# Prognostic Value of Total Lesion Glycolysis Measured by $^{18}$F-FDG-PET/CT in Patients with Colorectal Cancer

SHIMPEI OGAWA[1], MICHIO ITABASHI[1], CHISATO KONDO[2], MITSURU MOMOSE[2], SHUJI SAKAI[2] and SHINGO KAMEOKA[1]

*Departments of [1]Surgery II and [2]Diagnostic Imaging and Nuclear Medicine, Tokyo Women's Medical University School of Medicine, Shinjuku-ku, Tokyo, Japan*

**Abstract.** *Aim: [$^{18}$F]Fluorodeoxyglucose positron-emission tomography with computed tomography ($^{18}$F-FDG-PET/CT) was assessed regarding its utility in prediction of outcomes after curative resection of colorectal cancer. Patients and Methods: Preoperative $^{18}$F-FDG-PET/CT was performed in 325 patients with colorectal cancer. Maximum standardized uptake value ($SUV_{max}$), mean SUV ($SUV_{mean}$), metabolic volume (MV), and total lesion glycolysis (TLG) were measured. Patients were divided into groups using cut-offs for overall survival (OS). $^{18}$F-FDG-PET/CT parameters and other clinicopathological factors were investigated as prognostic factors. Results: The 5-year OS rates in the low and high $SUV_{max}$, $SUV_{mean}$, MV, and TLG groups were 91.4% and 87.0% (p=0.238), 90.8% and 88.2% (p=0.453), 91.7% and 83.8% (p=0.006), and 92.1% and 70.1% (p=0.001), respectively, indicating poorer outcomes in patients with high MV and TLG. In multivariate analysis, high TLG, age ≥65 years, rectal tumor location, and pN(+) were independent factors predicting a poor prognosis. Conclusion: TLG in $^{18}$F-FDG-PET/CT is a prognostic parameter for colorectal cancer after curative resection.*

Positron-emission tomography (PET) with the glucose analog [$^{18}$F]fluorodeoxyglucose ($^{18}$F-FDG) is used to diagnose stage and recurrence of colorectal cancer (1). The metabolic volume (MV), an index reflecting the size and expansion of tissues with high glucose metabolism, and total lesion glycolysis (TLG), the product of MV and the $SUV_{mean}$, can all be used to judge the therapeutic effects and may predict for outcomes (2, 3). Associations of the metabolic activity on $^{18}$F-FDG-PET scans with the tumor biology and prognosis of colorectal cancer have occasionally been described, but only in experimental studies involving a small number of patients (4, 5). To our knowledge, $^{18}$F-FDG-PET parameters have not been evaluated as prognostic factors in a large number of patients with colorectal cancer after curative resection without preoperative adjuvant therapy.

Prognostic factors are important indices for predicting outcomes and planning treatment. Pre-treatment identification of prognostic factors using reproducible measurements without variation among observers is particularly useful for determining the optimal treatment strategy and improving therapeutic outcomes. Thus, the objective of the present study was to investigate pre-treatment $^{18}$F-FDG-PET/CT indices, including the $SUV_{max}$, $SUV_{mean}$, MV, and TLG, as potential predictors of outcome after curative resection for colorectal cancer without preoperative adjuvant therapy.

*Correspondence to:* Michio Itabashi, Department of Surgery II, Tokyo Women's Medical University School of Medicine, 8-1, Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan. Tel: +81 333538111 Ext. 39251, Fax: +81 352697334, e-mail: itabashi@surg2.twmu.ac.jp

*Key Words:* Total lesion glycolysis, TLG, $^{18}$F-FDG PET/CT, colorectal cancer, prognostic value.

## Patients and Methods

*Patients.* Between January 2005 and December 2011, a total of 402 patients who had undergone $^{18}$F-FDG-PET/CT before colorectal cancer resection at our hospital were identified in our $^{18}$F-FDG-PET/CT database. Of these patients, 53 had stage IV disease; 16 had multiple colorectal carcinomas; four had colitic cancer; and four underwent R1 resections. These patients were excluded, leaving 325 patients for inclusion in this study and for retrospective analysis. Primary colorectal cancer was confirmed by endoscopic biopsy. Patients did not receive preoperative radiotherapy or chemotherapy. The study was approved by the Institutional Review Board (no.3043) and informed consent was obtained from all patients (Table I).

*$^{18}$F-FDG-PET/CT.* Patients fasted for at least 5 h before intravenous administration of 18F-FDG (3.7 MBq/kg). After a rest period of approximately 1 h, a whole-body scan was performed using a PET/CT scanner (Biograph Sensation 16; Siemens Medical Solution, Malvern, PA, USA). The protocols for acquisition, reconstruction, and image fusion have been described in detail elsewhere (6). Two experienced nuclear medicine physicians assessed the $^{18}$F-FDG-PET/CT images visually, with reference to PET/CT fusion and CT images, until consensus was reached. Positive $^{18}$F-FDG-PET findings were defined as a focal

accumulation of $^{18}$F-FDG greater than that in the surrounding tissue, excluding any physiologically increased uptake.

$SUV_{max}$ was calculated using activity values in a volume of interest (VOI) placed manually over the visible area of a target lesion on each PET image. MV ($cm^3$) was measured from the $^{18}$F-FDG-PET/CT images by an SUV-based automated contouring program (Syngo; Siemens Medical Solutions). $^{18}$F-FDG-PET/CT data were transferred to a workstation and intensity values (radioactivity concentrations) were converted to SUVs. An observer interactively selected a VOI that covered each hypermetabolic lesion. The margin of the target lesion inside the VOI was automatically produced and voxels greater than a threshold of 30% of $SUV_{max}$ in the VOI were defined to measure tumor volumes and $SUV_{mean}$ (Figure 1). The threshold for measuring tumor volumes was validated in spherical phantom experiments performed in our laboratory (6). TLG was calculated by multiplying $SUV_{mean}$ by MV.

*Surgery and pathology*. The median time to surgery after PET was 9 (range=1-81) days. R0 resection of the intestine, including resection of the tumor with regional lymph node dissection, was performed in all patients. Postoperative adjuvant chemotherapy was performed for pT4 or pN(+) cases as a rule. The depth of invasion, grade of lymph node metastasis, histological type, and vascular invasion were evaluated by pathologists. Stages are reported using the tumor-node-metastasis (TNM) classification in the American Joint Committee on Cancer Cancer Staging Manual (7).

*Statistical analysis*. The cut-off values of $SUV_{max}$, $SUV_{mean}$, MV, and TLG for survival were determined by analyzing receiver operating characteristic (ROC) curves. The ROC curves were plotted to estimate the most discriminating cut-off value for each parameter to maximize its sensitivity and specificity in predicting survival. The patients were divided into two groups based on the cut-off value for each factor. By dichotomising each parameter based on its cut-off value, a Kaplan–Meier survival curve was generated. A log-rank test was then used to compare overall survival (OS) between each pair of groups. OS was calculated from the date of surgery to the time of death or last follow-up visit.

Prognostic factors were extracted from PET parameters ($SUV_{max}$, $SUV_{mean}$, MV, and TLG) and clinicopathological factors associated with colorectal cancer [gender, age, location, macroscopic type, maximum tumor diameter, pathologic T stage (pT), histopathological grade, lymphatic invasion or venous invasion, pathologic N stage (pN), carcinoembryonic antigen (CEA) level, body mass index (BMI), number of retrieved lymph nodes, and use of postoperative adjuvant chemotherapy]. Univariate and multivariate analyses using Cox proportional hazard models were used to identify prognostic factors. In each analysis, a value of $p<0.05$ was considered to be significant. All analyses were performed using JMP ver. 10.0.2 for Windows® (SAS Institute Inc., Cary, NC, USA).

## Results

The median duration of follow-up in the 325 patients was 56.9 months, and 37 patients died during the follow-up period. The cut-off values for $SUV_{max}$, $SUV_{mean}$, MV, and TLG determined from the ROC curves were 11.30 g/ml [area under the curve (AUC)=0.510, 95% confidence interval (CI)=0.413-0.606], 5.38 g/ml (AUC=0.508, 95% CI=0.412-0.603), 25.23 $cm^3$ (AUC=0.589, 95% CI=0.484-0.686), and 341.89 (AUC=0.562, 95% CI=0.460-0.659), respectively. Patients were divided into groups based on their values for each factor being below (low group) and at or above (high group) the cut-off value. The low and high $SUV_{max}$, $SUV_{mean}$, MV, and TLG groups included 178 and 147 patients, 153 and 172 patients, 230 and 95 patients, and 284 and 41 patients, respectively.

The OS rate did not reach 50% in any group, and the median survival could not be calculated. The 5-year OS rates in the low and high $SUV_{max}$, $SUV_{mean}$, MV, and TLG groups were 91.4 and 87.0% ($p=0.238$), 90.8 and 88.2% ($p=0.453$), 91.7 and 83.8% ($p=0.006$), and 92.1 and 70.1% ($p=0.001$), respectively, showing significantly poorer outcomes in patients with high MV and high TLG (Figure 2).

In univariate analysis of prognostic factors, MV ($p=0.009$), TLG ($p=0.005$), age ($p=0.039$), location ($p=0.045$), pT ($p=0.010$), and pN ($p=0.010$) were significant factors. In multivariate analysis, high TLG [hazard ratio (HR)=3.41, 95% CI=1.27-9.51; $p=0.016$], age ≥65 years (HR=2.37, 95% CI=1.20-4.91; $p=0.013$), rectal tumor location (HR=2.92, 95% CI=1.46-5.95; $p=0.003$), and pN(+) (HR=2.15, 95% CI=1.10-4.28; $p=0.023$) were extracted as independent poor prognostic factors (Table II).

## Discussion

SUV is a semi-quantitative index of $^{18}$F-FDG accumulation, and its maximum value, $SUV_{max}$, is often included in imaging reports (1). Normally, the tumor activity and grade of malignancy are high in tumors with a high SUV. The prognosis of patients with a high $SUV_{max}$ is poor for some types malignant tumors, and $SUV_{max}$ has been proposed as a prognostic factor in some reports (8, 9), but not in others (10, 11). For example, in a study of 163 patients with resectable colorectal cancer, Lee *et al*. found that $SUV_{max}$ was not a significant predictor of recurrence or disease-free survival (11). $SUV_{max}$ is the value of only one voxel and does not reflect glucose metabolism of the entire tumor, and a high value may be detected even when glucose metabolism is enhanced in only one part of a tumor. Thus, $SUV_{max}$ does not indicate whether an area with a high value is wide or narrow, which can make it difficult to identify the expansion of active lesions within malignant tumors accurately based on SUVmax alone (12).

MV represents the volume of the region with an SUV higher than a specific level, and TLG is the product of MV and SUVmean. Thus, MV and TLG are volume-based parameters. The tumor volume can also be measured on CT and magnetic resonance imaging scans (13, 14), but these measurements may not be accurate because malignant tumors have irregular shapes and their boundaries are unclear

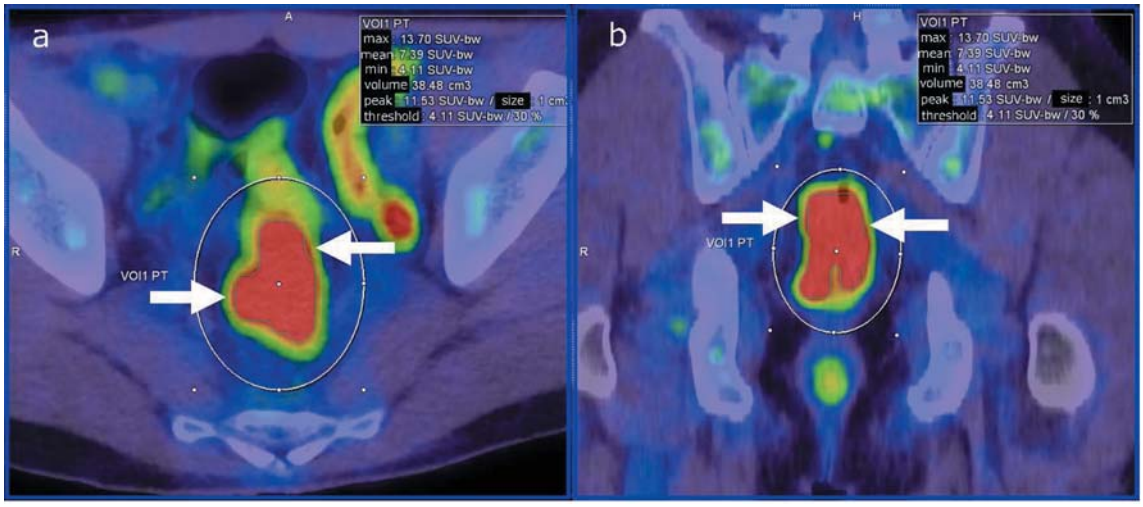


Figure 1. *Images of [$^{18}$F]fluorodeoxyglucose positron-emission tomography combined with computed tomography ($^{18}$F-FDG-PET/CT) in the case of a 38-year-old man with rectal cancer. The maximum standardized uptake value ($SUV_{max}$), mean SUV ($SUV_{mean}$), and metabolic volume (MV) were measured using an automated volume-of-interest (VOI) tool. The margin of the target lesions inside the VOI was automatically produced, and voxels greater than a threshold of 30% of the $SUV_{max}$ in the VOI were accurately defined (arrows). The results are displayed in the upper right. Total lesion glycolysis (TLG) was calculated as MV × $SUV_{mean}$. a: Axial view. b: Coronal view.*

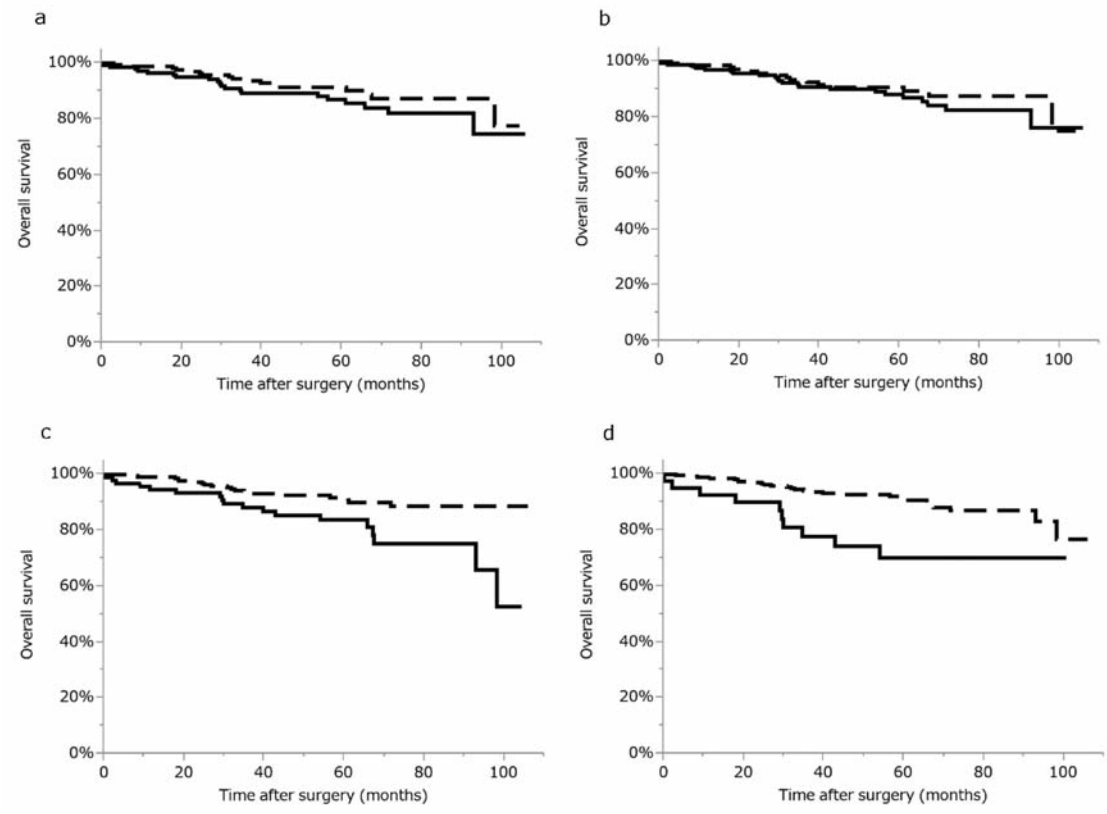


Figure 2. *Overall survival curves after surgery for colorectal cancer according to maximum standardized uptake value (SUVmax) (p=0.238) (a), $SUV_{mean}$ (p=0.453) (b), metabolic volume (p=0.006) (c), and total lesion glycolysis (p=0.001) (d). Patients were dichotomised according to the cutoff value for each parameter; dashed line: low group, full line: high group.*

Table I. *Clinicopathological characteristics of patients. Values in parentheses are percentages unless indicated otherwise.*

| | Number of patients (n=325) |
|---|---|
| Gender | |
| Male | 180 (55.4) |
| Female | 145 (44.6) |
| Age (years)* | 65 (29-93) |
| <65 | 156 (48.0) |
| ≥65 | 169 (52.0) |
| Location | |
| Colon | 202 (62.2) |
| Rectum | 123 (37.8) |
| Macroscopic type | |
| 0 | 19 (5.8) |
| 1 | 28 (8.6) |
| 2 | 239 (73.5) |
| 3 | 33 (10.2) |
| 4 | 6 (1.8) |
| Maximum tumor diameter (mm)* | 40 (10-130) |
| <40 | 155 (47.7) |
| ≥40 | 170 (52.3) |
| Pathological T stage | |
| T1 | 33 (10.2) |
| T2 | 48 (14.8) |
| T3 | 190 (58.5) |
| T4 | 54 (16.6) |
| Histopathological grade | |
| G1 | 132 (40.6) |
| G2 | 175 (53.8) |
| G3 | 8 (2.5) |
| G4 | 10 (3.1) |
| Lymphatic invasion | |
| L0 | 37 (11.4) |
| L1 | 288 (88.6) |
| Venous invasion | |
| V0 | 231 (71.1) |
| V1 | 94 (28.9) |
| Pathologic N stage | |
| N0 | 202 (62.2) |
| N1 | 85 (26.2) |
| N2 | 38 (11.7) |
| CEA | |
| ≤5 | 230 (70.8) |
| >5 | 95 (29.2) |
| BMI | |
| ≤25 | 253 (77.8) |
| >25 | 72 (22.2) |
| Number of retrieved lymph nodes | |
| <12 | 133 (40.9) |
| ≥12 | 192 (59.1) |
| Postoperative adjuvant chemotherapy | |
| No | 174 (53.5) |
| Yes | 151 (46.5) |

*Median (range). CEA, Carcinoembryonic antigen; BMI, body mass index.

in many cases. A nonviable, necrotic region is also likely to be present, making it difficult to assess how much the measured volume reflects the viable tumor region (10). In contrast, MV and TLG in $^{18}$F-FDG-PET are calculated from the SUV, which does reflect tumor activity (12). These parameters reflect the volume of the viable tumor region and, thus, may more accurately reflect the tumor activity and grade of malignancy compared to $SUV_{max}$.

In the current study, OS did not differ significantly between the low and high $SUV_{max}$ and $SUV_{mean}$ groups, but was significantly different between the low and high MV and TLG groups. TLG also emerged as an independent prognostic factor in multivariate analysis, along with many other clinicopathological factors, and the outcome was poor in patients with a high TLG. T and N factors are typical prognostic factors after resection of colorectal cancer without distant metastasis. In this study, the T factor was significant in univariate analysis, but did not emerge as a significant factor in multivariate analysis. The N factor was an independent prognostic factor in multivariate analysis, but the HR of 2.15 for the N factor was lower than that of 3.41 for TLG. Since cases of TNM stage IV were excluded from this study, pN0 cases corresponded to stage I or II disease, and pN(+) cases corresponded to stage III. Thus, it is possible that TLG is a useful prognostic factor of patients after curative resection of colorectal cancer. The HR for TLG was also higher than those for age and location, suggesting the importance of TLG with respect to outcome.

Measurements using an automated VOI-defining tool reduce variation in the results among observers that may occur due to time constraints, labor requirements, the relatively low PET resolution, and blurring in the use of manual VOIs (10, 15). A VOI containing the 3-dimensional tumor region displayed on PET/CT was defined using an automated tool, and $SUV_{max}$, $SUV_{mean}$, and MV of the PET accumulation region corresponding to the tumor region in the VOI are automatically measured without variation among observers (15). Thus, the measurements in this study are highly reproducible and reliable.

There are several limitations in the study. Firstly, there is no standard method for setting the VOI measurement threshold, although various methods for imaging of tumors have been reported (15, 16). We set the threshold at 30% of $SUV_{max}$ based on the results of a phantom study at our institution (6). Because MV and TLG changes depend on the threshold, further investigation of the optimal threshold is necessary. Secondly, the study was performed retrospectively at a single institution; thus, the finding of a high TLG on $^{18}$F-FDG-PET/CT as a prognostic factor after curative resection of colorectal cancer without preoperative adjuvant therapy requires confirmation in a prospective multicenter study in a large number of patients. In addition, medical costs have to be considered in the decision to perform $^{18}$F-FDG-PET/CT as a routine test before surgery. It remains to be investigated whether routine testing is advantageous or should only be performed in patients for whom the test is known to be advantageous.

Table II. *Univariate and multivariate analysis of overall survival*.

| | Number of patients (%) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *p*-Value | Hazard ratio (95% CI) | *p*-Value |
| Gender | | | | | |
| Male | 180 (55.4) | 1.25 (0.65-2.45) | 0.508 | | |
| Female | 145 (44.6) | 1.00 | | | |
| Age (years) | | | | | |
| <65 | 156 (48.0) | 1.00 | | 1.00 | |
| ≥65 | 169 (52.0) | 2.00 (1.03-4.05) | 0.039 | 2.37 (1.20-4.91) | 0.013 |
| Location | | | | | |
| Colon | 202 (62.2) | 1.00 | | 1.00 | |
| Rectum | 123 (37.8) | 1.94 (1.02-3.74) | 0.045 | 2.92 (1.46-5.95) | 0.003 |
| Macroscopic type | | | | | |
| 0, 1, 2 | 286 (88.0) | 1.00 | | | |
| 3, 4 | 39 (12.0) | 1.90 (0.76-4.09) | 0.156 | | |
| Maximum tumour diameter (mm) | | | | | |
| <40 | 155 (47.7) | 1.00 | | | |
| ≥40 | 170 (52.3) | 1.09 (0.57-2.11) | 0.788 | | |
| Pathologic T stage | | | | | |
| pT1, pT2 | 81 (24.9) | 1.00 | | 1.00 | |
| pT3, pT4 | 244 (75.1) | 3.65 (1.31-15.17) | 0.010 | 2.74 (0.93-11.72) | 0.069 |
| Histopathological grade | | | | | |
| G1, G2 | 307 (94.5) | 1.00 | | | |
| G3, G4 | 18 (5.5) | 2.85 (0.85-7.19) | 0.084 | | |
| Lymphatic invasion | | | | | |
| L0 | 37 (11.4) | 1.00 | | | |
| L1 | 288 (88.6) | 1.23 (0.44-5.13) | 0.718 | | |
| Venous invasion | | | | | |
| V0 | 231 (71.1) | 1.00 | | | |
| V1 | 94 (28.9) | 1.91 (0.97-3.66) | 0.060 | | |
| Pathologic N stage | | | | | |
| pN0 | 202 (62.2) | 1.00 | | 1.00 | |
| pN(+) | 123 (37.8) | 2.35 (1.23-4.63) | 0.010 | 2.15 (1.11-4.28) | 0.023 |
| CEA (ng/ml) | | | | | |
| ≤5 | 230 (70.8) | 1.00 | | | |
| >5 | 95 (29.2) | 1.76 (0.90-3.37) | 0.099 | | |
| BMI ($kg/m^2$) | | | | | |
| ≤25 | 253 (77.8) | 1.26 (0.59-3.12) | 0.577 | | |
| >25 | 72 (22.2) | 1.00 | | | |
| Number of retrieved lymph nodes | | | | | |
| <12 | 133 (40.9) | 1.44 (0.75-2.76) | 0.267 | | |
| ≥12 | 192 (59.1) | 1.00 | | | |
| Postoperative adjuvant chemotherapy | | | | | |
| No | 174 (53.5) | 1.00 | | | |
| Yes | 151 (46.5) | 1.11 (0.58-2.14) | 0.762 | | |
| $SUV_{max}$ | | | | | |
| Low | 178 (54.8) | 1.00 | | | |
| High | 147 (45.2) | 1.47 (0.77-2.84) | 0.240 | | |
| $SUV_{mean}$ | | | | | |
| Low | 153 (47.1) | 1.00 | | | |
| High | 172 (52.9) | 1.28 (0.67-2.53) | 0.451 | | |
| MV ($cm^3$) | | | | | |
| Low | 230 (70.8) | 1.00 | | 1.00 | |
| High | 95 (29.2) | 2.42 (1.26-4.63) | 0.009 | 1.12 (0.45-2.55) | 0.796 |
| TLG | | | | | |
| Low | 284 (87.4) | 1.00 | | 1.00 | |
| High | 41 (12.6) | 3.22 (1.48-6.47) | 0.005 | 3.41 (1.27-9.51) | 0.016 |

CEA, Carcinoembryonic antigen; CI, confidence interval; BMI, body mass index; $SUV_{max}$, max of standardized uptake value; $SUV_{mean}$, mean of standardized uptake value; MV, metabolic volume; TLG, total lesion glycolysis.

To our knowledge, this is the first study on the association of $^{18}$F-FDG-PET/CT parameters with outcomes after curative resection of colorectal cancer without pretreatment. The outcomes of patients with a high preoperative TLG were poor, suggesting that TLG may serve as a prognostic factor in colorectal cancer after curative resection without preoperative adjuvant therapy.

## Acknowledgements

The Authors declare no conflicts of interest in regard to this study.

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*Received March 7, 2015*
*Revised March 16, 2015*
*Accepted March 18, 2015*