**Relationship between 18F-Fluorodeoxyglucose Accumulation and KRAS/BRAF Mutations in Colorectal Cancer**

Kenji Kawada1, Yuki Nakamoto2, Mayumi Kawada3, Koya Hida1, Takuya Matsumoto1, Teppei Murakami1, Suguru Hasegawa1, Kaori Togashi2, and Yoshiharu Sakai1

**Abstract**

Purpose: Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) has been widely used in the management of colorectal cancer (CRC). However, the relationship between FDG accumulation and KRAS/BRAF mutations has not yet been investigated. The purpose of this study was to investigate whether KRAS/BRAF mutations affect FDG accumulation in CRC.

Experimental Design: Retrospective analysis was conducted in 51 patients with CRC who underwent FDG-PET/computed tomographic (CT) scans for staging before primary tumor resection. The maximum standardized uptake value (SUVmax) for the primary tumor and the tumor-to-liver ratio (TLR) were calculated from FDG accumulation and compared between KRAS/BRAF mutated and wild-type groups. Expression levels of glucose transporter-1 (GLUT1) and hexokinase type-II (HXK-II) were assessed by immunohistochemical analysis.

Results: Both SUVmax and TLR were significantly higher in the KRAS/BRAF-mutated group compared with the wild-type group (P = 0.006 and 0.001, respectively). Multivariate analysis indicated that SUVmax and TLR remained significantly associated with KRAS/BRAF mutations (P = 0.016 and 0.01, respectively). KRAS/BRAF status could be predicted with an accuracy of 75% when a SUVmax cutoff value of 13 or 14 was used. GLUT1 expression in cancer cells was positively correlated with FDG accumulation and KRAS/BRAF status whereas HXK-II expression was not.

Conclusion: FDG accumulation was higher in CRC with KRAS/BRAF mutations. FDG-PET/CT scans may be useful for predicting the KRAS/BRAF status of patients with CRC and thus aid in determination of therapeutic strategies for patients with CRC. *Clin Cancer Res; 18(6); 1–8. ©2012 AACR.*

**Introduction**

Positron Emission Tomography (PET) with 18F-fluorodeoxyglucose (FDG) is a less invasive diagnostic tool used for detecting malignant tumors. Clinical benefits of conventional PET imaging are limited by a relative paucity of anatomic information. This limitation has been largely overcome by the introduction of combined PET/computed tomography (CT), which provides spatially coregistered functional and anatomic images. This technique can be used to evaluate glucose metabolism *in vivo* by measuring uptake of FDG, a glucose analogue. FDG is transported into the cell through glucose transporters (GLUT), and then phosphorylated by hexokinases (HXK) to FDG-6-phosphate, which becomes trapped within the cell. It has been conceivable that FDG accumulation in tumor cells largely depends on the GLUT1 and the rate-limiting glycolytic enzyme, hexokinase type-II (HXK-II). Several recent studies on colorectal cancer (CRC) have reported that increased GLUT1 expression is the most essential factor for FDG accumulation when compared with HXK activity (1).

It was recently reported that the increase in GLUT1 expression and glucose uptake is critically dependent on KRAS and BRAF mutations in CRC cell lines (2). GLUT1 expression is 3- 22-fold higher in clones with mutated KRAS or BRAF than isogenic clones with wild-type alleles. CRC cells with mutated KRAS or BRAF exhibited enhanced glucose uptake, glycolysis, and survived in low-glucose conditions; all of these phenotypes required GLUT1 expression.

KRAS mutations occur in approximately 40% of CRCs, and a number of studies have shown that KRAS mutations in CRC predict a lack of responses to therapies with antibodies targeted to the epidermal growth factor receptor (EGFR; refs. 3–6). KRAS mutational testing has been
incorporated into routine clinical practice as a part of treatment for metastatic CRC. Cetuximab and panitumumab, which are anti-EGFR monoclonal antibodies, are now recommended only for patients whose tumors have wild-type KRAS. In addition to KRAS mutations, the clinical utility of BRAF mutational testing has been supported by several retrospective studies (7–10). BRAF is reported to be mutated in 5% to 12% of CRCs (7, 11–13). KRAS binds to and activates BRAF, thereby activating mitogen-activated protein kinase (MAPK) signaling pathways (14). Interestingly, KRAS and BRAF mutations are mutually exclusive (11, 12, 15), suggesting they may have a similar function.

The present study aimed to investigate whether KRAS/BRAF mutations are associated with FDG accumulation, and whether FDG-PET/CT scans can be used to predict KRAS and BRAF status of primary CRC. In addition, we examined whether GLUT1 and/or HK-II are associated with FDG accumulation into CRC by immunohistochemical analysis. To our knowledge, this is the first study to deliver the data on the potential of FDG-PET/CT scans for prediction of KRAS/BRAF status, and suggests that FDG-PET/CT scans may play a key role in determining therapeutic strategies for patients with CRC by noninvasively determining tumor response to anti-EGFR–based therapy.

**Patients and Methods**

**Study population**

A total of 63 patients with CRC underwent FDG-PET/CT scans before tumor resection at Kyoto University Hospital between April 2009 and September 2010. The diagnosis of CRC was confirmed by pathologic examination of surgical specimens. No patients received prior chemotherapy and/or radiation therapy. Twelve patients were excluded because they had the following nontumor-related factors that can affect FDG accumulation (16–18): uncontrolled diabetes mellitus; that is, blood glucose level ≥150 mg/dL (n = 3); severe stenosis with cessation of oral intake and administration of antibiotics (n = 4); complete obstruction requiring a decompression tube (n = 3); and severe inflammation with C-reactive protein (CRP) ≥5.0 mg/dL (n = 2). Finally, a total of 51 patients were included in this retrospective study. All tumors were larger than 20 mm, which minimize bias of partial volume effect (19). This study protocol was approved by the Institutional Review Board of Kyoto University, Kyoto, Japan, and patients provided their consent for data handling.

**PET imaging and analysis**

PET/CT scans were carried out with a combined PET/CT scanner (Discovery ST Elite; GE Healthcare). This system integrates a PET scanner with a multidetector-row CT (16 detectors), and permits the acquisition of coregistered CT and PET images in a single examination. Patients fasted for at least 4 hours before FDG administration. We checked patients’ plasma glucose levels just before injecting FDG, and there were no patients whose blood glucose level exceeded 150 mg/dL in this study. Data acquisition started approximately 60 minutes (range, 49–79 minutes; average, 63.6 minutes) after the injection of a standard dose of 3.7 MBq/kg of FDG. Initially, starting at the level of the upper thigh, the low-dose CT scans were carried out with the following parameters: 40–60 mA, 120 kV, 0.6-second tube rotation, and 3.75-mm section thickness. The CT images were acquired during shallow breathing, and scanning included the area from the upper thigh to the skull. Immediately after CT, a PET emission scan was carried out with an acquisition time of 2 to 3 minutes per bed position. The total acquisition time was approximately 20 minutes. The CT data were used for attenuation correction, and images were reconstructed using the 3-dimensional iterative reconstruction algorithm called VUE Point Plus.

For quantitative analysis, a board-certified radiologist/nuclear medicine physician (Y. Nakamoto) assessed FDG accumulation on a workstation (Advantage Workstation, GE Healthcare) by calculating the standardized uptake value (SUV) in the regions of interest placed over the suspected lesions and the normal liver. The SUV was calculated using the following formula: $SUV = \frac{C_{dc}}{D_i/W}$, where $C_{dc}$ is the decay-corrected tracer tissue concentration (in Becquerel per gram); $D_i$ is the injected dose (in Becquerel); and $W$ is the patient’s body weight (in gram). For evaluating primary CRC, the highest SUV in a primary tumor was taken as $SUV_{max}$, and the tumor-to-liver SUV ratio (TLR) was also calculated as follows: $TLR = \frac{SUV_{max}}{SUV_{liver}}$, where the liver SUV was taken as the average of SUVs at 5 points in the normal liver tissues.

**KRAS and BRAF mutational analysis**

DNA was extracted from formalin-fixed, paraffin-embedded tumor tissue sections by the QIAamp FFPE Tissue Kit
(QIAGEN KK). KRAS exon 2 and BRAF exon 15 were amplified by PCR. The PCR products were directly sequenced by an ABI 3130 Genetic Analyzer (Applied Biosystems) according to the manufacturer’s instruction.

**Expressions of GLUT1 and HXK-II**

Five-micrometer formalin-fixed paraffin sections were used for immunohistochemical staining with anti-GLUT1 (Abcam) and anti-HXK-II (Cell Signaling Technology) antibodies, using citrate-steam recovery. The stainings of GLUT1 and HXK-II were evaluated by scoring the percentage of positively stained cells as follows: low, <10% cells stained; moderate, 10%–50% cells stained; high, >50% cells stained.

**Statistical analysis**

All values are expressed as means ± SD. Differences in SUV\(_{\text{max}}\) or TLR between mutated and wild-type KRAS/BRAF were tested by a Mann–Whitney U test. The statistical significance of differences in Table 2; Supplementary Tables S2 and S3 was determined by the \(\chi^2\) test or Mann–Whitney U test. Expression levels of GLUT1 and HXK-II between the 2 groups were assessed by a \(\chi^2\) test. All analyses were 2 sided, and a \(P\) value of less than 0.05 was considered statistically significant. To determine the factors associated with KRAS and/or BRAF mutational status in Table 3, multivariate logistic regression analysis was used and factors with a \(P\) value of 0.25 or less were included in the model. Relationships between variables were determined by the Pearson correlation coefficients. Statistical analyses were conducted with the SPSS Software, version 11.50 (SPSS Inc.).

**Results**

**Patients’ population**

Patients and tumor characteristics are listed in Table 1. All patients underwent primary tumor resection within 28 days after FDG-PET/CT scans (average 13.6 days, range 1–28 days). KRAS mutations at codons 12 and 13 were found in 19 and 3 (37% and 6%, respectively) of 51 available primary tumors, whereas a BRAF mutation at codon 600 (V600E) was found in only one (2%). All patients with mutated KRAS tumors had wild-type BRAF tumors, consistent with results of previous studies which indicate that KRAS and BRAF mutations occur in a mutually exclusive pattern (11, 12, 15). Increased FDG accumulation was verified in all primary tumors when compared with normal liver tissues. SUV\(_{\text{max}}\) and TLR of the primary tumors were 14.5 ± 6.8 and 7.5 ± 3.6, respectively. Figure 1 shows typical FDG-PET/CT scans of the patients with mutated KRAS (Fig. 1A, top) and wild-type KRAS (Fig. 1B, top).

**Correlation between SUV\(_{\text{max}}\)/TLR and KRAS/BRAF mutations**

On the basis of KRAS and BRAF mutation analysis of the primary tumors, patients were classified into 2 groups; patients with wild-type KRAS and BRAF (wild-type KRAS/BRAF; \(n = 28\)) and patients with either mutated KRAS or BRAF (mutated KRAS/BRAF; \(n = 23\)). Table 2 shows the results of univariate analysis of each factor. No significant differences between these 2 groups were found in terms of age, sex, blood glucose level, serum CRP level, serum carcinoembryonic antigen (CEA) level, T-category, N-category, M-category, histologic type, lymphatic invasion, venous invasion, primary tumor size, and FDG uptake in
normal liver tissues. However, a significant difference in FDG accumulation into the primary tumors was found between these 2 groups (Fig. 2). Namely, SUV_{max} was significantly higher in primary tumors with mutated KRAS/BRAF than in primary tumors with wild-type KRAS/BRAF (17.3 ± 7.1 and 12.1 ± 5.7, respectively; \( P = 0.006 \); Fig. 2A). TLR was also significantly higher in primary tumors with mutated KRAS/BRAF than those with wild-type KRAS/BRAF (9.2 ± 3.9 and 6.1 ± 2.6, respectively; \( P = 0.001 \); Fig. 2B). In the multivariate analysis including factors with a \( P \) value of 0.25 or less, only SUV_{max} remained significantly correlated with KRAS and BRAF mutations [Table 3; OR, 1.17; 95% confidence interval (CI), 1.03–1.33; \( P = 0.016 \)]. Similar results were found when SUV_{max} was substituted with TLR (Table 3; OR, 1.40; 95% CI, 1.08–1.80; \( P = 0.01 \)). We then sought to determine the threshold for optimal differentiation between these 2 groups. Receiver operating characteristic curve analysis revealed that the highest accuracy (75%) was obtained with a particular SUV_{max} cutoff value (Supplementary Table S1). With a cutoff value of 13, sensitivity and specificity for the prediction of KRAS and BRAF mutations were 74% (17 of 23) and 75% (21 of 28), respectively (positive predictive value (PPV), 71%, 17 of 24; negative predictive value (NPV), 78%, 21 of 27; accuracy, 75%, 38 of 51). With a TLR cutoff value of 7, sensitivity and specificity were 70% (16 of 23) and 71% (20 of 28), respectively (PPV, 67%, 16 of 24; NPV, 74%, 20 of 27; accuracy, 71%, 36 of 51). Taken together, these results suggested that FDG-PET/CT scans can be predictive of KRAS and BRAF status of primary CRC.

### Correlation between \(^{18}\)F-FDG accumulation, GLUT1 expression, and HKK-II expression

Regarding FDG accumulation into primary tumors, univariate analysis of each clinicopathologic factor indicated that only KRAS and BRAF status was significantly correlated with SUV_{max} and TLR (\( P = 0.006 \) and 0.001, respectively; Supplementary Tables S2 and S3). Primary tumor size was not correlated with SUV_{max} and TLR (\( P = 0.681 \) and 0.776, respectively; Supplementary Fig. S1). The relationship between stage I–IV classification and FDG accumulation was not statistically significant (\( P = 0.751 \); the Kruskal–Wallis test).

Next, GLUT1 and HKK-II expression were investigated by immunohistochemical analysis of the 51 primary tumors (Fig. 1A and B, bottom). Quantitatively, GLUT1 expression in cancer cells was positively correlated with SUV_{max} and TLR whereas HKK-II expression was not (Fig. 1C). SUV_{max} was significantly higher in tumors with high GLUT1 expression (\( n = 13; 21.1 ± 6.4 \)) than tumors with moderate (\( n = 28; 13.0 ± 5.6; P < 0.01 \)) or low GLUT1 expression.

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**Table 2. Univariate analysis of factors associated with KRAS/BRAF status**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Mutated KRAS/ BRAF (n = 23)</th>
<th>Wild-type KRAS/ BRAF (n = 28)</th>
<th>Univariate P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/female</td>
<td>15/8</td>
<td>0.57</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Mean ± SD</td>
<td>102 ± 11</td>
<td>0.50</td>
</tr>
<tr>
<td>CRP</td>
<td>Mean ± SD</td>
<td>0.3 ± 0.3</td>
<td>0.41</td>
</tr>
<tr>
<td>CEA</td>
<td>Mean ± SD</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>&lt;5.0</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>≥5.0</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>T-category</td>
<td>Tis, T1, T2</td>
<td>11</td>
<td>0.23</td>
</tr>
<tr>
<td>N-category</td>
<td>Negative</td>
<td>12</td>
<td>0.39</td>
</tr>
<tr>
<td>M-category</td>
<td>Negative</td>
<td>20</td>
<td>0.65</td>
</tr>
<tr>
<td>Histologic type</td>
<td>Well/moderate</td>
<td>20</td>
<td>0.71</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>Negative</td>
<td>14</td>
<td>0.77</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>Negative</td>
<td>10</td>
<td>0.23</td>
</tr>
<tr>
<td>Tumor size, mm</td>
<td>Mean ± SD</td>
<td>49.4 ± 22.6</td>
<td>0.63</td>
</tr>
<tr>
<td>SUV_{max}</td>
<td>Mean ± SD</td>
<td>17.3 ± 7.1</td>
<td>0.006</td>
</tr>
<tr>
<td>FDG uptake in</td>
<td>Mean ± SD</td>
<td>1.9 ± 0.2</td>
<td>0.33</td>
</tr>
<tr>
<td>normal liver</td>
<td>TLR</td>
<td>Mean ± SD</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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**Table 3. Multivariate analysis of KRAS/BRAF status in patients with CRC (n = 51)**

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (0.97–1.13)</td>
</tr>
<tr>
<td>T-category</td>
<td>6.08 (1.02–36.3)</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>0.26 (0.05–1.23)</td>
</tr>
<tr>
<td>SUV_{max}</td>
<td>1.17 (1.03–1.33)</td>
</tr>
</tbody>
</table>

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**Note:** SUV_{max} at a cutoff value of 13 had a sensitivity of 74% (17 of 23) and a specificity of 75% (21 of 28) with a PPV of 71% (17 of 24) and an NPV of 78% (21 of 27) for the prediction of KRAS and BRAF mutations. With a TLR cutoff value of 7, sensitivity and specificity were 70% (16 of 23) and 71% (20 of 28), respectively (PPV, 67%, 16 of 24; NPV, 74%, 20 of 27; accuracy, 71%, 36 of 51).
expression \( (n = 10; 10.1 \pm 3.8; P < 0.01) \). TLR was also significantly higher in tumors with high GLUT1 expression (11.3 \pm 3.4) than tumors with moderate (6.5 \pm 2.7; \( P < 0.01 \)) or low GLUT1 expression (5.4 \pm 2.1; \( P < 0.01 \)). Meanwhile, SUV\(_{\text{max}}\) and TLR were comparable in tumors with high GLUT1 expression than those with moderate and low GLUT1 expression (\( P < 0.01 \) for Mann–Whitney U test). In addition, a significant correlation was confirmed between KRAS/BRAF status and GLUT1 expression (\( P < 0.001 \)) but not between KRAS/BRAF status and HXK-II expression (\( P = 0.80; \) Table 4). These results can suggest that KRAS and BRAF mutations increase FDG accumulation into primary CRCs, possibly by upregulation of GLUT1 expression, but not HXK-II expression.

**Discussion**

FDG-PET/CT scans have been widely used for diagnosis, monitoring treatment response, surveillance, and prognostication of a variety of cancers. However, the underlying molecular biology behind the clinical observations of FDG accumulation has not yet been elucidated. This study shows that SUV\(_{\text{max}}\) and TLR are significantly higher in KRAS/BRAF-mutated tumors than wild-type tumors, which indicates that, in CRC, FDG accumulation might reflect genetic mutations, that is, KRAS and BRAF.

Studies have shown that FDG accumulation in human cancer cells depends largely on 2 classes of proteins GLUTs and HKs (1). FDG is transported into the cell via a family of 14 facilitative GLUTs, and then phosphorylated by HKs to FDG-6-phosphate, which becomes trapped within the cell. Although different types of tumors have distinct expressions of different GLUTs, upregulation of GLUT1 is common in most cancers and is linked to tumor stage and patient prognosis (20, 21). In addition, increased levels of HK (primarily, HK-II of the 4 types in mammalian tissue) have also been implicated in many cancers (22, 23). Although biologic correlates of FDG accumulation in CRC are less well studied, several studies have suggested that GLUT1-mediated FDG accumulation is more essential than HK activity in CRC (1). Consistent with these reports, our study also indicated that GLUT1 expression was positively correlated with SUV\(_{\text{max}}\) and TLR whereas HXK-II expression was not. Other GLUT proteins (e.g., GLUT3) and enzymes downstream of HK (e.g., pyruvate dehydrogenase-kinase 1) may be involved in FDG accumulation into cancer cells (1), and this is a matter for further study.

The mechanisms underlying FDG accumulation into cancer tissues are complex. These factors include tumor-related (e.g., histologic differentiation, vascular factors, hypoxia, and tumor size) and nontumor-related
components (e.g., diabetes mellitus and inflammation; ref. 16–18). In this study, patients with uncontrolled diabetes mellitus and severe inflammation with severe stenosis and obstruction were not included. Yun and colleagues recently reported that the increase of GLUT1 expression and glucose uptake is critically dependent on KRAS and BRAF mutations in CRC cell lines (2). In vitro assays with these cell lines indicated that KRAS and BRAF mutations caused about 2.0- to 3.0-fold increase in glucose uptake by upregulation of GLUT1 expression (2). As expected from the in vitro study, primary tumors with mutated KRAS/BRAF showed about 1.5- to 1.7-fold increase in SUVmax and TLR compared with those with wild-type KRAS/BRAF (P < 0.01) in this clinical study.

Oncogenic activation of KRAS can influence several cellular processes that regulate morphology, proliferation, and motility (24), and KRAS mutations occur in a variety of human malignancies, most frequently in pancreatic cancer, non–small cell lung carcinoma and colon cancer. The majority of KRAS mutations result in amino acid substitutions in exon 2 at codons 12 and 13. On July 2009, the U.S. Food and Drug Administration updated the labels of 2 anti-EGFR monoclonal antibodies (cetuximab and panitumumab) indicated for the treatment of metastatic CRC to include information about KRAS mutations. Although the presence of wild-type KRAS gene does not guarantee the response to anti-EGFR monoclonal antibodies, a number of large studies have shown that cetuximab has significant efficacy in treatment of patients with metastatic CRC with wild-type KRAS tumors (25, 26). From a clinical perspective, predictors of outcome for patients with metastatic CRC who are candidates for anti-EGFR monoclonal antibody therapies have recently acquired a new strategic importance.

KRAS interacts with several effector proteins, including Raf kinases and phosphoinositide 3-kinases (PI3K). There is also growing evidence that BRAF mutation is also an important predictor of resistance to anti-EGFR monoclonal antibodies (7–9), whereas preliminary studies of PIK3CA have been conflicting (27, 28). However, the clinical impact of testing for BRAF will depend on the prevalence of BRAF mutation in CRC. In this study, BRAF mutation was found in only one patient (2%), which is lower than in previous population studies (7, 11–13) and may reflect racial differences. Notably, a single glutamic acid for valine substitution at codon 600 (V600E) accounts for approximately 90% of the BRAF mutations found in human cancers (11). With rare exceptions, V600E BRAF mutation is found in a mutually exclusive pattern with KRAS mutation, suggesting that these genetic events activate a set of common downstream effectors of transformation.

CRC cell lines with KRAS/BRAF mutations exhibit increased GLUT1 expression, increased glucose uptake, and increased glycolysis independent of hypoxia-inducible factor (HIF)-1α status in normoxic conditions (2), even though HIF-1α has been shown to regulate transcription of GLUT1 in hypoxic conditions (29). Unlike KRAS and BRAF, PIK3CA does not have a clear effect on GLUT1 expression in normoxic conditions (2). When CRC cells were treated under hypoxic conditions, mutated KRAS enhanced the translation of HIF-1α through PI3K pathway, whereas mutated BRAF enhanced the translation of HIF-2α through the MAPK/ERK pathway (30). Recently, it was reported that mitochondrial metabolism allowed for generation of reactive oxygen species required for KRAS-induced tumorigenicity through the MAPK/ERK pathway (31). The molecular mechanisms causing upregulation of glucose metabolism in CRC have not yet been investigated.

It remains unclear whether mutational testing of primary tumors is sufficient for correct characterization of metastatic tumors in all cases. Some studies have found a high (>90%) concordance of KRAS mutations between primary CRCs and metastases (32, 33). However, others have reported a relatively high number (>30%) of discrepant results and recommended to test the metastatic tumor rather than the primary tumor, because it is the metastatic disease that is responsible for the disease-specific morbidity and mortality (34–37). Tumor tissue samples resected by biopsy or surgery are necessary for mutational testing, but the samples from the metastatic tumors are often difficult to

![Figure 2](https://example.com/figure2.png)

**Figure 2.** A, analysis of SUVmax according to the status of KRAS and BRAF. SUVmax was significantly higher in patients with mutated KRAS or BRAF than in those with wild-type KRAS and BRAF (P = 0.006; exact Mann-Whitney U test). Bars, means. B, analysis of TLR according to the status of KRAS and BRAF. TLR was significantly higher in patients with mutated KRAS or BRAF than in those with wild-type KRAS and BRAF (P = 0.001; exact Mann-Whitney U test). Bars, means.

| Table 4. Relationship between KRAS/BRAF status and expressions of GLUT1 and HXK-II |
|---------------------------------|-----|-----|-----|
| GLUT1 expression               | Low | Moderate | High |
| Mutated KRAS/BRAF              | 2   | 8    | 13  |
| Wild-type KRAS/BRAF            | 8   | 20   | 0   |
| HXK-II expression              |     |      |     |
| Mutated KRAS/BRAF              | 1   | 7    | 15  |
| Wild-type KRAS/BRAF            | 0   | 11   | 17  |
obtain due to difficulty of access to the tumors and the need for an invasive procedure. In addition, heterogeneity of KRAS status within a single primary CRC tumor has been reported (7, 38, 39). Therefore, resected specimens for mutational testing may not reflect the macroscopic status of the whole tumor. This study showed that FDG-PET/CT scans can predict the KRAS/BRAF status of primary CRC with an accuracy of 75%. FDG-PET/CT scans may not be enough for predicting the KRAS/BRAF status determined by mutational testing but may reflect the macroscopic status of KRAS/BRAF mutations. Thus, elucidating whether FDG-PET/CT scans can be used to predict the KRAS/BRAF status of metastatic CRC represents the next challenge. The anatomic location of the metastatic CRC may need to be considered when it is significantly affected by respiratory motion (e.g., near the diaphragm).

In conclusion, this study is a relatively small, retrospective analysis, but highlights the fact that FDG accumulation in primary CRC with mutated KRAS/BRAF is significantly higher than in those with wild-type KRAS/BRAF, which may be attributed mainly to upregulation of GLUT1 expression. In this study, SUVmax and TLR of the one tumor with BRAF mutation were high (30.8 and 16.2, respectively). Although the larger number of patients with BRAF mutation is needed, these results indicate that FDG-PET/CT scans might be predictive of KRAS and BRAF mutations in CRC. Thus, this study provides a novel possibility of FDG-PET/CT scans to be used for noninvasive determination of therapeutic strategies for patients with CRC. To validate this idea, further prospective studies with a larger number of patients and clinical follow-up are needed. Furthermore, it should be investigated whether FDG-PET/CT scans might predict the actual response to anti-EGFR–based regimens as well as survival rates.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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