Relationship Between Dual-Time Point FDG PET and Immunohistochemical Parameters in Preoperative Colorectal Cancer: Preliminary Study

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Abstract

Purpose The clinical availability of 2-deoxy-2-[18F] fluoro-D-glucose (FDG) dual-time point positron emission tomography/computerized tomography (DTPP) has been investigated in diverse oncologic fields. The aim of this preliminary study was to evaluate the relationship between various immunohistopathologic markers reflecting disease progression of colorectal cancer and parameters extracted from FDG DTPP in colorectal cancer patients.

Materials and Methods Forty-seven patients with histologically confirmed colorectal cancer were analyzed in this preliminary study. FDG DTPP consisted of an early scan 1 h after FDG injection and a delayed scan 1.5 h after the early scan. Based on an analysis of FDG DTPP, we estimated the maximum standardized uptake value (SUV) of tumors on the early and delayed scans (SUV_{early} and $SUV_{delayed}$, respectively). The retention index (RI) was calculated as follows: $(SUV_{delayed} - SUV_{early}) \times 100 / SUV_{early}$. The clinicopathological findings (size and T and N stages) and immunohistochemical factors [glucose transporter 1 (GLUT-1), hexokinase 2 (HK-2), p53, P504S, and β -catenin] were analyzed by visual analysis.

Results The RIs calculated from the SUVs ranged from -1.8 to 73.4 (31.8 ± 15.5). The RIs were significantly higher in patients with high T stages (T3 and T4) than with low T stages (T1 and T2; $p < 0.05$). Among the immunohistochemical analytic markers, GLUT-1 had the highest positive staining rate (93.6%) compared to other markers. Based on univariable analysis, it was shown that the RI of high-level GLUT-1 expression was significantly higher than low-level GLUT-1 expression ($p = 0.01$), and the RI of high-level p53 expression was slightly higher than low-level p53 expression ($p = 0.08$). Multivariate analysis to investigate a link between RI and clinicopathologic parameters of colorectal carcinoma showed that GLUT-1, p53, and T staging were independently connected with increased RIs ($p < 0.05$, total) using backward selection methods. There was no significant statistical relationship between SUV_{early} and $SUV_{delayed}$ and clinicopathologic parameters in this study.

Conclusion The RIs obtained from preoperative colorectal cancers had a significant relationship to tumor size, T staging, GLUT-1, and p53, in contrast to SUV_{early} or $SUV_{delayed}$. Compared with previous reports, our results showed that RI can better predict GLUT-1 expression than HK-2 and other immunohistochemical markers. This study demonstrated that the RI might have the potential to be applied as a prognostic marker in preoperative colorectal cancer.

Keywords FDG PET · Dual-time point imaging · Colorectal cancer · Glucose transporter · Hexokinase

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Introduction

2-Deoxy-2-[18 F] fluoro-D-glucose (FDG) positron emission tomography (PET) or PET/computed tomography (CT) has a pivotal role in staging and restaging after and during curative or conservative treatment to differentiate recurrence

from post-treatment changes and to predict survival in oncology [1–4].

Recently, FDG dual-time point PET (DTPP) has been based on the phenomenon that, with time, FDG uptake in tumor tissues increases, while FDG uptake in normal or benign tissues decreases, which could differentiate malignant lesions from background normal or benign tissues [5, 6]. Whether or not the role or universal implementation of FDG DTPP has been determined, a recent study reported that the percentage of maximal standardized uptake value (SUV_{max}) change over time is a strong prognostic factor in patients with lung adenocarcinoma and is complementary to other well-known factors [7]. In addition, it has been demonstrated that the retention index (RI) of the standardized uptake value (SUV) raises the accuracy for diagnosis of metastases and is superior to early or delayed imaging in terms of differentiating malignant FDG uptakes from non-metastatic uptake [8, 9]. While many FDG DTPP studies have been published, the relationship between various parameters of FDG DTPP and immunohistochemical factors, such as Ki-67, p53, hexokinase (HK)-2, and glucose transporter (GLUT), has not been conducted in colorectal cancer. GLUT is known to perform transcellular transport of glucose or glucose analogs, such as FDG, and is classified to three classes, including many subtypes [10]. In the current study, GLUT-1 and -3 were analyzed. Although GLUT-3 is known to be expressed primarily in neurons and striated muscle, it has been reported that GLUT-3 has a positive relationship with tumoral FDG uptake in human colon cancer cell lines in an animal study [11]. HK-2 has a pivotal role in the phosphorylation of intracellular FDG in most cancer cells [12], but in colorectal cancer there are few reports on the relationship between HK-2 and FDG uptake [13, 14]. Although the expression of alpha methylacyl-CoA-racemase (P504S), known as a dietary enzyme participating in red meat digestion, is known to have a relationship with colon carcinoma [15, 16], and nuclear type of β -catenin has been shown to indicate a poor prognosis in colorectal cancer [17–19], there are no reports evaluating the link between P504S and β -catenin and FDG PET.

Therefore, the purpose of this study was to evaluate the relationship between FDG DTPP and the aforementioned immunohistopathologic parameters in preoperative colorectal cancer.

Materials and Methods

Patients

This retrospective study was approved by our institutional review board. Seventy-five patients with newly diagnosed colorectal carcinoma underwent preoperative FDG DTPP

and a conventional workup, including enhanced CT and magnetic resonance imaging (MRI), between August 2008 and February 2011. The eligibility requirements included: (1) primary colorectal cancer proven by pathology, (2) no history of neoadjuvant treatment before surgery, and (3) patients less than 80 years old. Twenty-eight patients were excluded for the following reasons: inadequate specimens ($n=4$), a history of chemotherapy or radiation therapy before surgery ($n=23$), and external referral ($n=1$). Patients with histological types such as pure mucinous or signet ring cell carcinomas often showing false-negative results on FDG PET were excluded in this study. All patients underwent curative resection within 4 weeks after FDG DTPP and provided informed consent with respect to the handling of their specimens.

FDG DTPP and Data Analysis

All FDG PET/CT studies were conducted with a Gemini GXL 6 PET/CT system (Philips, Hamburg, Germany). All patients fasted for at least 6–12 h before FDG injection to sustain serum glucose concentrations <150 mg/dl. Patients were encouraged to receive adequate water intake or 500 ml of intravenous half-normal saline before testing and to avoid aggressive exercise or saunas for 1–2 days. FDG ($259\text{--}444$ MBq) was injected into all patients 1 h prior to early FDG PET/CT scanning. All patients received instructions on shallow breathing and motion reduction during image acquisition. DTPP was performed twice: the early scan (~ 60 min) ranged from mid-cranium to mid-thigh, and the delayed scan (~ 150 min) included the abdominopelvic cavity. For attenuation correction and anatomic information, a low-dose CT scan was obtained. The CT parameters were as follows: six detector rows, 50 mA; 140 kV, 5 mm slice thickness, 5 mm increment, 1.0 pitch, 0.75 s rotation time, and a matrix size of 512×512 . After CT scanning, emission data acquisition was performed caudocranially in the three-dimensional mode with a 144×144 matrix. The emission scan time at each position was 90 s, which was the same in the early and delayed phases. Each bed position of the early and delayed scans was 7–11 and 4–5 beds, respectively. FDG PET images were reconstructed with a three-dimensional iterative reconstruction algorithm based on LOR. The transaxial and axial resolutions were 5.3 and 6.0 mm in full width at half-maximum. Data were reoriented in axial, sagittal, and coronal sections, and a three-dimensional rotating projection.

For reviewing PET/CT images, specific registration software (Philips Syntegra) was applied in all cases. FDG PET/CT images were interpreted by two experienced nuclear medicine physicians (board-certified and with 5 and 7 years of PET/CT experience), who were unaware of clinical data and pathological results, with the exception of colonofibrosopic

findings, to differentiate the exact location of tumor FDG uptake and non-specific gastrointestinal FDG uptake. Any equivocal findings or disagreements were resolved by consensus. The important positive standard was prominent, intense FDG uptake with a concentric or eccentric bowel wall thickening at a similar site in which the main tumor was located on colonofibrosopic evaluation. Various irregular gastrointestinal FDG activities without CT attenuation changes and corresponding colonofibrosopic findings were considered benign findings in consensus. For semi-quantitative analysis of FDG uptake, SUV was analyzed based on the patient's body weight (estimated decay-corrected FDG concentration/administered dose/body weight). Manually drawn regions of interest were placed in the highest FDG uptake of the tumor to calculate the maximum SUV twice (SUV_{early} and $SUV_{delayed}$). Like other DTPP studies, we calculated the retention index (RI) as follows: $RI = (SUV_{delayed} - SUV_{early}) \times 100 / SUV_{early}$.

Immunohistochemical Analysis and Scoring

Hematoxylin-eosin stained slides from each colorectal cancer were reviewed by a pathologist to select representative sections for tissue microarray (TMA). From individual paraffin-embedded colorectal cancers, a tissue cylinder with a diameter of 4 mm was arrayed into a recipient paraffin block. TMA blocks were sectioned at a thickness of 4 μ m, deparaffinized with xylene, rehydrated with ethanol, and washed. Sections were then immersed in 3% hydrogen peroxide to block endogenous peroxidase activity and incubated with primary antibodies. Antigen retrieval was carried by microwave heating with citrate buffer. The primary antibodies used are summarized in Table 1. Expressions were detected using a Bond Polymer Refine Detection kit (Leica Biosystems, Newcastle, UK). Antibody-antigen reaction was visualized using diaminobenzidine and counterstaining with Mayer's hematoxylin. All of the immunohistochemical slides were examined by a pathologist, and immunostaining was scored in a semi-quantitative fashion. Histologically, colorectal adenocarcinoma was graded as well (>95% with gland formation), moderately (50–95% with gland formation), and poorly differentiated (0–49% with gland formation) on the basis of the percentage of gland formation.

Lymphovascular invasion was defined by the presence of tumor emboli within vascular channels. All immunohistochemical variables were dichotomized. The positive staining pattern and scoring system are summarized in Table 2.

Statistical Analysis

Statistical analyses were performed with SPSS (version 13.0.0; SPSS, Inc., Chicago, IL). The relationship between SUV parameters and tumor markers or maximal tumor diameter was evaluated by Spearman's rank correlation. Univariate analysis of SUV parameters was conducted by the Kruskal-Wallis test and Mann-Whitney U non-parametric test. Multiple linear regression test was carried out to evaluate a multivariate analysis of RI and clinicopathologic parameters. A P-value <0.05 was considered statistically significant.

Results

Patient Characteristics

The characteristics of the preoperative colorectal cancer patients included in this study are demonstrated in Table 3. Forty-seven patients were enrolled in this study, which consisted of 29 males and 18 females with a mean age of 65.0 ± 11.6 years (range, 32–78 years). The histopathological evaluations were confirmed as pure adenocarcinoma ($n=46$) and adenosquamous carcinoma with an overall prominent moderately differentiated adenocarcinoma ($n=1$). The median tumor size was 50 mm (range, 11–120 mm). The clinical stages shown in this table were categorized according to the AJCC (6th guideline). Among three patients with distant metastases, two had liver metastases and one had multiple metastases to the small bowel, uterus, and ovaries. Eight patients underwent curative surgical treatment during the follow-up period. The other patients underwent intravenous chemotherapy with or without radiation therapy plus long-term oral chemotherapy or oral adjuvant chemotherapy alone. The median follow-up period was 14 months (range, 5–28 months).

Table 1 Primary antibodies used for immunohistochemistry

	Primary antibody	Clone	Manufacture	Dilution	Antigen retrieval ^a
GLUT-1, glucose transporter 1; GLUT-3, glucose transporter-3; HK-2: hexokinase-2; P504S, alpha methylacyl-CoA-racemase	Glut-1	EPR3915	Epitomics, Burlingame, CA	1:1000	No
	Glut-3	Polyclonal	Novus Biologicals, Littleton, CO	1:200	No
	HK-2	Polyclonal	Abnova, Taipei, Taiwan	1:50	No
	p53	DO-7	Novocastra, Newcastle, UK	1:100	Yes
	P504S	13H4	Dako, Carpinteria, Denmark	1:500	Yes
	β -Catenin	CAT-5H10	Zymed, San Francisco, CA	1:50	Yes

^aMicrowave in 10 mM sodium citrate buffer

Table 2 The patterns and scoring of immunohistochemical staining

Primary antibody	Positive staining pattern	Scoring
Glut-1	Membranous with/without cytoplasm	Low ^a /high (cutoff value: 50%)
Glut-3	Membranous (predominantly luminal surface)	Low/high (cutoff value: 50%)
HK-2	Cytoplasmic (para-Golgi)	Low/high (cutoff value: 50%)
p53	Nuclear	Low/high (cutoff value: 30%)
P504S	Cytoplasmic	Low/high (cutoff value: 50%)
β-catenin	Nuclear	Nonnuclear ^b /nuclear

GLUT-1, glucose transporter 1; GLUT-3, glucose transporter-3; HK-2: hexokinase-2; P504S, alpha methylacyl-CoA-racemase

^a This low grade scoring includes negative staining in the immunohistochemical analysis of this study

^b Nonnuclear; membranous and cytoplasmic expression

The Relationship Between Patient Characteristics and Various SUV Parameters

In 47 patients, all tumors with the exception of 1 had an SUV_{delayed} (mean±SD, 15.8±7.3) of the primary colorectal tumor that was greater than the SUV_{early} (11.8±5.2). There was a significant difference ($p<0.001$, Wilcoxon signed-

Table 3 Patient characteristics

Characteristics	No. of patients	%
Gender, male/female	29/18	
Age, years	65.0±11.6 (32–78)	
T stages		
T1	2	4.3
T2	5	10.6
T3	38	80.8
T4	2	4.3
N stages		
N0	21	44.7
N1	9	19.1
N2	14	29.8
N3	3	6.4
Differentiation		
Good	12	25.6
Moderated	30	63.8
Poor	5	10.6
Lymphovascular invasion		
Yes	13	27.7
No	34	72.3
Staging		
I	7	14.9
II	14	29.8
III	23	48.9
IV	3	6.4
CEA, range (ng/ml)	5.6±10.6 (0.5–66.1 ng/ml)	
CA 19–9, range(ng/ml)	32.7±42.9 (1.4–228.4 ng/ml)	

rank test) and correlation ($r=0.960$, $p<0.001$) between the SUV_{delayed} and SUV_{early}. The RI calculated from the SUVs ranged from -1.8 to 73.4 (31.8 ± 15.5). No significant correlation existed between the SUV parameters and the tumor markers, including carcinoembryonic antigen (CEA) and cancer antigen (CA) 19–9 ($p=0.780$ and $p=0.913$, respectively). In 38 patients with exact records regarding maximal tumor diameter, all three SUV parameters showed significant correlations (SUV_{early}: $r=0.377$, $p=0.02$; SUV_{delayed}: $r=0.452$, $p=0.004$; RI: $r=0.388$, $p=0.016$) compared with other clinicopathologic factors. In addition, three SUV parameters of this study had an insignificant relationship with other patient characteristics, such as tumor differentiation and lymphovascular involvement, but the RI was significantly higher in patients with high T stages (T3 and T4) than with low T stages (T1 and 2; $p<0.05$).

The Relationship Between Immunohistochemical Analytic Factors and Various SUV Parameters

Among diverse immunohistochemical analytical markers, GLUT-1 had the highest positive expression rate (93.6%). GLUT-3 and HK-2 had positive expression rates of 29.8% and 57.5%, respectively. The percentages of positive expression of p53 and P504S were 59.5% and 76.6%, respectively. Tumor cells revealed nuclear expression of β-catenin in 10 cases of 47 patients (21.3%). GLUT-1 was manifested mostly along the membranous portion with or without cytoplasmic staining, and GLUT-3 and HK-2 were expressed chiefly along the membranous portion. FDG DTPP and immunohistochemical staining of a 53-year-old patient with rectal cancer are shown in Fig. 1.

Through univariate analysis of three SUV parameters with respect to immunohistochemical factors, there was no significant relevance between immunohistochemical factors and SUV_{early} or SUV_{delayed} scans, although SUV_{early} and SUV_{delayed} of high-level GLUT-1 expression were slightly higher than low-level GLUT-1 expression, respectively ($p=0.24$ and $p=0.07$). Table 4 shows the univariate analysis of

Fig. 1 Dual time point FDG PET/CT and immunohistochemical analysis of a 53-year-old man with rectal cancer (T3/N2).

(a) The early FDG PET/CT demonstrates diffuse FDG uptake [maximal standardized uptake value (SUV_{max})=9.1] with concentric wall thickening. (b) The delayed FDG PET/CT 90 min after first scan shows more FDG uptake of the primary lesion (SUV_{max} =12.9) than the early scan. The retention index of this patient is 40.3, which is higher than the mean value (31.8 ± 15.3) of this study. C-H Immunohistochemical analysis showed GLUT-1, HK-2, p53, GLUT-3, P504S, and β -catenin in order (original magnification $\times 400$). Tumor cells showed positive membranous staining for GLUT-1 (c), positive nuclear staining for p53 (e), positive cytoplasmic staining for P504S (g), negative staining for HK-2 (d), and GLUT-3 (f), and normal membranous staining for β -catenin (h). Twenty-two months after low anterior resection had been performed, multiple enlarged lymph nodes with high FDG uptake (SUV_{max} range, 3.0–6.2) and high CEA (=38.3 ng/dl) suggestive of metastasis were found

RI according to diverse clinicopathologic variables. Figure 2 shows that the RI of high-level GLUT-1 was significantly higher than low-level GLUT-1 expression ($p=0.01$) compared with SUV_{early} and $SUV_{delayed}$. Figure 3 shows that the RI of high-level p53 expression was slightly higher than low-level p53 expression ($p=0.08$), comparing SUV_{early} and $SUV_{delayed}$ ($p=0.33$ and $p=0.25$, respectively), although the relationship did not show strong relevance. No significant relationship between HK-2, P504S, and β -catenin and SUV parameters was found. Table 5 shows the results of multivariate analysis to investigate a link between RI and clinicopathologic parameters of colorectal carcinoma. These parameters included T staging, N staging, differentiation, lymphovascular invasion, GLUT-1, GLUT-3, HK-2, P53,

P504S, and β -catenin. p53 (low vs. high) and T staging (T1-2 vs. T3-4) was shown to be significantly related to increased RI ($p=0.007$, both). When this analysis was performed by a backward selection method (not shown), GLUT-1, p53, and T staging were independently connected with increased RIs ($p<0.05$, total).

Discussion

This study is a preliminary report demonstrating the relationship between multiple parameters obtained from FDG DTPP and clinicopathological factors in preoperative colorectal cancers. The present study showed that the RI in the

Table 4 Univariate analysis of the retention index according to various clinicopathological variables

Variables		n	Median RI (IQR ^a)	P value ^b
T staging	T 1 & 2	7	18.7(11.1–29.3)	0.02
	T 3 & 4	40	34.2(26.5–44.7)	
N staging	Negative(N0)	21	29.3(17.8–42.4)	0.62
	Positive(N1–3)	26	33.3(24.5–45.7)	
Differentiation	Good	13	34.6(15.1–43.5)	0.99
	Moderate	29	31.8(23.1–42.4)	
	Poor	5	29.5(28.6–35.8)	
Lymphovascular invasion	Negative	34	31.8(17.5–40.6)	0.45
	Positive	13	29.5(24.5–38.9)	
GLUT-1	Low	9	17.5(10.2–28.4)	0.01
	High	38	34.4(25.0–42.6)	
GLUT-3	Low	36	29.3(23.2–40.6)	0.61
	High	11	34.4(21.5–45.7)	
HK-2	Low	30	28.8(17.5–39.2)	0.17
	High	17	38.5(25.8–43.8)	
P-504S	Low	35	33.9(17.4–40.6)	0.52
	High	12	28.2(23.4–43.9)	
P53	Low	40	28.9(11.1–50.1)	0.08
	High	7	41.4(35.4–73.4)	
β -Catenin	Nonnuclear ^c	37	29.4(12.5–50.1)	0.56
	Nuclear	10	32.3(9.8–52.3)	

GLUT-1, glucose transporter 1;
GLUT-3, glucose transporter-3;
HK-2, hexokinase-2; P504S,
alpha methylacyl-CoA-racemase

^aIQR interquartile range

^bP values were estimated
using the Kruskal–Wallis and
Mann–Whitney U tests

^cNonnuclear; membranous
and cytoplasmic expression

high GLUT-1 group was significantly higher than in the low GLUT-1 group, and the delayed SUV_{max} in the high GLUT-1 group was slightly higher than in the low GLUT-1 group, although statistical relevance was not strong. This study showed that RI was slightly different according to low- and high-level p53 expression.

Since FDG DTPP was introduced as an additional modified tool of FDG PET that enables distinguishing malignant lesions from inflammatory processes or benign lesions, recently, several useful aspects of DTPP have been evaluated in diverse benign disorders, such as diffuse interstitial lung

disease and osteomyelitis [20–23]. Although it was not determined that diverse variables, such as RI inferred from FDG DTPP, predict patient prognosis, some published reports have demonstrated that the change in lesional FDG uptake has a link with clinicopathological factors related to long-term prognosis and could predict patient survival in primary lung cancer and head and neck cancer [7, 24]. Sanghera et al. [24] reported that tumor stage and the percentage difference in 1- and 2-h SUV were a potential prognostic indicator of long-term survival. Even in benign lung disease, Umeda et al. [22] illustrated that RI for

Fig. 2 The relationship between RI (left) or SUV_{early} (right) and GLUT-1. A significant difference was found not in the SUV_{early} group ($p=0.42$), but in the RI group ($p<0.05$)

Fig. 3 The relationship among three SUV parameters, including SUV_{early} (open bars), $SUV_{delayed}$ (cross-hatched bars), and RI (hatched bars), according to the low and high level of p53 expression. Although there was no important statistical difference among them, RIs revealing a high expression of p53 were higher than the low expression of p53 ($p=0.08$) compared with SUV_{early} and $SUV_{delayed}$ ($p=0.86$ and 0.72 , respectively)

idiopathic interstitial pneumonia was significantly greater in patients with deteriorated pulmonary function than in cases without deteriorated pulmonary function after a 1-year observation period ($p<0.0001$). Recently, in primary lung cancer, Zhuang et al. [7] showed that patients with a $RI >25\%$ had a median survival of 15 months compared with 39 months for those with a $RI <25\%$; based on multivariate analysis using Cox proportional hazards regression, RI was independently correlated with the overall survival. Thus, the more the RI increases, the worse the prognosis is. In colorectal cancer, GLUT-1 has been introduced as one of the independent survival parameters. Haber et al. [25] showed that GLUT-1 was strongly associated with neoplastic progression in the colon, and assessment of the extent of

GLUT-1 immunostaining in colorectal carcinoma could identify patients with a poorer prognosis. Younes et al. [26] revealed that GLUT-1 expression in a high proportion of cancer cells was associated with a high incidence of lymph node metastasis. Even in early T1- and T2-stage colorectal carcinoma, GLUT-1 expression had a significant relationship with deep invasion, histological differentiation (moderate to poor), and depressed-type morphology, reflecting a poorer prognosis [27]. In the present study, RI was significantly higher in colorectal cancer patients with high-level GLUT-1 expression than in patients with low-level GLUT-1 expression. According to p53 expression as a prognostic factor in colorectal carcinoma [28–30], the RI was slightly higher in patients with high-level p53 expression than in patients with low-level p53 expression. Considering the RI differences according to p53, T staging, and GLUT-1 possibly reflecting patient prognosis in colorectal cancer, the RI of preoperative colorectal cancer might be a valuable tool to elucidate the prognosis of colorectal cancer after surgery similar to lung cancer and head and neck cancer. Of course, our results must be confirmed in further detailed and large-scale studies.

RI is defined as the gap between early and delayed maximal tumor uptake, indicated as a percentage in many studies, which may simply reflect the biological aggressiveness of the tumor. There has been relatively little information in the literature regarding the relationship between RI and clinical or immunohistochemical variables compared with diverse tumoral FDG uptake known as the SUV_{max} . Higashi et al. [31] demonstrated that the RI obtained from FDG-DTPP did not have a significant relationship with GLUT-1 expression, but showed a close relationship with the HK index ($p<0.05$). Tomita et al. [32] showed that RI correlated with VEGF/VPF expression in patients with schwannomas and other factors including GLUT-1, GLUT-3, HK-2, and CD31, and tumor size showed no correlation with SUV_{max} or RI. In our study, a significant relationship

Table 5 Multivariate analysis of the retention index in preoperative colorectal cancers

Variables	Unstandardized coefficients	Standard error	t	P
Tumor staging(T1-2 vs. T3-4)	18.9	6.7	2.834	0.007
Nodal staging(N0 vs. N1-3)	-3.68	4.6	-0.805	0.426
Differentiation(good and moderate vs. poor)	-0.4	7.0	-0.52	0.959
Lymphovascular invasion(negative vs. positive)	5.6	5.2	1.081	0.282
GLUT-1(low vs. high)	10.6	5.8	1.792	0.082
GLUT-3(low vs. high)	-0.4	5.1	-0.082	0.935
HK-2(low vs. high)	7.8	4.5	1.741	0.090
P53(low vs. high)	20.3	7.2	2.841	0.007
P504S(low vs. high)	5.5	4.9	1.124	0.269
β -Catenin(nuclear and non-nuclear)	-1.6	5.3	-0.313	0.756

Observation, 47; adjusted R^2 , 0.250; F -static 2.532; P -value, 0.02
 GLUT-1, glucose transporter 1;
 GLUT-3, glucose transporter-3;
 HK-2, hexokinase-2; P504S, alpha methylacyl-CoA-racemase

between RI and GLUT-1 was demonstrated ($p=0.01$) in preoperative colorectal cancer. It is presumed that immunohistopathologic factors possibly affecting RI might be different in regard to diverse oncologic diseases. GLUT-3 is known to play a role in FDG uptake of smooth muscle of the bowel wall, which is an important glucose transporter in ML-1 follicular thyroid carcinoma cells [33]. In our study there was no significant relationship among three tumoral FDG uptake variables and other immunohistochemical biomarkers (HK-2, P53, P504S, and β -catenin) in addition to GLUT-3. Few studies have reported the relationship between immunohistochemical parameters affecting FDG uptake such as GLUT and HK and markers of tumoral FDG uptake such as not only RI, but also SUV_{max} in the field of colorectal cancer. Further investigation will be needed to clarify the relationship between immunohistopathological factors related to FDG uptake and FDG DTPP or kinetic studies in primary colorectal cancer.

There were a few limitations in our study. Because of the small number of patients enrolled in this study, unlike other FDG PET studies, the SUV_{early} or $SUV_{delayed}$ difference between the low and high expression groups of GLUT-1 or HK-2 was not proven to be significant, although a very slight difference existed. Because of the good prognosis for preoperative colorectal cancer, the relationship between FDG DTPP or immunohistopathologic variables and survival was not investigated. After an adequate period to analyze patient prognosis, further studies involving a large number of patients will be required to ascertain the exact relationship between various immunohistopathologic parameters and diverse tumoral uptake extracted from FDG DTPP, including RI in colorectal cancer.

Conclusion

According to our preliminary study, the RI obtained from FDG DTPP of preoperative colorectal cancer was significantly higher in the high GLUT-1 group and high T stage than in the low GLUT-1 group and low T stage, and was slightly higher in the highly expressed p53 group than in the lowly expressed p53 group. A positive correlation between tumor size and RI was found. Although this study did not suggest strong effectiveness of diverse SUV parameters from a prognostic point of view, RI might have the potential to be applied as a prognostic marker in preoperative colorectal cancer.

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