SUVmax	Blood glucose (mg/dl)	Detected on CT	Simultaneous resection	Operation	Pathological findings of proximal lesion (size)
1	S	TA	13.1	87	Yes	Yes	Sigmoidectomy Right hemicolectomy	AC (35 mm)
2	A	C	23.1	88	Yes	Yes	Right hemicolectomy	AC (80 mm)
3	S	D	6.4	95	No	Yes	Left hemicolectomy	EC-SM (15 mm)
4	TA	A	12.1	80	No	Yes	Right hemicolectomy	AM-m (15 mm)
5	S	A	5.7	76	No	Yes	Subtotal resection of the colon	EC-M (10 mm)
		T	16.2					EC-M (40 mm)
		D	5.9					EC-M (18 mm)
6	S	D	7.8	90	No	Yes	Sigmoidectomy	AM-l (20 mm)
7	R	A	12.7	86	No	Yes	Subtotal resection of the colon	AM-h (15 mm)
		T	5.4					AM-l (12 mm)
		D	17.6					AM-h (20 mm)
8	D	TA	8.6	110	No	No	Descending colectomy	AM-h(r) (10 mm)
9	RS	A	5.8	67	No	No	Low anterior resection	EC-M(r) (10 mm)
		D	4.7					AM-l(r) (10 mm)
10	T	A	3.7	92	No	No	Transverse colectomy	AM-l (4 mm)
11	TD	T	5.2	103	No	No	Partial resection of TD	AM-m(r) (15 mm)
12	S	T	4.8	80	No	No	Sigmoidectomy	AM-l(r) (8 mm)

FDG, fluorodeoxyglucose; SUV, standardized uptake value; S, sigmoid colon; A, ascending colon; T, transverse colon; D, descending colon; R, rectum; AC, advanced cancer; EC, early cancer; AM, adenoma; l, low grade; m, moderate grade; h, high grade; SM, submucosal layer (depth of invasion); M, mucosal layer (depth of invasion); (r), resected endoscopically

Data collection and statistical analysis

The FDG-PET findings were verified retrospectively. Factors such as tumor size, histopathological diagnosis, PET-positive or PET-negative, and SUVmax of the proximal lesion in PET-positive cases were compiled. Tumor size was measured on the resected specimen or by endoscopic findings. Data were expressed as the median and range. Statistical analysis was undertaken using nonparametric methods, including the Mann-Whitney U-test, Fisher's exact probability test, and Spearman's rank correlation test. All statistical tests were two-sided and carried out at a significance level of 0.05.

Results

Characteristics of patients

Of the 52 cases of obstructive CRC, the location of the primary lesion was in the ascending colon in 11 cases, transverse colon in 12 cases, descending colon in 4 cases, sigmoid colon in 14 cases, and rectum in 11 cases. The age of patients ranged from 51 to 86 years (median 70 years); and the male/female ratio was 33:19. The blood glucose concentration 20 min before injection of FDG was in the range of 67–153 mg/dl (median 86.5 mg/dl). Accumulation of FDG in the primary lesion was seen in all 52 cases; and the SUVmax of the primary lesion of these cases was 5.3–25.0 (median 13.8). The 52 patients fell into two groups: 12 were PET-positive, and 40 were PET-negative.

PET-positive cases

Table 1 lists the 12 patients for whom abnormal FDG accumulation was observed in the proximal colon. Simultaneous resection of the proximal region of the colon was performed in 7 of the 12 cases (cases 1–7). In these seven cases, there were 11 lesions identified in the proximal colon. The SUVmax of these 11 lesions was 5.4–23.1 (median 12.1). The 11 proximal lesions in the seven patients were diagnosed as 5 adenomas, 4 early cancers, and 2 advanced cancers. In five of the seven patients, the proximal lesion was not detected by contrast-enhanced CT imaging. In the remaining five patients (cases 8–12), six proximal lesions were detected by PET; the lesions were not resected at the time of operation as they had not been detected by visual inspection or palpation. Postoperative endoscopy was subsequently performed in all five patients and endoscopic resection in four of the five. The SUVmax of these six proximal lesions was 3.7–8.6 (median 5.0). Pathological diagnoses of the six proximal lesions in these five patients were five adenomas and one early cancer, all of which were undetectable on enhanced CT scans before the surgery. Figure 1 shows case 3 as an illustration of proximal accumulation of FDG.

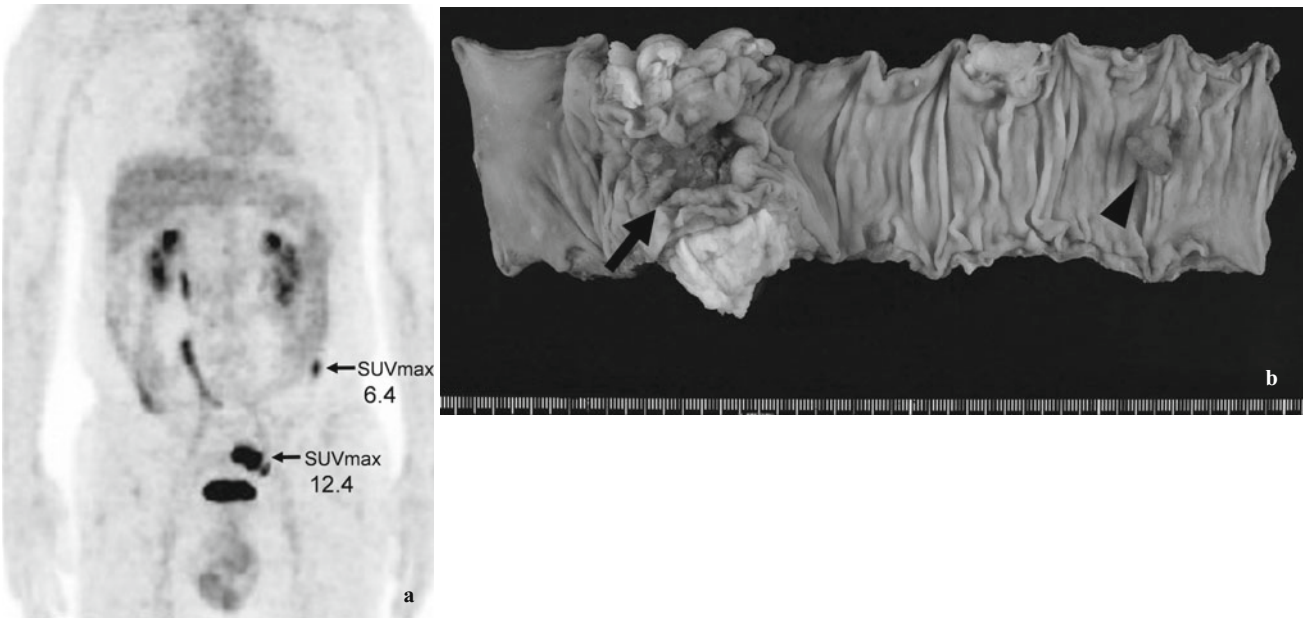

Fig. 1. Case 3. **a** Primary lesion is shown as an accumulation of ^{18}F-fluorodeoxyglucose (FDG), and its maximum standardized uptake value (SUVmax) is 12.4. The SUVmax of the proximal lesion is 6.4. **b** Histopathological examination diagnosed the primary lesion as advanced adenocarcinoma of the sigmoid colon (*arrow*) and the proximal lesion as early adenocarcinoma with a depth of invasion to the submucosal layer (*arrowhead*)

PET-negative cases

No FDG accumulation was observed in the proximal colon in the remaining 40 patients. In 25 of the 40, a lesion in the proximal region was diagnosed by endoscopy performed within 12 months after surgery. In the remaining 15 patients, the primary lesion was located in the right transverse colon or ascending colon; therefore, right hemicolectomy was performed, and a histopathological diagnosis was made at the time of surgery. No proximal lesion was present in the resected specimens from any of these 15 patients. In the 25 cases diagnosed by follow-up endoscopy, the period from operation to initial endoscopy ranged from 1 to 12 months (median 10 months). In 12 of the 25 patients, there were 15 neoplastic lesions proximal to the primary lesion, including 13 adenomas and 2 early cancers. The size of the 15 proximal lesions ranged from 2 to10 mm (median 5 mm), and the size of the 13 adenomas ranged from 2 to 7 mm (median 4 mm). The two early cancers included one 10-mm adenocarcinoma with invasion to the mucosal layer and one 5-mm adenocarcinoma with invasion to the submucosal layer. These tumors were completely resected by endoscopy 11 and 2 months after surgery, respectively.

Statistical analysis

There was a significant correlation between tumor size and SUVmax in the 17 PET-positive tumors ($P = 0.00016$; Spearman's rank correlation test) (Fig. 2). Even when two patients with advanced cancer were excluded from the analysis, there still was a significant correlation ($P = 0.0038$).

Combining the results of PET-positive and PET-negative groups, there were 12 PET-positive patients with a proximal lesion, and all PET-positive patients had a proximal lesion. There were 12 PET-negative patients with a proximal lesion, and 13 PET-negative patients without a proximal lesion. In addition, the entire group of 15 PET-negative patients in whom right hemicolectomy was performed showed no proximal lesion detected by histopathological diagnosis of the resected specimen (Table 2). There was a significant difference between PET-positive and PET-negative groups regarding existence of tumors, with the sensitivity and specificity at 50% and 100%, respectively ($P = 0.002$; Fisher's exact probability test). When the PET-negative patients in whom right hemicolectomy was performed were included, the difference was more significant ($P = 0.00001$).

There were 7 carcinomas and 10 adenomas in the PET-positive group and 2 carcinomas and 13 adenomas in the PET-negative group (Table 3). Statistical analysis showed no significant correlation between the presence of abnormal FDG accumulation in the proximal colon and the histopathological diagnosis of a proximal lesion ($P = 0.12$; Fisher's exact probability test).

The size of the 15 proximal tumors in PET-negative patients ranged from 2 to 10 mm (median 5 mm),

Table 2. Distribution of patients with respect to existence of a proximal lesion and abnormal FDG accumulation on PET

PET	Tumor (+)	Tumor (–)
(+)	12	0
(–)	12	13 (28)[a]

PET, positron emission tomography; (+), accumulation of FDG in the proximal region; (–), no accumulation in the proximal region; Tumor (+), a proximal lesion was found; Tumor (–), no proximal tumor was found

[a] New total number when the 15 cases of right hemicolectomy are added

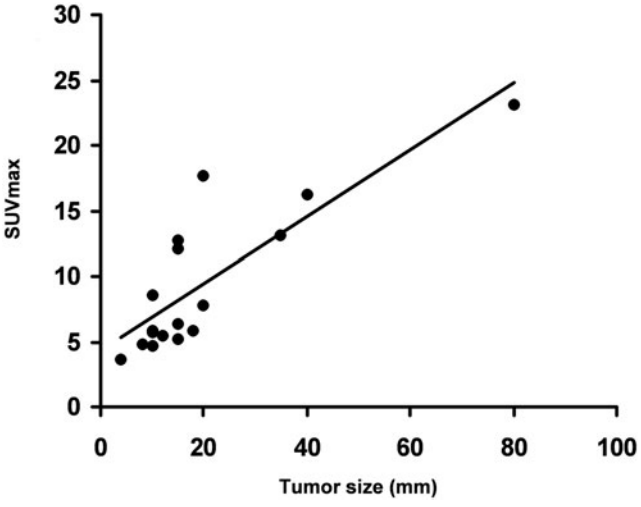

Fig. 2. Scatter plot shows the dependence of SUVmax on tumor size. Spearman's rank correlation test demonstrates a positive correlation between the two variables ($r_s = 0.791$, $P = 0.00016$)

Table 3. Distribution of lesions with the postoperative histopathological diagnosis of a proximal lesion classified by abnormal FDG accumulation and histopathology

PET	Carcinoma[a]	Adenoma[a]
(+)	7	10
(–)	2	13

[a] Histopathological diagnosis

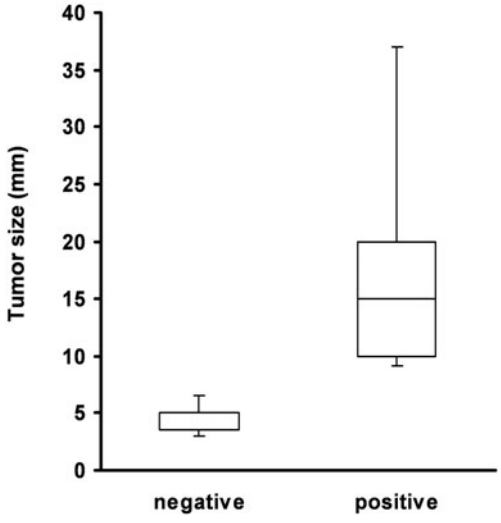

Fig. 3. Box and whisker plot shows the distribution of tumor size in positron emission tomography (PET)-negative and PET-positive cases. The box represents the 25th and 75th percentiles; the median is shown by a horizontal line in the PET-positive case. The whiskers represent the 90th and 10th percentiles. There was a significant difference in tumor size between PET-negative and PET-positive cases ($P = 0.00014$, Mann-Whitney U-test)

whereas that the size of the 17 proximal tumors in PET-positive patients ranged from 4 to 80 mm (median 15 mm) (Fig. 3). There was a significant difference in tumor size between the PET-negative and PET-positive groups ($P = 0.00014$, Mann-Whitney U-test). The cutoff value for the proximal lesion size that best divides the results of PET-negative and PET-positive data with optimum sensitivity and specificity can be determined by receiver operating characteristic (ROC) curve analysis. When the cutoff value is set at 8 mm, the sensitivity is 94.1% and the specificity 93.3%. In the PET-positive group there were 16 tumors ≥8 mm and 1 tumor <8 mm, whereas in the PET-negative group there was 1 tumor ≥8 mm and 14 tumors <8 mm (Table 4).

Table 4. Distribution of tumors classified by abnormal FDG accumulation on PET and size of the tumor in the proximal region

PET	Tumor ≥ 8 mm	Tumor < 8 mm
(+)	16	1
(–)	1	14

Discussion

Management of cases in which endoscopic examination of the proximal region is impossible due to a stricture of obstructive CRC has been controversial. Intraoperative colonoscopy has been one of the tools for investigating proximal lesions.[8,9] In cases of obstructive CRC, however, the preoperative bowel preparation necessary for accurate diagnosis by endoscopy is hazardous because it may cause intestinal perforation. Intraoperative irrigation of the proximal colon may be considered, but it is time-consuming and may contaminate the surgical field.

Computed tomography colonography (CTC) is coming into widespread clinical use and is one of the superior tools for diagnosing CRC. For the detection of colorectal polyps of >1 cm, it is comparable to colonos-

copy, and its advantages include the capability of detecting extracolonic abnormalities.[10] It is believed that CTC also requires the same full cathartic bowel preparation as colonoscopy,[11] although Liedenbaum et al.[12] recently reported that CTC with limited bowel preparation had high diagnostic accuracy for detection of adenomas and carcinomas and sensitivity similar to that of colonoscopy for relevant lesions. On the other hand, Chaparro et al.[13] disagreed with the accuracy of CTC by demonstrating high heterogeneity to previous reports.

FDG-PET is an accurate imaging technique for staging multiple malignancies. Semiquantitative analysis of FDG-PET images can be carried out by calculating the SUV, which represents the metabolic activity of the tumor corrected for injected dose and patient weight. The SUVmax, despite being a semiquantitative measure, can be used to supplement visual interpretation of the PET image as it can be used to evaluate metabolic changes in the tumor.[6]

PET/CT, a combined modality, has become a new standard imaging approach for the diagnosis and management of many cancer patients.[14] Although PET/CT is a more recent and advanced technique, PET is still the mainstay of nuclear medical imaging. Nagata et al.[15] suggested that PET/CT colonography may become the primary diagnostic tool for examining the colon proximal to the obstructive CRC. The small sample size (two cases) of this study is, however, not sufficient to draw a definite conclusion in this regard; and hence a detailed study is warranted.

Gu et al.[16] reported that the sensitivity of PET in CRC diagnosis was 100%, with a mean SUV of 8.0 (3.1–11.9). Tumor size and depth of invasion were associated with higher SUVs ($P = 0.0004$ and 0.042, respectively). SUV is one of the most important single parameters for lesion differentiation.[17] Although there has been no report demonstrating the cutoff point of the SUV between malignant and benign tissues, the high sensitivity of this measurement allows for detection of lesions that other modalities may overlook.[17,18] FDG-PET has high specificity for detecting colonic adenomas, although the technique has low sensitivity for lesions <1 cm.[19,20]

When evaluating FDG accumulation in a potential colonic lesion on FDG-PET, it is important to pay attention to any physiological uptake that might cause false-positive results. In addition, physiological uptake may yield a false-negative result by masking a true lesion. The diagnostician must be familiar with these points.[21,22] In this study, a specialist in nuclear medicine was always in charge of implementation of the delayed phase and interpretation of its result. Based on our conclusion that there was no false-positive test, physiological uptake was properly managed in the current study. In the PET-negative group, we reviewed each case twice to confirm that there was no suspicious physiological uptake that might have masked a true lesion. There have been no guidelines or criteria for judging the physiological uptake up to now; efforts for establishing them seem to be in progress.

This study had four main results, as follows. (1) SUVmax significantly correlates with the size of the proximal lesion when FDG accumulates. (2) Abnormal FDG accumulation in the proximal colon indicates the existence of a proximal lesion with a sensitivity of 50% and a specificity of 100%. (3) PET does not appear to be proficient in differentiating between cancer and adenoma. (4) An accumulation of FDG in the proximal region predicts the existence of a tumor of ≥ 8 mm, whereas no accumulation of FDG predicts either no tumor or the existence of a tumor < 8 mm. The information obtained before surgery by FDG-PET in the proximal region can be useful because it enables us to estimate the existence and the size of the proximal lesion. Without any information regarding a proximal lesion other than CT or other diagnostic modalities, such a lesion could easily be overlooked during palpation and visual inspection even if it is large one. Missing proximal cancers may necessitate reoperation, which is a burden on the patient. Meanwhile, PET has low sensitivity for detecting a small lesions that could be an early cancer. Needless to say, so long as there are early cancers that are undetectable on FDG-PET, early follow-up endoscopy is strongly recommended for any case of obstructive CRC except for patients who undergo right hemicolectomy. We experienced a couple of cases in which reoperation might have been necessitated if FDG-PET had not been performed preoperatively. In terms of the ability of FDG-PET to evaluate colorectal neoplastic lesions, this study is in agreement with previous reports.[16–20] For preoperative investigation of obstructive CRC, however, we believe that FDG-PET is superior to other diagnostic modalities.

This study may have some clinical and statistical limitations. The significance of preoperative PET varies subject to the location of the obstructive tumor. When the primary lesion is situated on the right side of the colon, the common operation is usually right hemicolectomy, which is not influenced by the FDG-PET results. Second, statistical analysis in this study did not take into account the length of the intestine that could not be observed by endoscopy. In the strict sense, an appropriate statistical analysis could be done when it is limited to cases with the obstructive lesion at a single location (e.g., the rectum). We separated the cases with right hemicolectomy in PET-negative cases to minimize the influence of this point.

Conclusion

FDG-PET can be used to estimate the existence of a proximal lesion and its size. A tumor ≥8 mm can be demonstrated with high sensitivity as abnormal accumulation of FDG in the proximal region. Therefore, PET provides useful preoperative information about obstructive CRC in cases where endoscopic examination of the proximal region is impossible due to a pathological stricture.

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