·Clinical Research·

Using ^{18}F-FDG positron emission tomography/computed tomography to judge benign or malignant colorectal hypermetabolic lesions

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[Abstract] Background and Objective: The colorectum is long and its position is not fixed. The thickness of the colorectal wall is unfixed because it changes following wall contractions. The metabolism of the colorectum is not stable and abnormal metabolism results from smooth muscle movement, gland action, spasm, inflammation, and so on. These anatomic and physiologic factors can bring a few difficulties in correctly judging colorectal information on ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) scans. This study was to discuss the imaging characterstics of colorectal hypermetabolic lesions in ^{18}F-FDG PET/CT and their value to clinical diagnosis. Methods: According the metabolic characteristics and the shape of the lesion, 118 colorectal hypermetabolic lesions of 74 patients were detected by ^{18}F-FDG PET/CT and separated to 6 groups (localized/CT$^+$, localized/CT$^-$, segmented/CT$^+$, segmented/CT$^-$, diffuse/CT$^+$, diffuse/CT$^-$). To contrast groups and the qualitative data, a R×C χ^2 test was performed to judge statistical differences. Results: In the 118 lesions, 50 were determined to be malignant and 68 nonmalignant. A total of 30 lesions were in the localized/CT$^+$ group (23 malignant, 7 non), 35 to the localized/CT$^-$ group (22 malignant, 13 non), 4 to the segmented/CT$^+$ group (4 malignant, 0 non), 35 to the segmented/CT$^-$ group (1 malignant, 34 non), 0 to the diffuse/CT$^+$ group, 14 to the diffuse/CT$^-$ group (0 malignant, 14 non). The rates of nonmalignant lesions in the segmented/CT$^-$ and diffuse/CT$^-$ groups (97.1%, 100%) and of malignant lesions in the segmented/CT+ groups (100%) were similar, so these three groups were combined to a nonlocalized group. The group of diffuse/CT$^+$ was deleted. There were significant differences among the three groups of nonlocalized, localized/CT$^+$, and localized/CT$^-$($P < 0.001$). The localized/CT$^+$ and localized/CT$^-$ groups were combined into one localized group because no significant difference was found between them ($P = 0.229$). There was a significant difference between the nonlocalized and the localized groups ($P < 0.001$). Conclusions: On ^{18}F-FDG PET/CT, colorectal hypermetabolic lesions in the diffuse/CT$^-$ or segmented/CT$^-$ groups were highly likely to be nonmalignant and those in the segmented/CT$^+$ group were highly likely to be malignant. Lesions in the localized/CT+ or localized/CT$^-$ groups had only a normal likelihood of being malignant. To correctly diagnose colorectal hypermetabolic lesions, it is necessary to analyze the PET of the metabolism and the CT of the anatomy together. Especially for the metabolic lesions of the localized/CT$^-$ group, we cannot easily make the judgment of malignant or nonmalignant unless we refer to the relevant clinical data.

Key words: Colorectal neoplasm, fluorodeoxyglucose, FDG, PET/CT, diagnostic imaging

The lengthy and tortuous journey, the unstable positioning of the colon and rectum, and variations in intestinal wall thickness during intestinal peristalsis have brought about significant

difficulties for computed tomography (CT) diagnosis. Glucose metabolism is unstable in the colon and rectum, and smooth muscle peristalsis, gland secretion, spasms, and inflammation can also cause abnormal metabolism, which leads to certain difficulty in diagnosis using ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET). Based on precise CT positioning, ^{18}F-FDG PET/CT reflects the metabolic profile in the body. Is this feature useful in improving its significance in colon and rectum? Herein, we investigated the significance of colorectal hypermetabolic lesions on ^{18}F-FDG PET/CT for clinical diagnosis by analyzing a total of 118 colorectal hypermetabolic lesions in 74

patients.

Materials and methods

Patient selection

Among all patients that received PET/CT at the nuclear medicine unit of Sun Yat-sen University Cancer Center during 2005-2007, a total of 74 patients with colorectal hypermetabolic lesions on ^{18}F-FDG PET/CT were randomly selected. Of these patients, 47 were men and 27 were women, with a median age of 59.5 years. Of these patients, 64 were treatment-naïve and 10 had received previous treatment. All patients had PET/CT more than 1 month after the last antitumor treatment.

Diagnostic criteria for colorectal hypermetabolic lesions

Diagnosis was generally based on visual observation. Local tissue in the colon and rectum with a FDG concentration that was significantly higher than the patient's cardiac blood pool was considered a hypermetabolic lesion.

Classifications

The included images were reviewed in a blinded fashion by specialists. Only PET/CT images of the colon and rectum were provided to the reviewing specialists and the corresponding clinical information was not disclosed. Based on FDG distribution and CT morphologic features, the hypermetabolic lesions were classified.

Classification based on metabolism The colon and rectum were first divided into five segments: the cecum/ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum. Based on FDG distribution and the affected scope of the metabolic lesions, the metabolic lesions were classified as localized, segmented, or diffuse.

Localized lesions: the lesion was seen as a localized mass that was not significantly in a parallel distribution along the bowel; or the metabolic lesion had a parallel distribution along the bowel but affected less than 50% of one segment.

Segmented lesions: the metabolic lesion was obviously in parallel distribution along the bowel, affecting more than 50% of one segment but fewer than two segments.

Diffuse lesions: the metabolic lesion was obviously in parallel distribution along the bowel, affecting more than two segments.

Classification based on CT findings Lesions of each type were further classified as CT$^+$ or CT$^-$ based on their anatomic features on CT.

CT$^+$: Significantly abnormal structural changes were seen in the colon and rectum, including obvious nodules, masses, or significant thickening of the intestinal wall. That is, (benign or malignant) lesions in the colon and rectum could be established merely based on the CT image, without reference to any other clinical information.

CT$^-$: No significant structural abnormality was seen in the colon and rectum; no significant local space-occupying signs or significant intestinal wall thickening was seen. Based merely on the CT images and without reference to any other clinical information, colorectal lesions were not ascertained.

Final classification Eventually, the metabolic lesions were classified as localized/CT$^+$, localized/CT$^-$, segmented/CT$^+$, segmented/CT$^-$, diffuse/CT$^+$, and diffuse/CT$^-$.

Qualitative (malignancy) evaluations

Pathology or diagnosis at discharge and some follow-up results were used as evidence for the qualitative evaluation of the metabolic lesions. Most of the malignant cases were pathologically confirmed. Four cases were not pathologically confirmed, but other clinical evidence, such as imaging, lab tests, or clinical manifestations, were adequate to support the diagnosis of malignancy. Established antitumor treatment was given as well, therefore these four cases were also rated as malignancy. If no relevant clinical evidence and data were found to support the diagnosis of malignancy, the case would be defined as nonmalignancy based on the diagnosis at discharge and some of the follow-up data.

Data processing

Lesion classification and qualitative evaluation results were compared and analyzed. According to the study objective, malignant lesion rates were translated into nonmalignant lesion rates for certain categories. Categories with small numbers of cases and similarly distributed data were merged and any insignificant data were excluded.

Statistical analyses

χ^2 test and χ^2 partition for R $\times$ C contingency tables were used to reveal the statistically significant differences in malignant or nonmalignant lesion rates between the various categories. Further analysis was performed to investigate the significance of different categories of hypermetabolic lesions in predicting the nature (benign or malignant) of the lesions. All data were analyzed by SPSS version 11.5.

Results

Classification and qualitative evaluation

In 74 patients, a total of 118 colorectal hypermetabolic lesions were identified. The correlations between the classification of the lesions and the qualitative evaluation are shown in Table 1. Typical images are shown in Figure 1 (localized/CT$^+$, localized/CT$^-$, segmented/CT$^+$ and segmented/CT$^-$) and Figure 2 (diffuse/CT$^-$).

Table 1 The relationship between groups and qualitative results

Group	Patient No.	Malignant	Benign	Rate of malignancy
Localized/CT$^+$	30	23	7	76.7%
Localized/CT$^-$	35	22	13	62.9%
Segmented/CT$^+$	4	4	0	100%
Segmented/CT$^-$	35	1	34	2.9%
Diffuse/CT$^+$	0	0	0	–
Diffuse/CT$^-$	14	0	14	0

Distribution of metabolic lesions

Among 65 localized metabolic lesions, the majority (25) were distributed in the rectum, followed by the ascending colon (15),
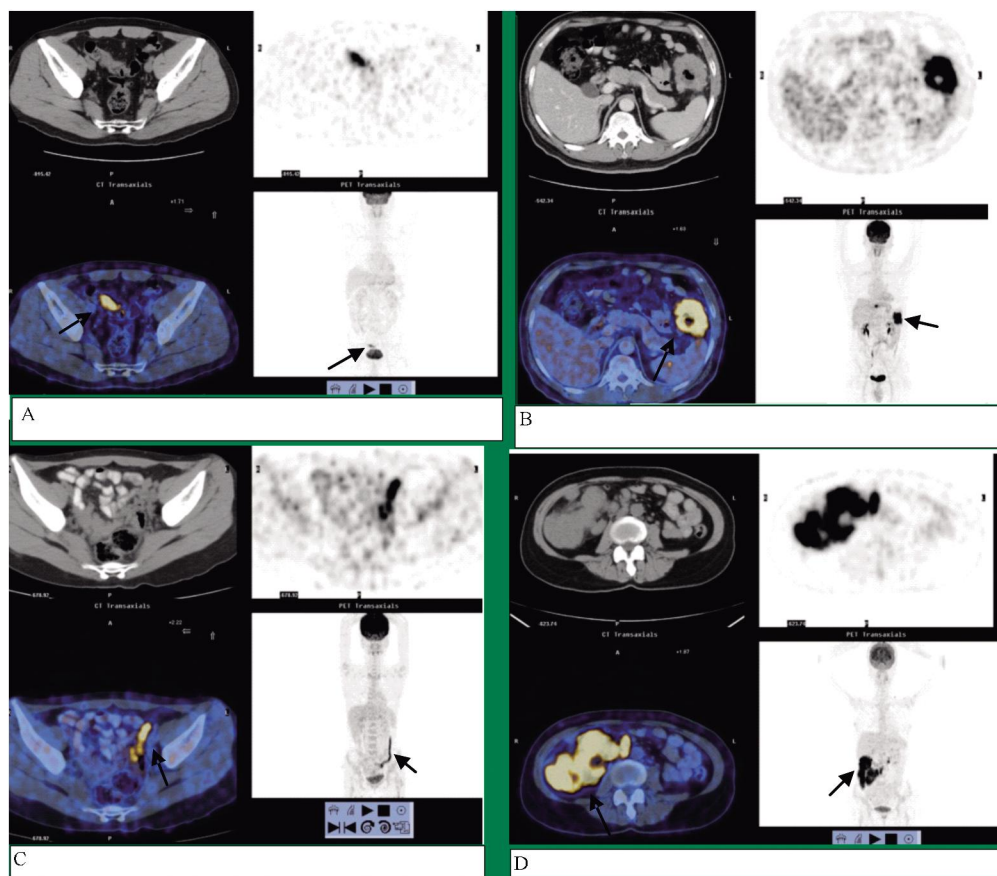
Figure 1   Localized/CT⁻, localized/CT⁺, segmented/CT⁻, and segmented/CT⁺

A, localized/CT⁻: sigmoid colon local hypermetabolism. The shape of the colon is normal. Pathology shows adenocarcinoma I~II. B, localized/CT⁺: splenic flexure of colon local hypermetabolism. The local wall of the colon shows obvious irregular thickening. Pathology shows adenocarcinoma II. C, segmented/CT⁻: descending colon and the near part of sigmoid colon segmented hypermetabolism. The shape of the colon is normal. Follow-up shows nonmalignant (benign). D, segmented/CT⁺: right hemicolon segmented hypermetabolism. The wall of colon obviously thickening and showing lumps. Pathology shows NHL, DLBCL.
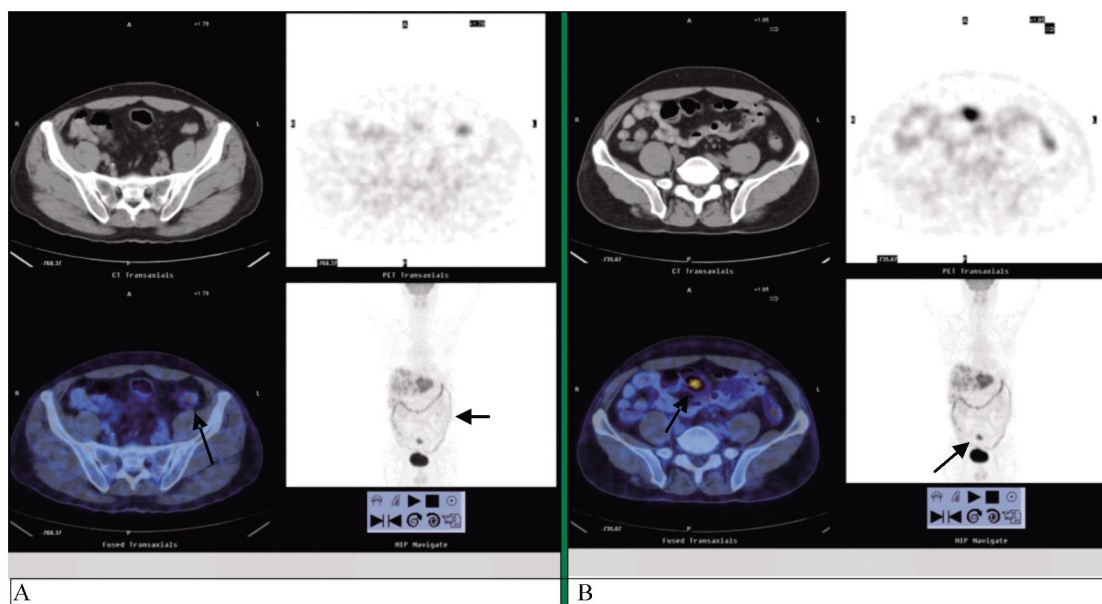

Figure 2   Diffuse/CT⁻ and localized/CT⁻

A and B belong to one patient. A, diffuse/CT⁻: ascending, transverse, and descending colon all diffused hypermetabolism. The shape of the colon is normal. Follow-up shows nonmalignant (benign). B, localized/CT⁻: sigmoid colon local hypermetabolism. The shape of the local colon is normal. Pathology shows sigmoid colon moderately differentiated adenocarcinoma.

the sigmoid colon (14), the transverse colon (10, with 4 in the splenic flexure and 3 in the hepatic flexure), and the junction of the descending and sigmoid colon (1). Among the 39 segmented metabolic lesions, 28 affected less than one segment and 17 were seen in the ascending colon, 6 in the descending colon, 3 in the rectum, and 2 in the sigmoid colon. Another 11 metabolic lesions affected two segments of the bowel, with 5 in the descending/sigmoid colon, 3 in the ascending/transverse colon, 2 in the rectum/sigmoid colon and 1 in the transverse/descending colon. Segmented metabolic lesions were mainly seen in the ascending colon, with a total of 20 metabolic lesions affecting the ascending colon. All 14 diffuse metabolic lesions were classified as diffuse/CT$^-$, indicating that the bowel was extensively affected; 6 of these lesions affected the entire bowel, 5 affected the ascending/transversal/descending colon, 2 affected the transversal/descending/sigmoid colon and 1 affected the descending/sigmoid colon/rectum.

Qualitative (malignancy) evaluations

Among the 118 colorectal metabolic lesions, 50 lesions were defined as malignant lesions, including 46 pathologically confirmed lesions and 4 clinically confirmed lesions (2 colon cancers, 1 rectal cancer, and 1 lymphoma). The malignant lesions included 25 colon cancers, 19 rectal cancers, 5 lymphomas (all of them were diffuse large B-cell lymphoma (DLBCL) on histology) and 1 malignant melanoma. A total of 68 lesions were defined as nonmalignant, of which 13 were microscopically confirmed, including 7 adenomatous polyps, 1 adenomatous hyperplasia with severe atypical hyperplasia, 1 local mucosal non-cancerated protuberance, 1 villous adenoma, and 3 chronic inflammations. Another 35 lesions were defined as nonmalignant based on follow-up data (follow-up time ranged from 3 months to 2 years, with a mean follow-up time of 6.2 months); another 20 lesions were defined based on the diagnosis at discharge (because no clinical evidence of malignancy was found).

A total of 23 localized/CT$^+$ malignant lesions included 9 colon cancers, 10 rectal cancers, 3 lymphomas, and 1 malignant melanoma. Among the 22 localized/CT$^-$ malignant lesions, 16 were colon cancers and 6 rectal cancers. In the 4 segmented/CT$^+$ malignant lesions, 2 were rectal cancers and 2 were lymphomas. The only 1 segmented/CT$^-$ malignant lesion was rectal cancer. All 14 diffuse/CT$^-$ metabolic lesions were defined as benign.

Data processing

As shown in Table 1, the malignant lesion rates of 2.9% and 0% for the segmented/CT$^-$ and diffuse/CT$^-$ lesions, respectively, were translated into nonmalignant lesion rates of 97.1% and 100%. The diffuse/CT$^+$ category was insignificant and was thus excluded.

Since the nonmalignant lesion rates for the segmented/CT$^-$ (97.1%) and the diffuse/CT$^-$ categories (100%) were similar to the malignant lesion rate for the segmented/CT$^+$ category (100%), with comparable distribution. The sample size was too small in the segmented/CT$^+$ category, so these three categories were incorporated as a 'nonlocalized' category. Thus, a χ^2 test for 3×2 contingency table was conducted (Table 2).

Statistical analyses

Significant differences were seen in the χ^2 test for the 3×2 contingency table (χ^2 = 18.753, P < 0.001). No significant difference was found between the localized/CT$^+$ and the localized/CT$^-$ categories (χ^2 = 1.446, P = 0.229), which were thus incorporated as a 'localized' category. Significant differences were seen between nonlocalized and localized lesions (χ^2 = 16.647, P < 0.001).

Table 2 3×2 crosstabulation

Group	Count 1 (accepted count)	Count 2 (accepted count)	Total
Localized/CT$^+$	23 (24.7)	7 (5.3)	30
Localized/CT$^-$	22 (28.8)	13 (6.2)	35
Nonlocalized	52 (43.6)	1 (9.4)	53
Total	97	21	118

Discussion

As functional imaging examinations, PET and PET/CT have shown huge advantages in diagnosing many diseases, particularly malignant tumors, ever since they were put into clinical application. Currently, the most frequently used tracer agent is ^{18}F-FDG, which is used to reflect glucose metabolism distribution in the body. However, glucose metabolism is subject to the influence of numerous uncertain factors, which are more prominent in the gastrointestinal tract. This hinders the accurate diagnosis with PET or PET/CT in clinical practice. Kamel et al.[1] analyzed 3218 patients who received ^{18}F-FDG PET/CT examinations and found that 98 (3%) had incidental gastrointestinal ^{18}F-FDG accumulation. Israel et al.[2] performed a retrospective analysis on 4390 patients with PET/CT and revealed incidental gastrointestinal FDG accumulation in 58 patients, with 82.4% of the accumulation events in the colon. Ding et al.[3] conducted ^{18}F-FDG examinations in 320 healthy individuals who were undergoing routine medical examinations and found physiologic uptake in the colon and rectum in 270 of them. The threshold standardized uptake value (SUV$_{max}$) was 3.1 ± 0.9, with significantly parallel distribution along the bowel. Due to the involuntary peristalsis of the colorectal muscular layer, the involuntary secretion of intestinal mucosa, and the occasional physiologic concentration of FDG in the colon and rectum resulting from the activity of bowel bacteria, together with locally active glucose metabolism arising from benign lesions including bowel mucosal inflammation and polyps, false positive lesions may be yielded. Therefore, when a colorectal hypermetabolic lesion is identified in PET/CT, its significance in the clinical diagnosis of malignant colorectal lesions has yet to be investigated, and is the objective of this study.

Currently no standardized PET/CT diagnostic criteria have been set for malignant colorectal lesions. Particularly, no consensus has been reached in terms of FDG metabolism measures in PET. In most of the literature, an SUV of 2.5 is used as the diagnostic threshold for colon cancer,[3-5] but SUV is not a

stable parameter. As a semiquantitative analytic parameter, SUV is susceptible to the influence of many variable factors, including drug dosage, blood sugar level, resting state, treatment approach, and physiologic metabolism. All these factors can lead to variations in SUV. Obviously it has certain limitations to use an individual SUV level as a diagnostic criteria. In other research, organs including the liver were used as controls. The metabolic level of the lesions was visually observed, compared to that of the control organs, and thus diagnosed. Tatlidil *et al.*[6] used the liver as a control organ in their study of 27 patients with incidental colon hypermetabolic lesions. The metabolic level in the liver is relatively stable. Although visual observation is a subjective method, this control can exclude the influence from some uncertain factors. However, the authors find in their clinical practice that the metabolic level of the liver can be unstable as well. For example, responses to certain medical treatments can result in diffuse hypermetabolism in the liver and spleen. In this study, the cardiac blood pool was used as the control. Unlike solid organs, the cardiac blood pool is considered hardly susceptible to the influence of other factors and tends to have more stable metabolism.

Among the 74 patients in our study, a total of 118 hypermetabolic lesions were identified. By analyzing the distribution of these metabolic lesions, the metabolic lesions could be primarily classified as localized, segmented, or diffuse. In this study, we tried to design quantitative classification criteria to the extent possible. To objectify the results, the large intestine was first divided into five segments; [7] the lesions were then classified based on the affected scope (shown as the number of segments affected) and the shape of the lesions. Tatlidil *et al.*[6] classified incidental hypermetabolic lesions into four categories based on PET image features: single-nodule, multiple-nodule, segmented, and diffuse, but the classification criteria were not specified. Gutman *et al.*[7] classified incidental abnormal uptake lesions into merely two categories: single nodule and multiple nodule. In this study, we didn't use the category of multiple nodule. Because when multiple-nodular lesions were found, the nature might not be homogenous across different nodular lesions; some of them might be benign and others might be malignant. Therefore, we classified this type of lesion as localized and used the specific number to present the quantity of the lesions. According to our results, localized lesions accounted for 55.1% (65/118), followed by segmented (33.1%, 39/118), and diffuse lesions (11.2%, 14/118).

Since the bowel is lengthy, tortuous, and movable, is unstable in terms of its position, and its wall thickness varies with peristalsis, the value of sectional anatomy-based CT in diagnosing bowel diseases is limited, particularly when tumorous lesions are shown as either localized nodules or intestinal wall thickening rather than significant masses. These changes are indistinguishable from normal bowel function and tumors are thus unrecognized. In PET/CT, the CT scanning is not entirely a conventional one, but used as a systemic scanning. It is therefore weaker in terms of local imaging than diagnostic CT. Hence, to facilitate the blinded review of the images and to ensure the objectivity of the CT classification results, CT findings were only classified into two categories: findings of significant space-occupying masses were rated as CT^+ while other findings, including suspected or possible masses or normal images, rated as CT^-.

The objective of this study was to look for clinically significant evidence to help predict the nature of a lesion (benign or malignant). It was thus not practically significant to merely compare malignant lesion rates across different categories. Because there might be huge numerical difference in the malignant lesion rates across certain categories, these categories had consistent significance in predicting the nature of the lesions. Examples included the segmented/CT^+, diffuse/CT^-, and segmented/CT^- categories. There were huge numerical differences in the malignant lesion rates across these categories (100%, 0, and 2.9%, respectively), but all these categories provided highly probable predictions on the nature of the lesion. Segmented/CT^+ signaled a high probability of malignant lesions, while diffuse/CT^- and segmented/CT^- lesions were most probably nonmalignant. That is, when colorectal hypermetabolic lesions were of these three categories, they were consistently significant in terms of facilitating the prediction of the nature of the lesion. Therefore, we translated the malignant lesion rate into a nonmalignant lesion rate in this study. For diffuse/CT^- lesions, the malignant lesion rate of 0 was translated into a nonmalignant lesion rate of 100%. For segmented/CT^- lesions, the malignant lesion rate of 2.9% was translated into a nonmalignant lesion rate of 97.1%. Thereby, these three categories were incorporated as nonlocalized based on the significance they provided in predicting the nature of the lesion, regardless of the difference in their malignant lesion rates. As shown in the statistical analyses of this study, the malignant lesion rates for the localized/CT^+ and the localized/CT^- categories were 76.7% and 62.9%, respectively, without significant differences between them ($P = 0.229$). That is, the significance of the localized/CT^+ and the localized/CT^- categories were consistent in predicting the nature of the lesion, and they were therefore incorporated into one localized category. The statistical analysis in our study showed significant differences between the localized and nonlocalized categories ($P < 0.001$). That is, these two categories were different in their significance for predicting the nature of the lesions. When a colorectal hypermetabolic lesion was nonlocalized (segmented/CT^+, diffuse/CT^- and segmented/CT^-), we could make highly probable predictions; while for localized (localized/CT^+ and localized/CT^-) lesions, we could only make a less probable predictions.

In addition, by comparing the malignant lesion rates of the segmented/CT^+ and localized/CT^+ categories, it was revealed that, with comparably active FDG metabolism and significant anatomic and morphologic changes, the chance for malignant lesions increased with the length of the lesion. When the lesion affected more than 50% of a segment, the chance for a malignant lesion was almost 100%. When comparing the malignant lesion rates of localized/CT^+ and segmented/CT^+ categories, it was found that, when FDG metabolism was active but no significant anatomic or morphologic changes were seen, the more localized the lesions were, the higher the possibility for malignant lesions. When hypermetabolic lesions affected more

than 50% of a segment, the chance for a malignant lesion rapidly decreased. Almost all the diffuse colorectal hypermetabolic lesions were rated as diffuse/CT⁻ and the chance for malignant lesions was almost 0.

Colorectal cancer is one of the most common digestive tract tumors, with an ever-increasing incidence and mortality worldwide. It is estimated that the incidence and mortality has increased by 27% and 28%, respectively, in 2007[8]. The pathology of colorectal cancer is primarily adenocarcinoma. ^{18}F-FDG PET/CT is highly sensitive and specific in revealing colorectal cancers. Zhao et al.[4] performed PET exams on 94 patients with colon cancers and found that the sensitivity and specificity were 92% and 83.3%, respectively. Zhou et al.[5] conducted ^{18}F-FDG PET examinations in 36 old patients with colorectal cancer and found 34 localized FDG hypermetabolic lesions, with an accurate diagnostic rate for primary lesion of 94.4%. Cohade et al.[9] found in their study that PET/CT could further improve the accuracy of colon cancer staging or restaging from 78% to 89%. Among the 50 malignant lesions in our study, a total of 44 colorectal cancers were identified, with 22 colon cancers (primarily in the sigmoid and ascending colon) and 22 rectal cancers, that is, bowel cancers accounted for 88.0%. Lymphoma is another common malignant tumor in the colon and rectum. The pathology is mostly mucosa-associated lymphoid tissue (MALT) lymphoma and DLBCL; it is often seen in the rectum and cecum. In this study, we identified five lymphomas in all, with three in ileocecus, one in ascending colon near the hepatic flexure and another in the rectum. The pathology was DLBCL in all of these lymphomas, with an incidence of 10.0%. Moreover, we also identified one malignant melanoma in the rectum, with a SUV_{max} of around 14.7 and an incidence of 2.0%. When diagnosing colorectal hypermetabolic lesions, we can make more accurate predictions on the nature of the lesions by relating to the incidence and common sites of various tumors.

In conclusion, when diagnosing colorectal hypermetabolic lesions in PET/CT, we must incorporate the information provided by both PET and CT. Distribution of the metabolic lesions, as well as anatomic and morphologic changes, should be taken into consideration. In addition, incidence and frequent sites for the various malignant colorectal tumors should also be incorporated. Based on such a comprehensive analysis, a correct diagnosis should not be out of reach. In particular, for localized hypermetabolic lesions without tangible CT lesions, uninformed determinations of the nature of the lesion should be avoided; the diagnosis should be made in relation to the relevant clinical information and patient history.

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