ORIGINAL ARTICLE

Recent Chemotherapy Reduces the Maximum-Standardized Uptake Value of ^{18}F-Fluoro-Deoxyglucose Positron Emission Tomography in Colorectal Cancer

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Background/Aims: The aim of this study was to evaluate the influence of recent chemotherapy on the patterns of the maximum-standardized uptake value (M-SUV) and sensitivity of ^{18}F-fluoro-deoxyglucose positron emission tomography/ computed tomography (^{18}F-FDG-PET/CT) in colorectal cancer. **Methods:** We retrospectively analyzed the FDG-PET/CT of 509 patients who underwent surgery for colorectal cancer. Subgroup analysis was performed according to chemotherapy status; 401 patients were not treated with chemotherapy and 108 patients were treated with chemotherapy within 6 months prior to surgery. Pathologic analysis of the surgical specimen was used as the gold standard. **Results:** The M-SUV was significantly lower in patients treated with chemotherapy than in those not treated with chemotherapy in pathologically confirmed same stages of disease. The difference in the sensitivity of the M-SUV according to chemotherapy status was greatest using a cutoff M-SUV value of 6.4 (p<0.001). The longest diameter of the primary tumor was the most important factor that correlated with M-SUV of the primary tumor irrespective of the chemotherapy effect (p<0.001). The M-SUV of the primary tumor was not an independent predictor of lymph node metastasis in colorectal cancer. **Conclusions:** The results indicate that the M-SUV of FDG-PET/CT should be interpreted in the context of concurrent chemotherapy. **(Gut Liver 2014;8:254-264)**

Key Words: Drug therapy; FDG-PET/CT; Colorectal neoplasms

INTRODUCTION

Colorectal cancer is a leading cause of cancer morbidity and mortality around the world. In 2012, approximately 140,000 people were diagnosed and 50,000 people died of cancer of the colon and rectum in the United States.[1] To determine the appropriate therapies, noninvasive imaging techniques are essential to accurately identify the extent of disease involvement.

[18]F-fluoro-deoxyglucose positron emission tomography/ computed tomography (^{18}F-FDG-PET/CT) evaluates the metabolic activity in tissue and can recognize tumor cells based on their accelerated glucose metabolism. Previous studies have reported that FDG-PET/CT as an indicator of treatment response has significant predictive and/or prognostic values in various cancers, such as esophageal cancer, gastric cancer,[2] head and neck squamous cell cancer,[3] nonsmall cell lung cancer,[4] breast cancer,[5] and even rectal cancer.[6-10] In a prospective cohort study, de Geus-Oei et al.[11] have reported that the change in the maximum-standardized uptake value (M-SUV) in FDG-PET/CT is a significant predictor for overall survival and progression-free survival in colorectal cancers.

Recent studies have reported that the M-SUV cutoff value for the detection of colorectal cancers is between 2.5 and 5.[12-14] Luboldt et al.[14] have reported that among 84 patients who underwent FDG-PET/CT and colonoscopy, the use of an M-SUV cutoff value of 5 resulted in a sensitivity and specificity of 89% and 93%, respectively, for the diagnosis of colorectal neoplasms. Rosen et al.[12] have used an SUV cutoff of 2.5 with reported sensitivity of 84% and specificity of 60% and have stated that elevated SUV values are not always indicative of a malignant

process. In the assessment of response after neoadjuvant or adjuvant chemotherapy, the change in the M-SUV in FDG-PET/CT scans has been suggested as a marker to determine whether the tumor responded to the chemotherapy.[15]

Although the M-SUV in FDG-PET/CT has been suggested to be an important indicator of treatment response, Glazer *et al.* suggested that PET/CT after chemotherapy reduce the sensitivity for evaluation of colorectal hepatic metastases.[16] However, a few studies focusing on primary site of colorectal cancer have confirmed the change in the M-SUV in FDG-PET/CT after chemotherapy in relation to the gold standard test providing the pathological stage of disease. Because chemotherapy could decrease the metabolic activity of tumors, we postulated that the M-SUV itself could be adversely affected by chemotherapy. The purpose of our study was to evaluate the influence of chemotherapy on the characteristics of the M-SUV patterns of FDG-PET/CT in colorectal cancer patients treated with chemotherapy compared to the M-SUV patterns in those not treated with chemotherapy.

MATERIALS AND METHODS

1. Study population

The medical records of 556 patients diagnosed with colorectal cancer who underwent FDG-PET/CT and surgery between March 2002 and June 2011 were retrospectively reviewed for demographic data, medical history, and chemotherapy status. Inclusion criteria were the patients diagnosed with colorectal cancers who received FDG-PET/CT followed by surgery within 1 month. Total population was divided into two groups: patients treated with chemotherapy within 6 months before FDG-PET/CT scan and those not treated with chemotherapy. The patients not treated with chemotherapy were newly diagnosed with colorectal cancers and first treatment for them was surgery for radical excision. FDG-PET/CT was performed before the surgery. In patients treated with chemotherapy, we enrolled patients when they underwent chemotherapy within 6 months before FDG-PET/CT scan. The patients treated with chemotherapy consisted of patients who received the neoadjuvant chemotherapy/chemoradiation, patients who underwent adjuvant chemotherapy after diagnosed with colorectal cancers, and patients who newly diagnosed with colorectal carcinoma after diagnosed with other cancers as shown in Table 1. In total of 556 patients, 47 patients with diabetes mellitus, hyperthyroidism, and active infection were excluded.

FDG-PET/CT reports were reviewed to identify the M-SUV, the highest value among the SUVs of primary tumors in the colorectum and the lymph nodes around the tumors. Pathology reports were reviewed to obtain findings and match them to the FDG-PET/CT findings. Tumor staging was classified according to the tumor, node, metastasis classification of the American Joint Committee on Cancer (AJCC) 7th edition, and tumor grading was classified according to the AJCC recommendations.

Table 1. Brief History of Chemotherapy in Patients Treated with Recent Chemotherapy

Patient group (n=108)	Mean time to FDG-PET/CT, mo	Chemotherapy regimen* (n)	Diagnosis of cancer before colorectal cancer
Patients receiving neoadjuvant chemotherapy (n=11)	1.6	FOLFOX (6)	-
	1	FOLFIRI (2)	-
	1	XELOX (2)	-
	1	FOLFOX plus Avastin (1)	-
Patients receiving neoadjuvant chemoradiation (n=41)	2	5-Flurouracil (34)	-
	2	FOLFOX (3)	-
	2	Capecitabine (2)	-
	1	XELOX (1)	-
	4	FL (1)	-
Patients receiving adjuvant chemotherapy (n=52)	4.2	FOLFOX (22)	-
	5	FL (18)	-
	2.6	FOLFIRI (9)	-
	5.5	Capecitabine (3)	-
Patients diagnosed with colon cancer after chemotherapy for other cancers (n=4)	6	CMF (1)	Breast cancer
	6	NP (1)	Lung cancer
	6	TS-1 (1)	Gastric cancer
	6	CVP (1)	Gastric MALToma

FDG-PET, fluoro-deoxyglucose positron emission tomography; CT, computed tomography; FOLFOX, 5-fluorouracil, leucovorin (folinic acid), and oxaliplatin; FOLFIRI, 5-fluorouracin, leucovorin (folinic acid), and irinotecan; XELOX, capecitabine and oxaliplatin; FL, 5-fluorouracil and leucovorin (folinic acid); CMF, cyclophophamide, methotrexate, and 5-fluorouracil; NP, cisplatin and vinorelbine; CVP, cyclophophamide, vincristine, and prednisone; MALToma, mucosa-associated lymphoid tissue lymphoma.
*Chemotherapy regimen as defined below.

Growth findings in each gross pathologic specimen were analyzed according to Japanese classification colorectal carcinoma: four categories of polypoid, ulcerofungating, ulceroinfiltrative, and flat types.[17,18]

Recent chemotherapy is defined as chemotherapy administered within 6 months prior to surgery. Among the 509 patients, 401 patients were not treated with recent chemotherapy and 108 patients were treated with recent chemotherapy before surgery. This study was approved by the Seoul National University Hospital and Boramae Medical Center Institutional Review Board.

2. FDG-PET/CT imaging protocol and image interpretation

^{18}F-FDG PET/CT was performed using dedicated PET/CT scanners (Gemini, Gemini TF; Philips, Cleveland, OH, USA) (Biograph 40, Biograph 64; Siemens, Knoxville, TN, USA). Patients were fasted for at least 6 hours prior to PET/CT scanning. ^{18}F-FDG

(5.18 MBq/kg) was administered intravenously, and 125 mL of a barium sulfate solution (1.5% weight-volume barium sulfate suspension, EZCT; Taejoon Pharm, Seoul, Korea) was administered orally to achieve optimized image quality for the evaluation of the intestines. Immediately before scanning, blood sugar levels were checked to confirm blood glucose levels of <140 mg/kg. At 60 minutes after FDG injection, a CT scan was obtained for attenuation correction, and an emission scan was then obtained from the skull base to the proximal thigh. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization) and transferred to a dedicated work station for further analysis.

To evaluate the ^{18}F-FDG uptake of a lesion, the standardized uptake value (SUV) was calculated as follows: SUV=[FDG activity concentration (Bq/mL)]×[total lean body weight (kg)]/[injected FDG activity (Bq)]. A region of interest was placed on the lesion, and the maximum SUV was measured using a vendor-provided program.

A physiological finding was defined by an SUV of 2.5 and 5.0 based on institutional experience and the literature.[12,14] We defined a true-positive PET/CT finding as a focus of FDG avidity with an SUV ≥5.[14]

3. Statistical analyses

Categorical variables were described as numbers and percentages and compared between groups using the chi-square test or Fisher exact test. Continuous variables were expressed as the mean±SD and compared by the t-test. Two-way analysis of variance was performed to test the difference in the M-SUV of the primary tumor in each AJCC stage between patients treated and not treated with chemotherapy.

We conducted a linear regression to assess which variables were related to the M-SUV of the primary tumor (or M-SUV of the lymph node) in each group. First, a simple linear regression model was performed. Then, statistically significant variables (p<0.05) were included in the multiple linear regression model. The final model was found using a stepwise selection procedure.

To evaluate whether the M-SUV in primary tumor could predict lymph node metastasis or not, the area under the curve (AUC) was calculated using receiver operating characteristic curves of the M-SUV of the primary tumor for predicting the lymph node metastasis. In addition, to determine whether chemotherapy caused reduced sensitivity, the differences in the sensitivities between the two groups were examined using the chi-square test or Fisher exact test and a variety of cutoff values for the M-SUV.

p-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 20 (IBM Co., Armonk, NY, USA) and R version 2.15.1 (http://www.r-project.org).

RESULTS

1. Baseline patient characteristics

A total of 509 consecutive patients with colorectal cancer between March 2002 and June 2011 underwent FDG-PET/CT followed by surgery within 1 month. Of the 509 patients evaluated, 401 patients did not receive chemotherapy. The other 108 patients underwent chemotherapy prior to surgery (Table 2). As shown in Table 2, mean age of patients not treated with recent chemotherapy was 66 years old, which was significantly higher than that of patients treated with recent chemotherapy. There was no significant difference in sex of the patients. Also, pathologic findings were not different between two groups. The mean longest diameter of the tumor was 5.33 cm in patients not treated with recent chemotherapy, which was significantly larger than 3.43 cm in patients treated with recent chemotherapy. In patients treated with recent chemotherapy, primary tumor location was proximal colon in 12 (11.21%), distal colon in 18 (16.82%), and rectum in 70 (65/42%). The AJCC stages did not differ significantly between two groups. Particularly, depth of invasion was pathological T3 stage main in both groups, 65% of total population. In comparison of the metastasis rates, the rate in patients treated with recent chemotherapy showed negativity higher than in those not treated with recent chemotherapy: 55% versus 46% in negative rates of lymph node metastasis and 84% versus 75% in those of distant metastasis respectively.

Among 108 patients treated with chemotherapy, 11 patients received neoadjuvant chemotherapy and 41 patients underwent chemoradiation therapy. The patients treated with neoadjuvant chemotherapy or chemoradiation therapy had the surgery to removing the primary tumors in the colorectum. Fifty-two patients who were diagnosed with colorectal cancers have received adjuvant chemotherapy. FDG-PET/CT scan in these 52 patients was performed for response evaluation. Surgery was performed to resolve the complication of bleeding, mass obstruction, and perforation. Remaining four patients were diagnosed with newly colorectal cancer after received chemotherapy for cancers originating from organs other than colorectum. The mean duration between chemotherapy and FDG-PET/CT was 3.3 months (minimum, 1 month; maximum, 6 months) (Table 1).

2. Differences in the M-SUV in the same pathologic stage of colorectal cancer by chemotherapy

The mean M-SUV in the primary tumor was significantly lower in patients treated with chemotherapy compared with patients not treated with chemotherapy (7.64±5.64 vs 10.86±5.65, p<0.001) (Table 3). In each AJCC stage from 0 to IV, the M-SUV in patients not treated with chemotherapy was higher than that in patients treated with chemotherapy (p<0.001).

The mean M-SUV of AJCC stage II patients not treated with chemotherapy (11.47±5.70) was higher than that of AJCC stage II, III, and IV patients treated with chemotherapy (9.33±6.71,

Table 2. Baseline Patient Characteristics

Characteristic	Patients not treated with recent chemotherapy (n=401)	Patients treated with recent chemotherapy (n=108)	p-value
Age, yr	66.21±11.53	60.94±10.87	<0.001
Sex			0.513
Male	260 (64.84)	74 (68.22)	
Female	141 (35.16)	34 (31.78)	
Pathology			0.501
Adenocarcinoma	380 (94.76)	100 (92.59)	
Signet ring cell	2 (0.50)	1 (0.93)	
Mucinous	13 (3.24)	6 (5.56)	
Others*	6 (1.50)	1 (0.93)	
Longest diameter of tumor, cm	5.33±2.62	3.43±1.99	<0.001
Tumor location†			<0.001
Proximal colon	132 (33.17)	12 (11.21)	
Distal colon	146 (36.68)	18 (16.82)	
Rectum	117 (29.40)	70 (65.42)	
Others	6 (1.49)	8 (7.41)	
AJCC stage‡			0.222
0	6 (1.49)	1 (0.93)	
I	38 (9.47)	12 (11.11)	
II	118 (29.42)	43 (39.81)	
III	135 (33.41)	33 (30.55)	
IV	104 (25.18)	19 (17.59)	
Depth of invasion			0.641
pTis§	6 (1.5)	1 (0.96)	
pT1	19 (4.74)	4 (3.70)	
pT2	34 (8.48)	15 (13.89)	
pT3	262 (65.34)	68 (62.96)	
pT4	80 (19.95)	20 (18.51)	
Lymph node metastasis			0.115
Negative	183 (45.63)	59 (54.63)	
Positive	218 (54.37)	49 (45.37)	
Distant metastasis			0.039
Negative	300 (74.81)	91 (84.26)	
Positive	101 (25.19)	17 (15.74)	

Data are presented as mean±SD or number (%).
AJCC, American Joint Committee on Cancer.
*Other types of colon cancer include sarcoma, small cell carcinoma, large cell neuroendocrine carcinoma, and malignant melanoma; †Proximal colon, the region from the cecum to the transverse colon: distal colon, the region from the splenic flexure to the sigmoid colon; ‡AJCC 7th edition; §Tis, carcinoma *in situ*: intraepithelial or invasion of lamina propria.

6.95±4.68, and 8.54±4.63, respectively) (Table 3, Fig. 1A).

3. Difference in the M-SUV sensitivity according to chemotherapy status

The sensitivity of the M-SUV of the primary tumor was calculated based on the cutoff values of 2.5 and 5.0 reported in previous studies.[12,14] Using the cutoff value of 2.5 for the M-SUV of the primary tumor, the sensitivity in patients treated with recent chemotherapy was 87.96%, which was lower than the 96.76% sensitivity in patients not treated with recent chemotherapy (Table 4). The differences in the sensitivity between patients treated and not treated with chemotherapy decreased as the cutoff value was raised (Fig. 2). The difference in the M-SUV sensitivity according to chemotherapy status was greatest at the M-SUV cutoff value of 6.4 (p<0.001). When the M-SUV cutoff value was higher than 16, the sensitivity in patients who had undergone recent chemotherapy was not significantly different from that in patients who had not received chemotherapy.

4. The M-SUV and pathologic staging of colorectal cancer

The M-SUV in the primary tumor significantly correlated with the AJCC stage using a simple linear regression model (p<0.001) irrespective of receiving recent chemotherapy (Table 5). In both groups, the M-SUV in AJCC stages I to II changed from 7.32 to 10.93. The M-SUV did not significantly change between AJCC stage II and stage III (10.93±6.02 vs 10.51±5.4) (Table 3). Although marginal differences in the M-SUV were observed among AJCC stages, this variable was not included in the final multiple linear model with stepwise selection (Tables 5 and 6).

5. The M-SUV of the primary tumor in relation to clinicopathologic parameters

The M-SUVs of polypoid, ulceroinfiltrative, and ulcerofungating types[17,18] in patients treated with recent chemotherapy were lower than that those in patients not treated with recent chemotherapy (Table 7, Fig. 1B). The ulcerofungating primary tumor type among the growth types of the primary tumors displayed the highest M-SUV of 11.4, while the flat type displayed the lowest M-SUV of 0.8. In the ulceroinfiltrative type of the primary tumor, the M-SUV of 10.5 in patients not treated with recent chemotherapy was significantly different from 7.6 in patients treated with recent chemotherapy. The M-SUV in ulcerated tumors with ulceroinfiltrative and ulcerofungating types was higher than that in nonulcerated tumors with polypoid and flat types (Table 7).

Among tumor volume, the longest tumor diameter, growth type, AJCC stage, summation of SUVs of the lymph nodes, and the M-SUV of the lymph node in patients not treated with chemotherapy, the longest tumor diameter, growth type of the primary tumor, and the M-SUV in the lymph node showed strong associations with the M-SUV in the primary tumor in the multiple linear regression method (p<0.001) (Table 5). The corre-

Table 3. Differences in the Maximum-Standardized Uptake Value of the Primary Tumor in Pathologically Equivalent Stages according to Chemotherapy Status

	Total		Patients not treated with recent chemotherapy		Patients treated with recent chemotherapy		Differences, %	p-value
	No.	M-SUV	No.	M-SUV	No.	M-SUV		
Total	509	10.18±5.79	401	10.86±5.65	108	7.64±5.64	29.65	<0.001[†]
AJCC*								<0.001[‡]
0	7	6.14±7.45	6	7.17±7.61	1	0	100	
I	50	7.32±6.24	38	8.17±6.45	12	4.54±4.77	44.43	
II	161	10.93±6.02	118	11.47±5.70	43	9.33±6.71	18.65	
III	168	10.51±5.41	135	11.31±5.25	33	6.95±4.68	38.54	
IV	123	10.65±5.20	104	11.01±5.22	19	8.54±4.63	22.43	

Data are presented as mean±SD.
M-SUV, maximum-standardized uptake value; AJCC, American Joint Committee on Cancer.
*AJCC 7th edition; [†]p-value from t-test; [‡]p-value from two-way analysis of variance.
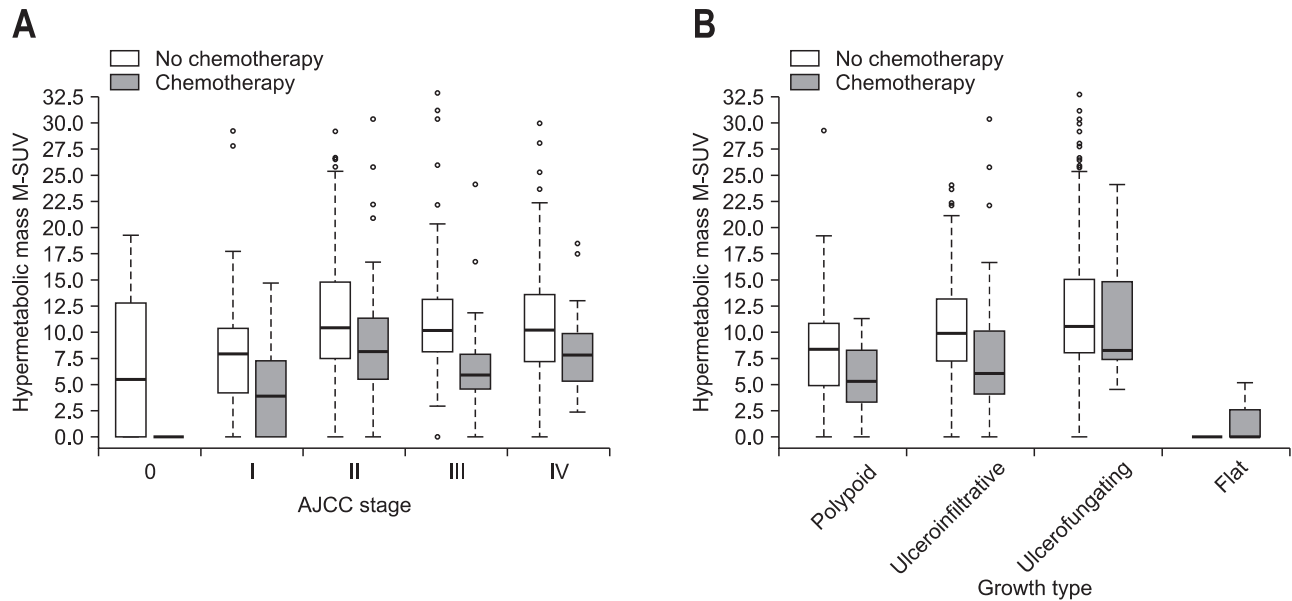
Fig. 1. Box and whisker plots of the maximum-standardized uptake value (M-SUV) in the primary tumor by chemotherapy status. The upper and lower end points of the whiskers represent the observed maximum and minimum, respectively. The upper and lower edges of the boxes represent the 75th and 25th percentiles, respectively. The line inside the box represents the median value. (A) Distribution of the M-SUV plotted against the American Joint Committee on Cancer (AJCC) 7th edition stage. (B) Distribution of the M-SUV plotted against growth type.

lation coefficient between the M-SUV and the longest diameter of the primary tumor was 0.372 (p<0.001).

In patients treated with chemotherapy, the longest diameter of the primary tumor showed a significant association with the M-SUV in the primary tumor in both simple and multiple linear regression models (p<0.001) (Table 5). The correlation coefficients between the M-SUV and the longest size of the primary tumor in patients treated with chemotherapy were not significantly different from those in patients not treated with chemotherapy (p=0.454) (Fig. 3).

6. Relationship between the M-SUV of the lymph nodes and clinicopathologic parameters

In patients not treated with chemotherapy, statistically significant factors in the multiple linear regression are three: polyp, total number of metaststic lymph nodes, and M-SUV of primary tumor (p<0.05). This sentence should be revised accordingly (Table 6). In patients treated with chemotherapy, only the total number of metastatic lymph nodes was significantly associated with the M-SUV of the lymph node in the multiple linear regression model.

Table 4. Reduced Sensitivity of the Maximum-Standardized Uptake Value according to the Cutoff Value in the Primary Tumor by Chemotherapy Status

Cutoff value	Patients not treated with recent chemotherapy	Patients treated with recent chemotherapy	p-value*
<2.5	13	13	
≥2.5	388	95	
Sensitivity at 2.5, %	96.76	87.96	<0.001
<5.0	35	37	
≥5.0	366	71	
Sensitivity at 5.0, %	91.27	65.74	<0.001

*p-value from the chi-square test.

### 7. Relationship between the M-SUV of the primary tumor and metastasis

In patients not treated with recent chemotherapy, the M-SUV in the primary tumor showed significantly associated with that in the lymph nodes in the multiple linear regression analysis (Tables 5 and 6). Regarding the predictability of the M-SUV in the primary tumor for lymph node metastasis, the primary tumor M-SUVs did not accurately predict lymph node metastasis by calculating AUC for lymph node metastasis: 0.540 (95% confidence interval, 0.482 to 0.598) (Fig. 4).

DISCUSSION

The predilection of cancer cells for accelerated glucose uptake and utilization is the biologic basis for FDG-PET imaging. Cancer cells with elevated expression of glucose transporter 1[19] or the glycolytic enzyme hexokinase[20] have been found to accumulate higher levels of FDG. Furthermore, conditions that alter host cell or tumor glucose metabolism have also been shown to alter the appearance of tumors on FDG-PET/CT, such as in patients with diabetes[21] or germ cell tumors with differentiation into a mature morphology.[22] We postulated that recent chemotherapy might also alter FDG uptake by altering tumor metabolism.

Most previous studies have shown that a change in the M-SUV is an important indicator of chemotherapy response.[6,8,9,11,23] However, whether the M-SUV changes after chemotherapy clearly reflect changes in the pathological stage may be questionable. In other words, the pathological stage after chemotherapy might not change quite as much as the FDG uptake. Previous studies have not provided data comparing the M-SUV in FDG-PET/CT after chemotherapy and the pathological stage, especially in primary site of colorectal cancer.

In the current study, the M-SUV of the primary tumor in patients treated with chemotherapy decreased to 30% compared to those not treated with chemotherapy, even though the patients
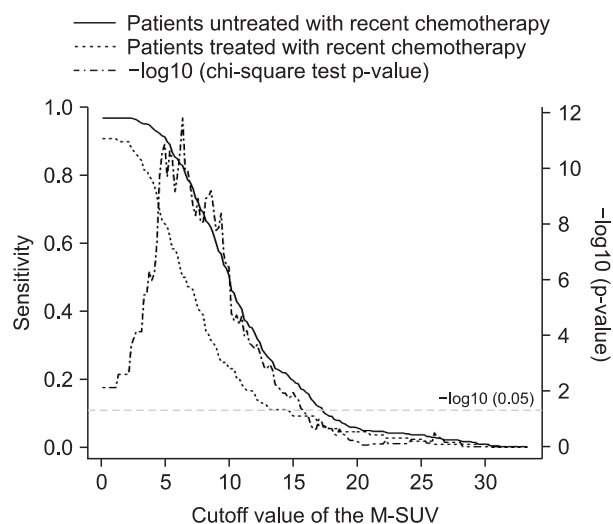
Fig. 2. Curves showing the change in sensitivity according to the cutoff value of the maximum-standardized uptake value (M-SUV) in the primary tumor by chemotherapy status.

had the same pathologically confirmed stages of colorectal cancer. The difference in the M-SUV sensitivity between the two groups was significant in the range of cutoff values between 0 and 16; the difference was greatest using the cutoff value of 6.4. In addition, the mean M-SUV of 8.17 observed in AJCC stage I patients not treated with chemotherapy was similar to that of 8.54 in AJCC stage IV patients treated with chemotherapy. The important implication of this decreased M-SUV level is that the sensitivity of FDG-PET/CT may decrease after recent chemotherapy and that cancer cell FDG uptake may be reduced after chemotherapy compared to the FDG uptake before chemotherapy. Restaging after chemotherapy based on FDG-PET/CT findings could be problematic.

The association patterns between the M-SUV and clinicopathologic parameters were influenced by recent chemotherapy in this study. In patients not treated with chemotherapy, the longest tumor diameter showed the closest association with the M-SUV of the primary tumor, followed by the pathologically measured tumor volume and the growth type of the tumor. The finding that larger-sized primary tumor showed higher M-SUVs supported the results of previous studies.[24] In patients treated with chemotherapy, only the longest tumor diameter showed a strong association with the M-SUV in colorectal cancer. The M-SUV in the primary tumor was strongly impacted by the tumor size and morphologic patterns of the primary tumor rather than the clinical cancer stages, differentiation, and carcinoembryonic antigen status, which are known to be the most important prognostic factors. Although the survival rates among the AJCC stage IIIC and IV patients were 44.3% and 8.1%, respectively,[25] the M-SUV of the primary tumor did not increase between stages III and IV.

In line with a previous study,[17] the M-SUVs in the polypoid and flat types of the growth types in gross surgical specimen

Table 5. Relationship between the Maximum-Standardized Uptake Value of the Primary Tumor and Clinicopathologic Parameters

Variable	Simple linear regression			Multiple linear regression		
	Estimate	F-statistic	p-value	Estimate	F-statistic	p-value
Patients not treated with chemotherapy						
Age	0.013	0.262	0.609			
Sex	-1.247	4.498	0.035	-1.622	5.458	0.020
CEA	-0.001	0.969	0.326			
Polyp	0.088	0.071	0.790			
Differentiation*		1.526	0.207			
Tumor volume	0.015	20.651	<0.001			
Longest diameter of tumor	0.711	48.774	<0.001	0.511	14.617	<0.001
Location†		0.145	0.930			
Growth type‡		6.794	<0.001		3.511	0.016
Total no. of metastatic lymph nodes	-0.003	0.005	0.942			
Distant metastasis	0.198	0.093	0.761			
AJCC stage§		3.358	0.010			
Summation of SUV of lymph nodes	0.296	12.689	<0.001			
M-SUV in lymph node	0.428	16.072	<0.001	0.305	6.960	0.009
Patients treated with chemotherapy						
Age	0.028	0.314	0.577			
Sex	0.063	0.003	0.957			
CEA	0.012	0.027	0.659			
Polyp	-5.240	1.557	0.217			
Differentiation*		1.520	0.224			
Tumor volume	0.045	4.641	0.034			
Longest diameter of tumor	0.920	12.482	<0.001	0.920	12.482	<0.001
Location†		0.509	0.677			
Growth type‡		3.203	0.017			
Total no. of metastatic lymph nodes	-0.022	0.019	0.890			
Distant metastasis	1.068	0.512	0.476			
AJCC stage§		2.363	0.059			
Summation of SUV of lymph nodes	0.152	0.424	0.516			
M-SUV in lymph node	0.236	0.576	0.450			

CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer; SUV, standardized uptake value; M-SUV, maximum-standardized uptake value.
*Well-differentiated, moderately differentiated, poorly differentiated and undifferentiated; †The proximal portion of the colon includes the cecum, appendix, ascending colon, hepatic flexure, and transverse colon. The distal portion of the colon includes the splenic flexure, descending colon, and sigmoid colon. Other sites include the anastomosis site; ‡Polypoid, ulceroinfiltrative, ulcerofungating, and flat types according to the Japanese classification of colorectal carcinoma in gross pathological specimens[17,18]; §AJCC 7th edition.

were lower than those in the ulceroinfiltrative and ulcerofungating types. The reason of this phenomenon could be explained by that most of polypoid and flat types had a tendency showing more typical development course from adenoma to adenocarcinoma than in other invasive types, such as ulceroinfiltrative and ulcerofungating types.[26] The microsatellite alterations and instability in ulcerated tumor types could explain higher uptakes of the M-SUV in the ulceroinfiltrative and ulcerofungating types than those in nonulcerated tumor types such as polypoid

and flat types.[27] Particularly, in the flat type, the results in this study suggested that flat type of colon cancer could be clinically difficult to detect for the diagnosis of colon cancer: the flat morphology in itself could be missed to find via colonoscopy and none was detected in the FDG/PET CT.

The M-SUV in the lymph nodes showed a significant association with the total number of pathologically confirmed metastatic lymph nodes (N classification in the AJCC stage) and the M-SUV of the primary tumor. In patients treated with

Table 6. Relationship between the Maximum-Standardized Uptake Value of Metastatic Lymph Nodes and Clinicopathologic Parameters

Variable	Simple linear regression			Multiple linear regression		
	Estimate	F-statistic	p-value	Estimate	F-statistic	p-value
Patients not treated with chemotherapy						
Age	−0.027	5.646	0.018			
Sex	−0.069	0.064	0.801			
CEA	0.001	2.457	0.118			
Polyp	0.353	4.798	0.029	0.449	7.299	0.007
Differentiation*		1.407	0.240			
Tumor volume	0.005	8.652	0.003			
Longest diameter of tumor	0.206	18.117	<0.001	0.121	3.221	0.074
Location[†]		1.121	0.340			
Growth type[‡]		1.039	0.387			
Total no. of metastatic lymph nodes	0.118	30.823	<0.001	0.098	13.379	<0.001
Distant metastasis	0.602	4.090	0.044			
AJCC stage[§]		6.472	<0.001			
M-SUV of primary tumor	0.090	16.072	<0.001	0.085	8.970	0.003
Patients treated with chemotherapy						
Age	−0.015	0.908	0.343			
Sex	0.082	0.050	0.824			
CEA	0.004	0.212	0.646			
Polyp	1.282	1.185	0.281			
Differentiation*		1.507	0.227			
Tumor volume	0.011	2.767	0.099			
Longest diameter of tumor	0.158	3.510	0.064			
Location[†]		0.640	0.591			
Growth type[‡]		0.480	0.751			
Total no. of metastatic lymph nodes	0.106	4.629	0.034	0.106	4.629	0.034
Distant metastasis	−0.285	0.376	0.541			
AJCC stage[§]		1.515	0.204			
M-SUV of primary tumor	0.023	0.576	0.450			

CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer; M-SUV, maximum-standardized uptake value.
*Well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated; [†]The proximal region of the colon includes the cecum, appendix, ascending colon, hepatic flexure, and transverse colon. The distal region of the colon includes the splenic flexure, descending colon, and sigmoid colon. Other sites include the anastomosis site; [‡]Polypoid, ulceroinfiltrative, ulcerofungating, and flat types according to Japanese classification of colorectal carcinoma in gross pathological specimens[17,18]; [§]AJCC 7th edition.

chemotherapy, only the total number of metastatic lymph nodes remained a significant factor. The F-statistics of the total number of metastatic lymph nodes in patients treated with chemotherapy was much lower than that in untreated patients (4.629 vs 30.823).

The M-SUV of the primary tumor in gastric cancers has been reported to be an independent indicator of lymph node metastasis.[28] Mochiki et al.[29] have reported that FDG uptake in gastric cancers is higher in primary tumors with group N3 lymph node metastasis than in those without lymph node metastasis. In lung and gynecologic cancers, the likelihood of lymph node metas-

tasis increases with an increase in the M-SUV of the primary tumor. However, in this study, the M-SUV in the primary tumors in colorectal cancers could not predict metastasis to lymph nodes. Accordingly, the M-SUV in the primary tumor of colon cancers should be clinically interpreted as distinct from that in the primary tumors unlike in gastric, lung, and gynecologic cancers. These differences of predictability of the primary tumor M-SUVs between colon cancer and other cancers could be explained by the difference of biology and heterogeneity between colorectal cancer cell and other types of cancer cells.[17,26,27]

This study contains several limitations. First of all, this study

Table 7. Differences in the Maximum-Standardized Uptake Value of the Primary Tumor according to Growth Types

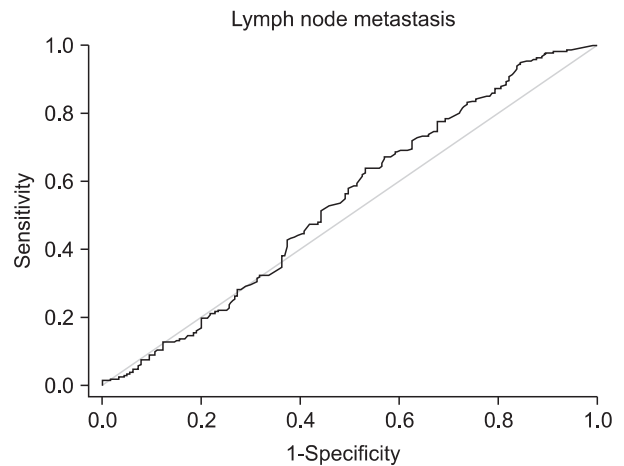| Growth type*	Patients not treated with recent chemotherapy		Patients treated with recent chemotherapy		p-value
	No.	Mean±SD	No.	Mean±SD	
Polypoid	36	8.569±6.108	10	5.463±3.561	0.130
Ulceroinfiltrative	174	10.456±4.477	55	7.625±6.093	0.002
Ulcerofungating	174	12.072±6.163	20	10.845±5.731	0.397
Flat	1	0	3	1.733±3.002	NA

NA, not applicable.

*Polypoid, ulceroinfiltrative, ulcerofungating and flat types according to the Japanese classification of colorectal carcinoma in gross pathological specimens.[17,18]
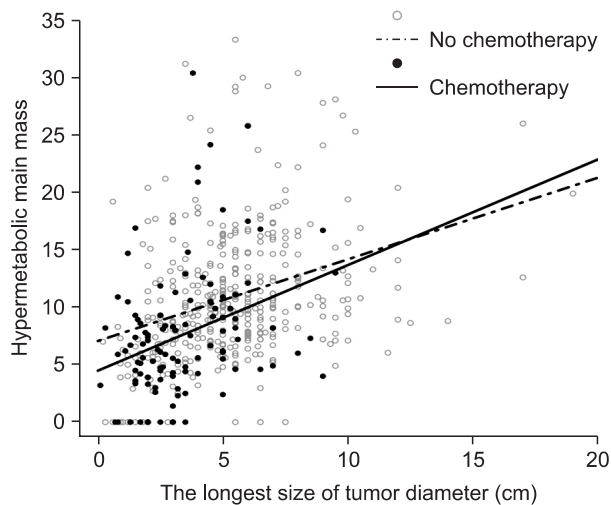
Fig. 3. Plot of the maximum-standardized uptake value against the longest tumor diameter by chemotherapy status. The lines indicate the models generated by multivariate regression analysis. ○ Indicates a tumor not treated with chemotherapy, and • indicates a tumor treated with chemotherapy. The difference between the two slopes was not significant (p=0.454).

Fig. 4. Receiver operating characteristic curve for the maximum-standardized uptake value (M-SUV) of the primary tumor in the group of patients not treated with recent chemotherapy. The prediction of lymph node metastasis of the primary tumor by the M-SUV was not significantly accurate. Area under the curve, 0.540; 95% confidence interval, 0.482 to 0.598.

was a retrospective cohort study with a heterogeneous group of patients treated with chemotherapy. The total population was consisted of four different patient groups and chemotherapy regimens in each group were various. However, considering that FDG-PET/CT scan with surgery was performed within short time of 6 months after chemotherapy, chemotherapy in itself was the most important factor for changes of general patterns and the sensitivity of FDG-PET/CT scan. Secondly, only a small number of cases were available for AJCC stages 0 and I. Thirdly, the cutoff value for the M-SUV of the primary tumor was defined as the value that maximized the sum of the sensitivity and specificity. However, because all of the patients studied here had already been diagnosed with colorectal cancers, deriving an appropriate cutoff value for the diagnosis of colorectal cancer was impossible in this patient population.

In summary, recent chemotherapy reduces the sensitivity of the M-SUV of FDG-PET/CT in colorectal cancer. To accurately interpret FDG-PET/CT scan results, recent chemotherapy in con-text of clinical situations should be required. A negative FDG-PET/CT scan does not exclude the presence of viable disease. Furthermore, the characteristics of M-SUV expression of FDG-PET/CT could be significantly different according to chemotherapy status. The M-SUV of the primary tumor could not predict the lymph nodes metastasis.

In conclusion, FDG-PET/CT should not be used as the sole determinant of the presence of cancer in this clinical situation. A new cutoff value for FDG-PET/CT in patients treated with recent chemotherapy should be determined in the future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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