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Original Article

Metabolic Tumor Volume and Total Lesion Glycolysis in PET/CT are Related with the Clinicopathological T Stage of Colorectal Cancer and Predict its Prognosis

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ABSTRACT

Introduction: Positron emission tomography (PET)/computed tomography (CT) plays an important role in cancer diagnosis. Recently, novel metabolic parameters obtained on PET/CT, such as metabolic tumor volume (MV) and total lesion glycolysis (TLG), have been reported to be diagnostic and prognostic biomarkers of various cancers. We evaluated the potential of these glucose metabolic parameters for the prognostic diagnosis of colorectal cancer (CRC), comparing them with conventional parameters such as the maximum standardized uptake value (SUV max) and maximum average SUV within a 1-cm^3 spherical volume (SUV peak).

Methods: This study included 82 patients who underwent surgical resection of CRC without distal metastasis between April 2015 and December 2017. They underwent [^{18}F]-fluorodeoxyglucose-PET/CT and measurement of MV, TLG, SUV max, SUV mean, and SUV peak. After classifying the patients into four groups by pathological T stage, the metabolic parameters of each group were compared between the left- and right-sided large intestine using nonparametric multiple comparison test, and their prognosis was analyzed using Cox proportional hazards regression analysis.

Results: The TLG value had a significant relation with the pathological T stage of the left-sided large intestine. Multivariate analysis of the clinicopathologic parameters (TLG, location, histological type, and T stage), revealed only the TLG of the primary tumor as an independent prognostic factor for recurrence within a year after surgery without distant metastasis.

Conclusions: Our study results may suggest that TLG in PET/CT reflects a pathological T stage and plays a role in the prognosis of patients with local CRC.

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KEYWORDS: FDG-PET/CT, colorectal cancer, metabolic parameter

Introduction

Positron emission tomography (PET) with [^{18}F]-fluorodeoxyglucose (^{18}F-FDG) is used to diagnose the stage and recurrence of colorectal cancer (CRC).[1)] There have been many reports on colorectal cancer using ^{18}F-FDG-PET/CT, which has high sensitivity and specificity for recurrence and distant metastasis after the operation.[1, 2)] It

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Table 1 Patient profile

	T stage	Tis + T1	T2	T3	T4	p-value
Primary lesion location	Number of patients	6	13	38	25	
	Right/Left side of CRC	1/5	2/11	6/32	14/11	<0.01
Micro-invasion	Negative/positive	3/3	3/10	3/35	1/24	0.01
	Left-sided CRC with micro-invasion	3	9	29	11	
	Right-sided CRC with micro-invasion	0	1	6	13	
Pathological staging						
N-stage	N0/N1/N2/N3	6/0/0/0	12/1/0/0	29/7/2/0	13/10/0/2	0.06
	Left-sided CRC with micro-invasion	3/0/0/0	8/1/0/0	23/5/1/0	6/5/0/0	0.37
	Right-sided CRC with micro-invasion	0/0/0/0	1/0/0/0	4/2/0/0	6/5/0/2	0.90
Histological types	W/D + M/D + Pap/P/D + Muc	5/1	10/3	31/7	16/9	0.45
	Left-sided CRC with micro-invasion	3/0	8/1	23/6	10/1	0.92
	Right-sided CRC with micro-invasion	0/0	1/0	5/1	6/7	0.24

Pathological staging: N stage in Japanese Classification of Colorectal Carcinoma (eighth edition), W/D: well-differentiated adenocarcinoma, M/D: moderately differentiated adenocarcinoma, P/D: poorly differentiated adenocarcinoma, Pap: papillary adenocarcinoma, Muc: mucinous adenocarcinoma. Statistics: Fisher's exact test

All patients were classified into four groups by pathological T stage, and each group was scored based on four backgrounds: location of the primary lesion, micro-invasion, pathological N-stage, and histological type. The four groups showed significant differences in the location of the primary tumor. Only a few patients with no micro-invasion were identified. None of the groups showed significant differences in lymph node metastasis and histological findings (mucinous/poorly adenocarcinoma and others).

indicates a high probability of relapse in patients with a maximum standardized uptake value (SUV max) of more than 5 for primary CRC,[3] and a prognosis of recurrence for patients with CRC liver metastasis.[4] However, the SUV max does not strictly reflect the metabolic activity of the entire tumor, despite its wide acceptance. Recently, the metabolic tumor volume (MV) and total lesion glycolysis (TLG) obtained on FDG-PET have been used as novel metabolic parameters to quantify glucose metabolism.[5, 6] The MV and TLG provide additional information regarding intratumoral variation; hence, they are considered reliable indicators of viable tumors[7, 8] and useful diagnostic and prognostic markers of several cancers, including lung and neck cancers.[9–11]

In this study, to validate the observation that MV and TLG are better biomarkers of CRC, we evaluated the association between pathological invasion depth of the primary tumor (T stage)[12] and each metabolic parameter (SUV max, SUV peak, SUV mean, MV, and TLG), and investigated the effect of the metabolic parameters on the outcome after curative resection of CRC without preoperative adjuvant therapy.

Materials and Methods

Patient population

A total of 123 patients, who consecutively underwent surgical resection of CRCs at Toho University Hospital, between April 2015 and December 2017, after examination with FDG-PET/CT, were enrolled in this retrospective study. Our inclusion criteria were as follows: 1) pathologically proven primary CRCs, 2) detectable FDG uptake in the primary tumor, 3) no distal metastasis (22 patients were in M1), and 4) no other malignant tumor (one patient had another malignant tumor). Patients who underwent neoadjuvant chemotherapy or radiation therapy before the operation were excluded (18 patients underwent neoadjuvant treatment, and were subsequently excluded). Consequently, 82 patients were included in this study.

The patient profiles are shown in Table 1. They were classified into four groups by the pathological T stage described in Japanese Classification of Colorectal Carcinoma (eighth edition) [12]: Tis + T1 (early CRC), T2, T3, and T4. In this study, we also identified a few patients (10/82, 12%) without micro-invasion (lymphatic, venous, and peri-neural invasion), as reported in a previous CRC study.[13] The previous study reported that patients without lymphatic invasion (2/62 patients) are few in number and exhibit no asso-

ciation with venous and peri-neural invasion. A recent systematic review and meta-analysis, evaluated the independent prognostic value of the site of a primary tumor (left-sided versus right-sided primary location) in patients with CRC.[14] Therefore, after excluding patients without micro-invasion, we divided each T stage group into two subgroups based on location of tumor (right group sided up to splenic flexure and left group including descending colon to anal) : N-stage (metastasis of lymph node) and histological type (mucinous or poor tubular adenocarcinoma) with micro-invasion. The four groups showed significant difference in the location (the left and right-sided large intestine) with Fisher's exact test ($p<0.01$), while no differences were observed between the N-stage and histological type groups.

Ethical approval

The study was conducted with approval of the ethics committee of Toho University Hospital (institutional approval no.: M17233).

PET/CT image acquisition

All patients fasted for at least 5 hours prior to ^{18}F-FDG-PET/CT imaging. Patients were administered 185 MBq FDG, and underwent routine PET/CT after 1 hour.

The PET/CT system used for this study is a Biograph mCT flow20 (Siemens Healthcare, Tokyo, Japan). The CT images were acquired with the following settings: 120 kV; 0.5 s/rotation; pitch, 1.2; and automatic adjustment of electric current with automatic exposure control. The PET data were acquired from the skull base of the patient to the ilium at 1.1 cm/s and from the ilium to the knee at 1.3 cm/s using continuous bed motion. The PET image was reconstructed using: three-dimensional-ordered subset expectation maximization method (iterations, 2; subsets, 21) + point spread function (PSF) + time of flight analysis; CT attenuation correction; matrix size, 200×200; pixel size, 3.54; and Gaussian filter (full-width at half-maximum = 6 mm). The PET/CT image reconstruction was harmonized without PSF, and SUVs were measured.

In this study, we used the EQ PET software (filter=5.8 m) for smoothing the digitally inputted image data using the Gaussian filter. This process yields the accurate SUV without deterioration of image quality after the time of flight and PSF analysis.

Measurement of metabolic parameters

Positive ^{18}F-FDG-PET/CT finding was defined as a focal accumulation of ^{18}F-FDG greater than in the surrounding tissue, excluding any physiologically increased accumulations. The volume boundaries were drawn sufficiently wide to include each target lesion in the axial, coronal, and sagittal FDG-PET images. Two nuclear medical physicians set the voxel of interest (VOI) for target lesions and measured metabolic parameters on the three-dimensional image viewer, syngo.via® (Siemens Healthcare). The margin of the target lesion inside the VOI was automatically traced, using signal intensity 40% greater than the threshold, to measure tumor volumes and SUV mean. The MV was defined as the sum of voxels and TLG was calculated as MV multiplied by the SUV mean. In case of multiple CRCs, we selected the VOI such that it included the most advanced pathological T and N stages, and measured its metabolic parameters.

For metabolic parameters, we also measured the sum of MVs of the primary tumors; TLG (SUV mean × MV) ; and conventional parameters: SUV, calculated using maximum activity values in a VOI placed manually over the visible area of a target lesion on each PET image (SUV max), the maximum average SUV within a 1-cm^3 spherical volume (SUV peak), and the average SUV within a VOI (SUV mean).

Statistical analyses

Relation between PET/CT parameters and pathological T stage in the two groups

We evaluated the increase in the glucose metabolic parameters (SUV max, SUV peak, SUV mean, MV, and TLG) with increasing invasion depth of the primary tumor and pathological T stage using Shirley-Williams'multiple comparison test in the two subgroups (left- and right-sided CRC).

Relation between PET/CT parameter and recurrence within the first year after surgery

The recurrence within the first year after surgery was assessed in patients (49 patients who underwent surgery between April 2015 and February 2017 were selected and the remaining 33 patients were excluded) with CRC by analyzing receiver operating characteristic (ROC) curves for SUV max, SUV peak, SUV mean, MV, and TLG. Optimal cut-off values were defined for the PET parameters to maximize sensitivity and specificity. The recurrence was based on the following criteria: new appearances of tumor were confirmed by CT or PET/CT following a tumor marker elevation or a follow-up CT, MRI, or PET/CT scan.

The patients were divided into two groups based on the optimal cut-off value of PET parameters obtained by ROC analysis; the progression free survival curves of these

Table 2 Relation between metabolic parameters and pathological T stage for colorectal cancer in the left-sided large intestine with pathological micro-invasion

Parameter	Control	T2	T3	T4
SUV max	Tis + T1	1.017	1.718 *	2.162 *
		1.645	1.716	1.739
SUV peak	Tis + T1	1.202	2.050 *	2.503 *
		1.645	1.716	1.739
SUV mean	Tis + T1	1.017	1.891 *	2.115 *
		1.645	1.716	1.739
MV	Tis + T1	1.017	2.135 *	2.781 *
		1.645	1.716	1.739
TLG	Tis + T1	1.942 *	2.607 *	3.257 *
		1.645	1.716	1.739

Shirley-Williams' multiple comparison test, *: statistically significant ($p<0.05$)
SUV max: maximal standardized uptake value, SUV peak: peak standardized uptake value, SUV mean: mean standardized uptake value, MV: metabolic tumor volume, TLG: total lesion glycolysis
The Shirley-Williams' multiple comparison test performed to relate the increase of glucose metabolic parameters with progression of T stage revealed that only TLG had a significant difference between pathological Tis + T1 (used as a control) and the other T stages.
In Table 2, the numbers in the lower column in each parameter represent the critical value, and the test statistic was represented in the higher one.

Table 3 Relation between metabolic parameters and pathological T stage for colorectal cancer in the right-sided large intestine with pathological micro-invasion

Parameter	Control	T3	T4
SUV max	T2	1.500	1.859 *
		1.645	1.716
SUV peak	T2	1.500	1.859 *
		1.645	1.716
SUV mean	T2	1.500	1.859 *
		1.645	1.716
MV	T2	0.500	1.647 *
		1.645	1.716
TLG	T2	1.500	1.973 *
		1.645	1.716

Shirley-Williams' multiple comparison test, *: statistically significant ($p<0.05$)
SUV max: maximal standardized uptake value, SUV peak: peak standardized uptake value, SUV mean: mean standardized uptake value, MV: metabolic tumor volume, TLG: total lesion glycolysis
There was no patient in the Tis + T1 stage; hence, the patients in the T2 stage were regarded as control. All parameters increased with progression of T stage, but the difference was not statistically significant, as revealed by Shirley-Williams' multiple comparison test.
In Table 3, the numbers in the lower column in each parameter represent the critical value, and the test statistic was represented in the higher one.

groups were analyzed using the Kaplan-Meier curve and log-rank test.

The effects of metabolic parameter, the tumor location, histological type, and T stage on recurrence within the first year after surgery

Among the glucose metabolic parameters, we selected those that exerted the largest effect on recurrence within the first year after surgery. The selected glucose metabolic and clinicopathological parameters (tumor location, histological type, and T stages) were regarded as covariance variables and analyzed using multivariate Cox hazard regression models. The histological type (poorly differentiated carcinoma, mucinous adenocarcinoma, or the others) and T stage under T2 or over T3 were based on criteria described by Japanese Association of Clinical Cancer Centers (five-year survival rate is more than 95% in Tis, T 1 and T2, and less than 95% in T3 and T4 without metastasis).[15]

All statistical analyses were performed using JMP® 13 (SAS Institute, Inc., Cary, NC, USA) and the Bell Curve for Excel (Microsoft, Redmond, WA, USA). For each analysis, a value of $p<0.05$ was considered significant.

Results

Relation between PET/CT parameters and pathological T stage in the two groups

For CRC in the left-sided large intestine, the TLG in all T stages, T2 to T4, was significantly higher than that in Tis + T1 (used as control), as revealed by Shirley-Williams'multiple comparison test; this implies that TLG increases with advancement of T stage (Table 2). The other glucose metabolic parameters in T2, however, were not higher than those in control. For CRC in the right-sided large intestine, we regarded T2 as control because there was no patient in the Tis + T1 stage. The TLG in T4 was higher than in control, while that in T3 was not (Table 3).

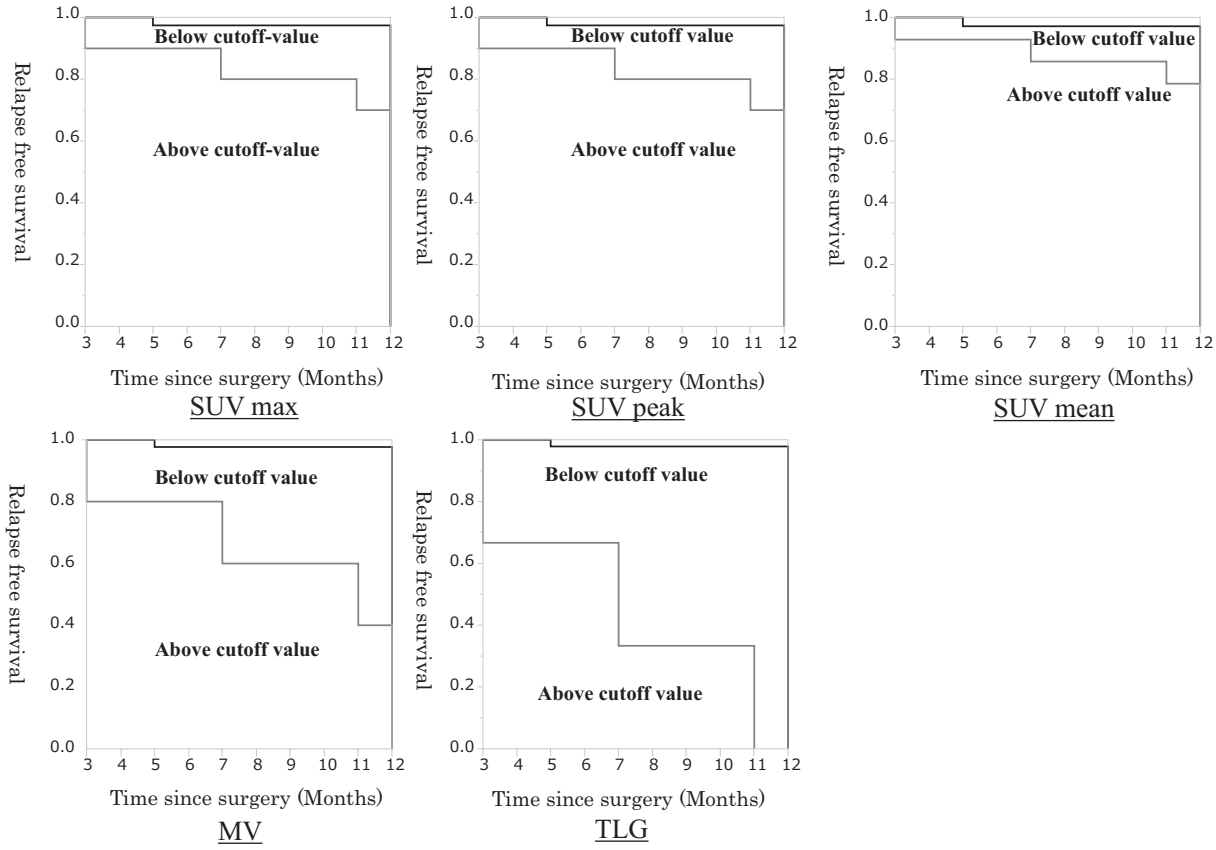

Fig. 1 Relapse free survival curve for the first year after surgery for colorectal cancer showing SUV max, SUV peak, SUV mean, MV, and TLG

The relapse free survival curves of the patients were divided by values below and above the cut-off values obtained using ROC analysis, respectively. For all the parameters, the curve for the values above the cut-off value showed more frequent recurrence than that for values below the cut-off value. SUV: standardized uptake value, MV: metabolic tumor volume, TLG: total lesion glycolysis, ROC: receiver operating characteristic

Table 4 Comparison of relapse free survival curves within the first year after surgery for colorectal cancer

Parameter	λ^2	Freedom	p-value (chi squared test)
SUV max	8.2038	1	0.0042 *
SUV peak	8.2038	1	0.0042 *
SUV mean	4.5726	1	0.0325 *
MV	23.1339	1	$<$0.0001 *
TLG	50.3392	1	$<$0.0001 *

Log-rank test, *: significant ($p<0.05$)

SUV max: maximal standardized uptake value, SUV peak: peak standardized uptake value, SUV mean: mean standardized uptake value, MV: metabolic tumor volume, TLG: total lesion glycolysis, ROC: receiver operating characteristic

The relapse free survival curves of the patients, divided by the values below and above the cut-off values obtained using ROC analysis, were compared using log-rank test. All glucose metabolic parameters, particularly MV and TLG, showed statistically significant differences.

Relation between PET/CT parameters and recurrence within the first year after surgery

For ROC analysis of SUV max, SUV peak, SUV mean, MV, and TLG in CRC, the areas under the curve were 0.71944, 0.72778, 0.70833, 0.75278, and 0.75833, respectively. The optical cut-off values of these parameters for the prognosis of recurrence (4 patients) were 14.91, 12.64, 10.11, 18.21, and 203.99, respectively. When the patients were divided into two subgroups based on the obtained optimal cut-off values, the relapse free survival curves of the subgroups showed significant differences within the first year after surgery between the values below and above the optimal values for all the PET parameters (Fig. 1, Table 4).

Effects of the tumor location, metabolic parameters, T stage, and histological type on recurrence within the first year after surgery

Among the glucose metabolic parameters, we selected TLG, which increased with advancement of T stage. We

Table 5 Impact of TLG, location, histological type, and pathological T stage of colorectal cancer on recurrence within the first year after surgery

Factor	P-value (Probability>Chi squared test)	Hazard ratio	Lower 95%	Upper 95%
TLG	0.0002	77.84	8.87	1681.64
Location (left/right)	0.9022	1.05	0.51	2.30
Histological type (por, muc/except por, muc)	0.8884	1.05	0.50	1.95
T stage (Tis + T1 + T2/T3 + T4)	0.9218	1.03	0.57	1.97

TLG: total lesion glycolysis, por: poorly differentiated carcinoma, muc: mucinous adenocarcinoma
We examined the effect of TLG, location, histological type, and pathological T stage on the recurrence within the first year after surgery using multivariate Cox hazard regression models. The result revealed that only TLG showed a statistically significant difference.

evaluated the effect of TLG, location of the primary lesion, histological type, and T stage on recurrence within the first year after surgery. Only TLG showed a significant prognostic ability (hazard ratio, 77.84; 95% confidence interval, 8.87-1681.64) (Table 5).

Discussion

The Japanese Society for Cancer of the Colon and Rectum guidelines propose postoperative adjuvant chemotherapy for patients with CRC who undergo R0 resection in order to prevent recurrence and improve the stage. For example, the FOLFOX regimen was approved for the postoperative adjuvant therapy for stage III colon cancer in August 2009 in Japan. Adjuvant chemotherapy, however, is not yet an established treatment approach for patients with stage II colon cancer. Therefore, it is necessary to clarify the applicability of postoperative adjuvant chemotherapy for stage II colon cancer. In addition, there is no consensus for the impact of lateral lymph node dissection and neo-adjuvant chemo-radiotherapy in Japan, Europe, and America. Considering the high risk of recurrence, a new predictor of the risk of recurrence in CRC, superior to the conventional risk factors (invasion depth, lymph node metastasis, etc.), is required for determining the appropriate treatment.

Although CT and magnetic resonance imaging are used to measure the volume of tumors,[16, 17] these techniques cannot accurately measure the volume of tumors with irregular shape or ill-defined boundary. It may be also difficult to differentiate the viable tumors from the non-viable ones or necrotic tissue; therefore, the measured volume does not reflect the viable tumor region.

In contrast, SUV max is often used in imaging-based reports of CRC[2] because SUV is thought to reflect tumor activity and grade of malignancy. It has been reported that high SUV max indicates worse prognosis of other malignant tumors.[18, 19] It is unclear whether SUV max is a prognostic factor.[20, 21] For example, Lee et al. found that SUV max was not a significant predictor of recurrence or disease-free survival in 163 patients with CRC.[22] The maximal value on a voxel in a tumor, SUV max represents only part of the tumor characteristics, and does not reflect glucose metabolism of the entire tumor. In the other words, SUV max does not adequately indicate the extent of high glucose metabolism or glucose metabolic volume.

However, MV represents the tumor volume with SUV values higher than a threshold, without morphometric information; TLG is the product of MV and SUV mean, reflecting the sum of FDG activity higher than a threshold in a tumor. Since MV and TLG are volume-based parameters,[6, 23] they may possibly indicate accurate tumor activity and the grade of malignancy, and may be expected to be a prognostic factor for tumor progression.

In a recent Japanese study, over survival was found to be significantly different in MV and TLG between the low and high groups.[6] It was also reported that TLG was associated with the outcome and was an independent prognostic factor in multivariate analysis with many other clinicopathological factors. Although both MV and TLG allow accurate tumor, node, metastasis staging in CRC,[24] it has not shown that these parameters are actually associated with prognosis. In this study, we investigated the potential of these parameters as prognostic factors that may aid in the selection of the appropriate treatment approach for CRC.

In this study, TLG showed a significant increase with the advancement of T stage in left-sided lesions. The other glucose metabolic parameters exhibited no significant difference between Tis + T1 (shallow invasion) and T2 stages,

although all parameters increased with advancement of pathological T stage. It was difficult to classify early stage CRC based on glucose metabolic parameters.

The histological type of CRC consists of poor differentiated adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, and so on. Poorly differentiated adenocarcinoma grows with less differentiation, its gland duct structure proliferates more indistinctly and discontinuously, while mucinous adenocarcinoma and signet ring cell carcinoma contain much mucus and spread heterogeneously with low density. Some CRCs with low density and diffuse and heterogeneous proliferation exhibit an invasion with lack of findings related to ulcer and convergence of mucosal fold on endoscopy or findings of interruption or tearing of each large intestine layer on ultrasonic endoscopy. In these cases, it is difficult to evaluate the depth of invasion before operation. Therefore, TLG may be expected to be more strongly related to the pathological depth of tumor invasion than conventional SUV max, since TLG reflects the distribution of glucose metabolism, and may reveal invasive cancers with poor morphological change.

In contrast, all metabolic parameters of right-sided lesions exhibited no statistically significant difference between pathological T2 and T3 stages. These results did not show the effectiveness of glucose metabolic parameters. One of the reasons behind this is that the number of patients with lesions in the right-sided large intestine was too small to show a statistically significant relation with pathological T stage. In the present study, right-sided CRCs had worse prognosis and distinct molecular characteristics, compared with the left-sided ones. This difference between right- and left-sided lesions could have an impact on the relation between glucose metabolic parameters and T stage.

The ROC analysis of the relation between the glucose metabolic parameters and prognosis revealed that SUV max and SUV mean had lower cut-off values and MV and TLG had higher cut-off values in the present study than in the previous Japanese report.[6] The difference in the cut-off values was due to the definitions of prognosis (death in the previous study vs. recurrence in ours), threshold for lesion VOI tracing on PET images (30% in the previous study vs. 40% in ours), and proportion of patients in the early stages of CRC. In a previous European study,[25] the cut-off values of MV and TLG were set at 100 and 500, respectively, which are higher than ours, because more patients in advanced stages of CRC with distant metastasis were included. As a result, on the Kaplan-Meier curve of relapse free survival, there were significant differences between the values below and above the cut-off values for the groups for all glucose metabolic parameters. The glucose metabolic parameters, especially MV and TLG, were shown to be grossly associated with the prognosis. In addition, we examined the impact of the glucose metabolic and clinicopathologic parameters on the prognosis within the first year after surgery using multivariate Cox hazard regression models. Among these, TLG was the independent prognostic factor.

Based on the results of our study, we expect MV and TLG to play the role of biomarkers to determine the suitability of neoadjuvant chemoradiation or neoadjuvant chemotherapy for the treatment of CRC. These would also be noninvasive clinical indicators for lymph node dissection since lymph node metastasis expands with increasing pathological depth of invasion. If the TLG of left-sided CRC, in particular, during the pretreatment PET/CT scan was more than cut-off values, neoadjuvant treatment or more extensive lymphadenectomy may be warranted.

In the future, we might need to investigate the relation between glucose metabolism and other prognostic factors, particularly considering the backdrop of gene mutations. A Japanese report[26] showed that SUV max had an odds ratio of 1.17, with an accuracy of 75%, for predicting mutations in *KRAS/BRAF* when using a cut-off value of 13, although *BRAF* mutation was found in only 2% of the study population. In recent years, CRC with *BRAF* mutation has emerged as a distinct biologic entity, typically refractory to standard chemotherapy regimens approved for the treatment of metastatic CRC and associated with a dismal prognosis. If it was demonstrated that this genetic mutation is associated with glucose metabolic parameters, they may expand therapeutic and/or clinical trial options before a patient undergoes clinical deterioration.

Our study has some limitations in terms of methods and the study population. Various thresholds of VOI have been used in the measurement of MV and TLG in previous reports[27, 28] and there is no standard method. Further investigation is necessary to determine the optimal threshold because MV and TLG values change depending on the threshold, although the threshold was set at 40% of SUV max in this study. This single-center retrospective study might have involved a bias in patient selection. We selected patients with pathological micro-invasion and no

distant metastasis, but the other factors, except the depth of tumor invasion, might be related with the glucose metabolic parameters. Although our study contained some patients without micro-invasion or metastasis, they might be affected by these other factors. The relations between glucose metabolic parameters and overall survival should be examined because new drugs have decreased the mortality of patients with CRC, and therefore, recurrence does not necessarily lead to death. The relation between glucose metabolic factors and conventional high risk factors should be examined in a prospective multicenter study, with a large number of patients exhibiting high mortality and more pathological backgrounds.

In conclusion, TLG is more strongly related to the pathological depth of tumor invasion than any conventional glucose metabolic parameter. It is expected to be a prognostic factor and useful biomarker for selecting the appropriate treatment for CRC.

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