

Limited Identification of Dual-time-point Positron Emission Tomography/Computed Tomography in Advanced Colorectal Neoplasms

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Abstract

Objective We investigated whether dual-time-point 18-Fluorodeoxyglucose (¹⁸FDG) positron emission tomography/computed tomography (PET/CT) could improve the positive predictive value for detecting advanced colorectal neoplasms (cancer, adenoma ≥10 mm or adenoma with high-grade dysplasia).

Methods We retrospectively searched for consecutive patients with a known primary cancer, who had a colonic ¹⁸FDG uptake incidentally found by PET/CT, followed by colonoscopy between January 2013 and August 2014. The clinical characteristics including the maximum standardized uptake value (SUVmax) were compared between advanced colorectal neoplasms and non-advanced lesions.

Results Forty-eight patients had 51 foci with an incidental focal colorectal uptake of ¹⁸FDG. Among these 51 foci, 28 foci were judged as being advanced neoplasms, whereas 23 foci identified as non-advanced lesions. Four cases were missed by PET/CT: two laterally spreading tumors (LSTs) with intramucosal cancer and two severe adenomas (<10 mm). The positive predictive value for the detection of advanced neoplasms was 55%. The per-spot performance of PET/CT showed that SUVmax was significantly higher in advanced neoplasms than in non-advanced lesions for the early-phase (10.1±4.9 vs. 6.5±3.2, p=0.029) and the delayed-phase (12.0±6.0 vs. 7.4±4.0, p=0.022). However, more importantly, there was a significant overlap of the SUVmax and no significant difference was found in the retention index (19.2±20.1 vs. 16.6±29.4, p=0.767).

Conclusion Dual-time-point PET/CT was found to have limited impact for identifying advanced colorectal neoplasms in spite of its high sensitivity and it might therefore not be able to identify either LSTs or small advanced neoplasms.

Key words: dual-time-point PET/CT, colonoscopy, advanced colorectal neoplasms

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Introduction

¹⁸Fluorodeoxyglucose (¹⁸FDG) positron emission tomography/computed tomography (PET/CT) is now recognized as a powerful evaluation modality in clinical oncology for tumor characterization, staging, restaging, surveillance and therapy

monitoring (1). A number of studies have shown PET/CT to be highly sensitive (range, 71-90%) for the detection of primary colonic neoplasms (2-5). The specificity of PET/CT in the detection of colorectal neoplasms, however, is limited due to its high false-positive rate including the physiologic uptake as well as inflammatory causes. One solution to resolve this disadvantage of PET/CT is thought to exclude the

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patterns of the physiologic bowel uptake such as the diffuse and heterogeneous uptake of ^{18}F FDG (6). Regarding the focal uptake, further evaluation with colonoscopy is recommended to exclude any underlying lesions (7, 8). Another solution might be to use dual-time-point imaging by PET/CT as some investigators have reported that they could differentiate benign from malignant lesions in a few types of cancers (9-11). This phenomenon may be related to the increased glucose consumption in cancer cells which need more energy to proliferate than normal cells and inflammatory cells, and thus it takes longer for the levels of ^{18}F FDG to plateau in cancer cells. Therefore, ^{18}F FDG accumulates more gradually in malignant lesions from the early-phase to the delayed-phase. Moreover, the relative change in the maximum standardized uptake value (SUVmax) between early- and delayed-time-point images, which is called the retention index (RI), has been used as the preferred indicator of malignancy (12). There is currently no consensus in regard to whether colorectal lesions should be imaged by dual-time-point imaging to improve the diagnostic accuracy.

The present retrospective study focused on colonic advanced neoplasms including advanced adenomas, which are thought to be high-risk precancerous lesions (13) and, therefore, the main target lesions, as colorectal cancer mortality can be reduced by the removal of these advanced adenomas (14). The primary endpoint in this study was to determine whether dual-time-point imaging could play a role in reducing false-positive PET/CT findings for the detection of advanced colorectal neoplasms, while the secondary endpoint was to identify the potential source of such false-negative PET/CT findings.

Materials and Methods

Patients

Electronic ^{18}F FDG PET/CT and colonoscopy databases were retrospectively searched to identify consecutive patients in whom the colonic ^{18}F FDG uptake was incidentally found and who then underwent colonoscopy between January 2013 and August 2014. The following data were retrieved from their medical records: Demographics, medical history, indications for performing PET/CT, the results of PET/CT, endoscopic findings including location, size, and the type of the polyp, and the histopathological results. The colon was divided into six segments in the PET/CT images and colonoscopic findings: proximal (cecum, ascending, transverse), distal (descending, sigmoid, rectum). Polyp type was classified by each endoscopist, basically according to the Paris endoscopic classification criteria (15) and, we included Isp, of which base is narrow like that of Ip, in the Ip group, because the Paris classification has no category for Isp, and LST, which is 10 mm or greater in size, superficial, and elevated like IIa, was included in IIa classification based on the Paris classification (15). An advanced neoplasm was defined as the presence of a cancer, an adenoma measuring 10 mm

or greater in diameter, or histological evidence of high-grade dysplasia.

The Institutional Review Board of Keio University Hospital approved this retrospective study and the requirement to obtain informed consent was waived (IRB No. 20140324).

PET/CT imaging

PET/CT was performed at Keio University Hospital, using a Biograph mCT system (Siemens Medical Solutions, Knoxville, TN, USA). All patients fasted for at least 6 hours before examination and the blood glucose level was measured before the injection of ^{18}F FDG. The patients were administered 3.7 MBq/kg ^{18}F FDG and underwent scanning 60 minutes thereafter in all 48 patients, and 120 minutes thereafter in 33 patients as the delayed-phase. If the images in the early-phase were considered to have a focal uptake, then a delayed-phase study was conducted, regardless of whether the radiologists were present or not. The low-dose spiral CT scan was performed for the whole body, followed by a three-dimensional PET emission scan with an acquisition time of 2 minutes for each bed position. At 2 hours after FDG injection, the conventional delayed emission scan for the whole abdomen was started with the same scan time for each bed position, after repositioning and additional CT scanning. Data were transferred to an AZE workstation (AZE, Tokyo, Japan). After all PET/CT images were subjected to visual and semi-quantitative analyses by the radiologists, they were then further reviewed by the supervising radiologist (K. M.), who made the final decision, after conferring with each other regarding the coronal, sagittal, and transverse images to achieve a consensus interpretation, if the event of any discrepancy in interpretation. The result of early-phase scanning of PET/CT was judged as being PET/CT positive, if it could detect an abnormal focal ^{18}F FDG uptake with a higher intensity than the normal liver parenchyma. All the other results were judged as being PET/CT negative. The FDG uptake pattern (small localized, large irregular localized, short segmental, and long segmental) in early images, and the FDG uptake position (moved or unmoved) in delayed images of 33 foci were specified by the radiologists, according to the classification of Minamimoto et al (16). The SUVmax, the ratio of uptake in a region of interest to average the whole body uptake, was also determined in the early- and delayed-phases. Using the SUVmax, we calculated the increasing rate (the retention index) (17) of the bowel ^{18}F FDG uptake in each group as follows: the Retention Index = {SUVmax (delayed image) - SUVmax (early image)} / SUVmax (early image) \times 100(%).

Interpretation of PET/CT and colonoscopy/histology results

The matching of the lesion location between the PET/CT and colonoscopy results was made only with the lesion location from the records of each report by the authors not involved in the examinations. The PET/CT findings were classified based on the colonoscopy findings and histology re-

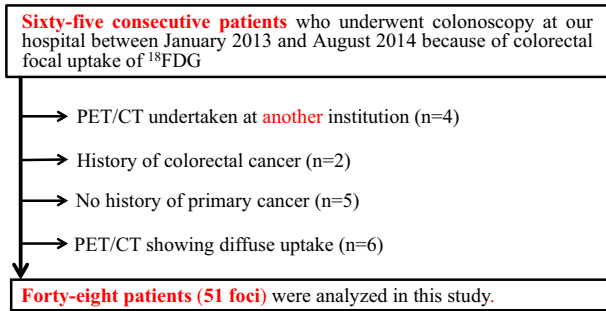


Figure 1. The patient selection process. The electronic FDG-PET/CT and colonoscopy databases were retrospectively searched to identify consecutive patients in whom the colonic FDG uptake was incidentally found and who then underwent colonoscopy between January 2013 and August 2014. Overall, 51 foci with an incidental colonic focal uptake of ¹⁸FDG were found in 48 patients after excluding 17 patients. ¹⁸FDG: 18-fluorodeoxyglucose, PET/CT: positron emission tomography/computed tomography

sults as described hereafter. A true positive finding was defined as a patient with a PET/CT positive finding who was identified with a histologically confirmed advanced neoplasm in the same colonic segment, or in the adjacent anatomical segment during endoscopy. A false positive finding was defined as a patient with a PET/CT positive finding who was not confirmed to have an advanced neoplasm in the corresponding segment.

Statistical analyses

Statistical differences between the subgroups were determined using the Mann-Whitney U test for continuous data and the chi-square test for categorical data. The positive predictive value was also calculated. All statistical analyses were performed by using the SPSS software program (SPSS version 21; SPSS, Tokyo, Japan). The mean values were expressed with SD. Statistical significance was considered to exist at $p < 0.05$.

Results

Sixty-five consecutive patients with a focal ¹⁸FDG uptake underwent colonoscopy within three months (5-92 days, Ave. 35 days) at our hospital between January 2013 and August 2014. Seventeen patients were excluded, including 4 who underwent PET/CT at other institutions, 2 with a history of colorectal cancer, 5 who had no history of primary cancer and 6 with a diffuse uptake of ¹⁸FDG, which was suggestive of a physiologic uptake. Because the five patients with no history of primary cancer were obviously younger, they were excluded to appropriately arrange the patients for the statistical comparison. The indications for PET/CT were oncologic staging or surveillance in all of the patients. Overall, 51 foci of the ¹⁸FDG uptake were found in 48 patients (Fig. 1). The patient characteristics for PET/CT are listed in Table 1. Thirty-three patients, among the 48, were male and

Table 1. Background of 48 Patients with Focal Colonic ¹⁸FDG Uptake on PET/CT.

Primary cancer	Patients, n (%)
Males: 33; Females: 15 Age: 47-91 years old (Average: 70.0 years)	
Lung cancer	14 (30)
Lymphoma	6 (13)
Oral cavity cancer	6 (13)
Breast cancer	4 (8)
Esophageal cancer	4 (8)
Gastric cancer	3 (6)
Pancreatic cancer	2 (4)
Endometrial cancer	2 (4)
Bone cancer	2 (4)
Other (thyroid cancer, renal cell cancer, prostate cancer, nasopharyngeal cancer, myeloma)	5 (10)

the mean age was 70 (range, 47-91) years old.

The colonoscopic findings were normal in 10 patients (21%) and endoscopic abnormalities were found in 38 patients (79%). Among these 51 foci, except for 10 foci which were confirmed to be normal, 41 foci had colonoscopic abnormal findings; 14 were cancers, comprising 9 early cancers, 1 lymphoma, 16 adenomatous polyps including 13 severe adenomas, and 3 non-neoplastic polyps including a hyperplastic polyp. As a result, 28 foci were judged as being advanced neoplasms, whereas 23 foci were judged as being non-advanced lesions. On a per-polypoid basis including early cancers, 22 (early cancers plus severe adenomas) and 6 polypoid lesions (moderate adenomas plus non-neoplastic polyps) were thought to be advanced and non-advanced lesions, respectively (Table 2). Whereas the PET/CT positive lesions included 28 true positive lesions and 23 false positive lesions, 4 advanced neoplasms were missed by PET/CT (PET/CT negative): 2 cases of laterally spreading tumors (LST) measuring 30 mm or 15 mm in diameter with intramucosal cancer; 2 cases of Is type severe adenoma measuring less than 10 mm in size (Table 3, 4). Therefore, the positive predictive value for the detection of advanced neoplasms by PET/CT was 55%.

At the patient level (n=48), the mean age for the patients with advanced neoplasms (n=28) was older than that for those with non-advanced lesions (n=20) (71.9 ± 9.1 vs. 66.5 ± 8.9 , $p = 0.048$). At the spot level (n=51), the mean SUVmax in advanced neoplasms (n=28) was higher than that in non-advanced lesions (n=23) (9.2 ± 4.5 vs. 6.4 ± 2.9 , $p = 0.011$) (Table 4).

At the polypoid level, 17 (77%) among a total of 22 PET/CT positive advanced neoplasms measured 10 mm or greater in size, and 14 (64%) were pedunculated type. On the contrary, 2 (50%) out of 4 PET/CT negative advanced neoplasms measured 10 mm or greater in size and no (0%) pedunculated type existed (Table 4).

In this study, dual-time-point PET/CT was performed in 33 patients with 20 advanced neoplasms and 13 non-

Table 2. Colonoscopy and Histology Results in 51 Foci with Focal ¹⁸F₁₈FDG Uptake on PET/CT.

	Advanced (n=28)	Non-advanced (n=23)
Neoplastic		
Lymphoma	1	
Advanced cancer	5	
Early cancer	9	
Adenoma (severe)	13	
(moderate)		3
(mild)		0
Non-neoplastic		
Polyp (hyperplastic, hamartomatous)		3
Colitis, erosion		2
Diverticulum		2
Hemorrhoid, mucosal prolapse syndrome		3
Normal colon		10

Table 3. Correlation between PET/CT and Colonoscopy/histology Results among 48 Patients.

	Colonoscopy/histology results	
	Advanced	Non-advanced
PET/CT-positive	28	23
PET/CT-negative	4	

advanced lesions. Whereas a large number of small localized uptake patterns were observed in the early images of both lesions, 2 of 5 advanced cancers and 1 lymphoma had a large irregular uptake patterns. Two of the 13 non-advanced lesions were judged to have a change of position (moved) in the delayed images. As shown in Fig. 2, the mean SUV_{max} for early-phase was, likewise, higher in advanced neoplasms than in non-advanced lesions (10.1±4.9 vs. 6.5±3.2, p=0.029). In addition, it was higher for the delayed-phase in advanced neoplasms than in non-advanced lesions (12.0±6.0 vs. 7.4±4.0, p=0.022). However, more importantly, a significant overlap of the SUV_{max} was found between these two groups. Additionally, there was no significant difference between these two groups in the RI (19.2±20.1 vs. 16.6±29.4, p=0.767) (Fig. 3).

Discussion

The 55% of Positive Predictive Value in this retrospective study is closely compatible to the 45-78% of PPV reported in previous studies for patients with primary cancer, who were recognized as having incidental advanced colorectal neoplasms on PET/CT (2-5). The SUV_{max}, a semiquantitative measurement, has been widely used to differentiate malignant from benign neoplasms on PET/CT (18, 19). However, a high SUV_{max} may also be found in various benign conditions because ¹⁸F₁₈FDG is not a neoplasm-specific substance. Indeed, Treglia et al. (20) showed that the SUV_{max} alone should not be used to differentiate between a malignant, premalignant and benign incidental colonic focal up-

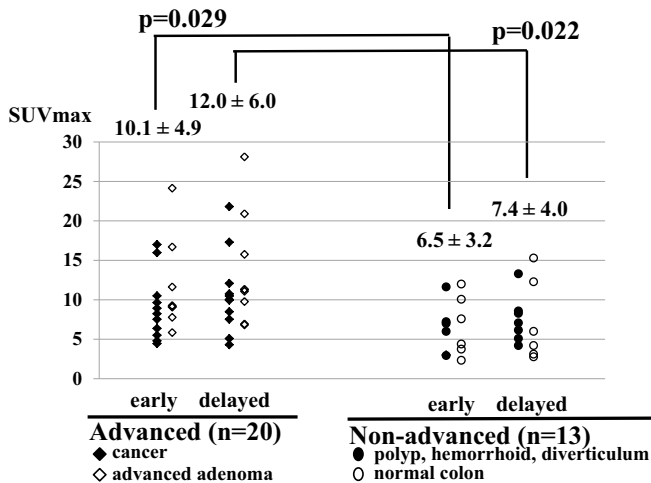
take because a significant overlap of the SUV_{max} was found between these groups. Our results are similar to those of their report in this point, although our data clearly demonstrate that advanced neoplasms had a significantly higher mean SUV_{max}, compared with that in non-advanced lesions.

To reduce the number of false-positive cases, resulting from focal ¹⁸F₁₈FDG accumulation, not only in benign lesions, such as inflammatory lesions, but also in the normal colon as judged by colonoscopy, dual-time-point PET/CT has been performed for a few types of cancers. Some reports display that the use of delayed PET/CT led to a reduction in the number of false-positive findings and increased the accuracy in the detection of cancer (9-11), suggesting that this procedure may be helpful in the management of the colorectal foci seen on initial PET/CT. However, our results do not correlate with these reports, as there was a significant overlap in the SUV_{max} in both the early- and delayed-phase and no significant difference was observed in the retention index between the two groups. The use of stricter criteria, such as the SUV_{max} plus the retention index, and/or changes in the position of delayed images might possibly increase PPV to some extent.

When comparing PET/CT positive advanced polypoid neoplasms to those PET/CT negative advanced polypoid neoplasms, most of the former measured 10 mm or greater in size and none of the latter showed a pedunculated in type. These results seem to correlate with previous studies which show the detection rates of PET/CT to positively correlate with the size of advanced colorectal neoplasms (3, 21) and that pedunculated lesions are more easily detected than non-pedunculated ones by PET/CT (2, 3). Kaku et al. (22) reported that LSTs, approximately 80% of which were located in the proximal colon (on the right side of the colon), accounted for 17.2% among the advanced neoplasms found in a large average-risk population undergoing screening colonoscopy. Interestingly, we detected 6 LSTs with intramucosal cancer (14-40 mm in diameter), all of which were

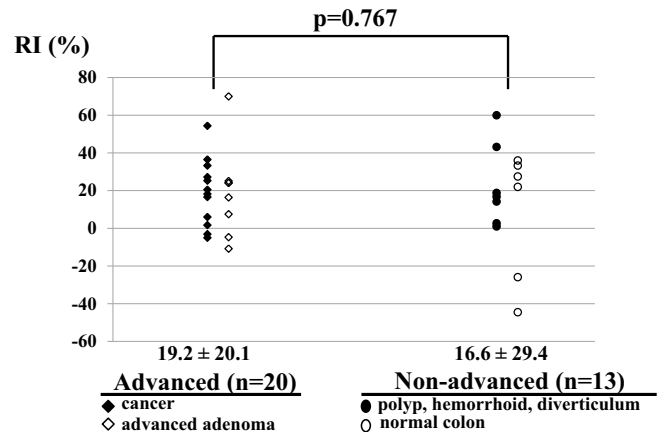
Table 4. Comparison of Clinical Characteristics between Advanced with PET/CT-positive and Non-advanced with PET/CT-positive, or Advanced with PET/CT-negative.

	PET/CT positive		p value ^a	PET/CT negative		p value ^a
	Advanced	Non-advanced		Advanced		
At patient level	(n=28)	(n=20)				
Sex (Male, Female)	19, 9	14, 6	0.875			
Age (year)	71.9 ± 9.1 ^b	66.5 ± 8.9	0.048			
At polypoid level	(n=22)	(n=6)		(n=4)		
Size (mm) (<10, 10≤)	5, 17	4, 2	0.064	2, 2	0.287	
Type [pedunculated (Ip, Isp), non-pedunculated (Is, IIa)]	14, 8	2, 4	0.194	0, 4	0.033	
At spot level	(n=28)	(n=23)				
Location (Proximal ^c , Distal ^d)	15, 13	11, 12	0.450			
SUVmax (early phase)	9.2 ± 4.5 ^b	6.4 ± 2.9	0.011			

^a In comparison to advanced with PET/CT-positive.^b Mean ± standard deviation^c Cecum to Transverse^d Descending to Rectum**Figure 2.** Comparison of the SUVmax between advanced and non-advanced lesions in both the early- and delayed-phase. The mean SUVmax for the early-phase and delayed-phase, respectively, was statistically analyzed using the Mann-Whitney U test. SUVmax: the maximum standardized uptake value

located in the proximal colon by colonoscopy, but 2 LSTs (15, 32 mm) could not be found by PET/CT alone. These findings should thus be carefully taken into consideration when interpreting PET/CT image, as LST, a non-pedunculated polypoid lesion, might be missed by PET/CT, even though they are normally sufficiently large in size.

Peng et al. (23) indicated that a false positive ¹⁸F-DG uptake is more commonly observed in the right colon. Our study did not demonstrate any statistical difference regarding the colonic location between the two groups, but 8 out of 10 with PET/CT positive normal colons according to colonoscopy were located in the right colon. Additionally, 4 out of 6 normal colons with dual-time-point imaging showed an increased ¹⁸F-DG uptake in the delayed-phase. A physiological

**Figure 3.** Comparison of the RI between advanced and non-advanced lesions. RI: retention index

focal uptake has been described within the right lower quadrant corresponding to the cecum and right colon, and it is thought to be related to the high concentration of glucose-metabolizing lymphatic cells in this area (24). Moreover, a physiological uptake in more than half of the normal colon areas increased significantly from the early to the delayed phase in dual-time-point PET/CT imaging (25). These reports, along with the findings of our study, collectively, suggest that dual-time-point PET/CT might not help to differentiate a malignant pathologic uptake from a physiologic uptake, especially in neoplasms located in the right colon.

The present study is associated with some limitations. The present study is limited due to the relatively small number of samples obtained from a single tertiary referral hospital and by its retrospective design. Additionally, a delayed PET scan could not be conducted for all of the subjects in the clinical practice and the comparisons between early PET and selected delayed PET might therefore have some bias. Secondly, we may have missed some colonic neoplasms by

colonoscopy, which is thought to be the gold standard diagnostic modality, and we also could not always determine the polyp type according to the Paris endoscopic classification criteria (15) in this retrospective study. Thirdly, PET/CT has a higher anatomical resolution than PET, but some lesions confirmed by colonoscopy may not perfectly match those detected by PET/CT. PET/CT colonography may serve as an alternate to PET/CT because it can create endoluminal images and more accurately localize lesions according to the findings of previous reports (26, 27).

In conclusion, giving the high sensitivity for detecting advanced colorectal neoplasms by PET/CT, whole colon evaluation by colonoscopy is required for patients with primary cancers, who have an incidental focal uptake of ¹⁸F-FDG in the colorectum. However, dual-time-point imaging by PET/CT may not be a more reliable tool for identifying patients needing colonoscopic examinations than initial imaging alone, since it might fail to detect LSTs as well as small advanced neoplasms.

The authors state that they have no Conflict of Interest (COI).

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