Annals of Nuclear Medicine Vol. 20, No. 9, 597–604, 2006

Evaluation of 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography in gastric carcinoma: relation to histological subtypes, depth of tumor invasion, and glucose transporter-1 expression

Akira YAMADA,* Kazuhiro OGUCHI,** Mana FUKUSHIMA,*** Yutaka IMAI**** and Masumi KADOYA*

*Department of Radiology, Shinshu University School of Medicine
**PET Center, Departments of ***Pathology and ****Radiology, Aizawa Hospital

Objective: Variable uptake of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) has been noticed in positron emission tomography (PET) studies of gastric carcinoma patients, with low uptake occurring especially in some particular histological subtypes and early carcinomas. But this phenomenon has not been adequately explained. The aim of the present study is to clarify FDG uptake in gastric carcinomas especially focusing on histological subtypes, the depth of tumor invasion, and glucose transporter-1 (GLUT-1) expression which is considered to be one of the major factors for higher FDG uptake in human malignant tumors. ***Methods:*** FDG-PET was performed on 35 preoperative patients with gastric carcinoma. Forty macroscopically distinguishable lesions on a surgical specimen were histologically classified into two subtypes: Cohesive type (papillary adenocarcinoma, tubular adenocarcinoma, and solid type poorly differentiated adenocarcinoma) or Non-cohesive type (signet-ring cell carcinoma and non-solid type poorly differentiated carcinoma). GLUT-1 expression was immunohistochemically determined. Histological parameters (GLUT-1 expression, histological subtypes, the depth of invasion, lymphatic permeation, venous invasion and tumor size) were evaluated, and factors for FDG uptake (detectability and the degree) and GLUT-1 overexpression were determined by multiple regression analysis. ***Results:*** Nineteen of 40 gastric carcinomas showed detectable FDG uptake (48%), multiple regression analysis revealed that both the depth of invasion and histological subtypes are independent factors that influence the detectable FDG uptake in gastric carcinoma ($R^2 = 0.66$). GLUT-1 expression was seen from an early cancer stage and the cohesive type was an independent factor influencing the overexpression of GLUT-1 ($R^2 = 0.66$). GLUT-1 expression was the most influential factor for the degree of FDG uptake in gastric carcinoma ($R^2 = 0.68$). ***Conclusions:*** This study provided important information on the clinical application of FDG-PET in gastric carcinoma that early or non-cohesive gastric carcinoma may show lower FDG uptake. Therefore, the usefulness of FDG-PET for the detection of gastric carcinoma is limited. But there is a possibility that FDG uptake associated with GLUT-1 expression may serve as a prognostic factor of gastric carcinoma representing tumor metabolism.

Key words: gastric carcinoma, adenocarcinoma, 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), glucose transporter type 1 (GLUT-1), positron emission tomography (PET)

INTRODUCTION

2-Deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography (FDG-PET) is based on the theory that malignant cells show increased glucose uptake and glycolysis (the Warburg effect),[1] while overexpression of glucose transporter 1 (GLUT-1) is considered to play a major role in the higher FDG uptake by malignant cells.[2–5] GLUT-1 is the molecular species that aids FDG transit from outside the cancer cell to inside the cell.

FDG-PET has been proven to be useful in the evaluation of various malignant neoplasms;[6–14] however, some

Received April 3, 2006, revision accepted August 23, 2006.
For reprint contact: Akira Yamada, M.D., Department of Radiology, Shinshu University School of Medicine, 3–1–1, Asahi, Matsumoto, Nagano 390–8621, JAPAN.
E-mail: a-yamada@hsp.md.shinshu-u.ac.jp

particular histological subtypes and early gastric carcinomas are recognized to show low FDG uptake, with the mechanism underlying this is not yet clarified.[15] From the view point of histological subtype, the intestinal type of gastric carcinoma according to Lauren has been reported to show higher FDG uptake compared to the non-intestinal type.[16,17] GLUT-1 expression in gastric carcinomas has been also considered to be associated with the intestinal type.[18,19] On the other hand, advanced gastric carcinoma has been reported to show higher FDG uptake and GLUT-1 overexpression compared to early gastric carcinoma.[19,20]

The relationship between higher FDG uptake and GLUT-1 overexpression has been implied in gastric carcinoma as well as other human malignant tumors, but such a relationship has not been fully investigated.

The aim of the present study is to clarify FDG uptake in gastric carcinomas especially focusing on histological subtypes, depth of tumor invasion, and GLUT-1 expression.

MATERIALS AND METHODS

Patients

This study group consisted of 40 lesions derived from 35 consecutive patients (24 men, 11 women; age, 42–83 y; mean age, 67.7) with histologically proven gastric carcinoma by surgical excision between April and December 2003. Macroscopically distinguishable lesions in one surgical specimen were counted as independent lesions. Patients with diabetes mellitus and/or previous anticancer therapy were excluded. All patients underwent physical examination, chest roentgenography, double-contrast barium radiography, upper endoscopy, abdominal contrast enhanced CT, and FDG-PET to determine the clinical stage within 2 weeks before surgery. All patients gave informed consent, and the study protocol was approved by the hospital ethics committee.

PET imaging

All patients fasted for at least 4 hours before PET imaging, and the blood glucose level was measured before intravenous injection of 200–300 MBq FDG. 50–60 min after injection of FDG, a static whole-body PET scan was performed using an Advance Nxi PET scanner (General Electric Medical Systems, Milwaukee, WI). Emission scans were obtained with a 2-min acquisition time at every table position, requiring 6 or 7 bed positions to cover the patient from the pelvis floor to the head. After emission scanning, transmission scans were obtained using ^{68}Ge with a 1-min acquisition time at every table position. The PET image was reconstructed by ordered subset expansion maximization (OSEM) algorithm with segmented attenuation correction (SAC), with the resulting resolution being approximately 4.5 mm full-width at half-maximum (FWHM).

Image analysis

PET images were compared with the corresponding surgical specimen and available morphological studies (double-contrast barium radiography, upper endoscopy, abdominal contrast enhanced CT). The degree of FDG uptake of the tumor area was evaluated on a subjective semiquantitative scale: no uptake, unclear uptake (diffusely increased FDG accumulation indistinguishable from physiological gastric uptake), low positive uptake and high positive uptake. Focally increased FDG uptake compared with surrounding tissue was considered to be positive. In the evaluation of detectability, no uptake and unclear uptake were considered to be undetectable, and low and high positive uptakes were considered to be detectable.

Histological examination

Tissue sections were prepared from formalin fixed and paraffin-embedded tissues of gastric carcinoma obtained at surgery from this study group. The histopathological parameters (histological subtypes, depth of invasion, lymphatic permeation, venous invasion and tumor size) were evaluated according to the General Rules for the Clinical and Pathological Recording of Gastric Carcinoma by the Japanese Gastric Carcinoma Society.[21]

In addition, we divided gastric carcinomas into two subtypes according to Uchino et al.,[22] a cohesive type, i.e., papillary adenocarcinoma, tubular adenocarcinoma, and solid type poorly differentiated adenocarcinoma, and non-cohesive type, i.e., signet-ring cell carcinoma and non-solid type poorly differentiated carcinoma. Mucinous adenocarcinoma was interpreted as either cohesive or non-cohesive, depending on the other predominant elements.[21]

Furthermore, to clarify the association of GLUT-1 expression and FDG uptake, we divided gastric carcinomas into four subgroups according to histological subtypes and the depth of invasion, 1) early non-cohesive gastric carcinoma (ENGC), 2) early cohesive gastric carcinoma (ECGC), 3) advanced non-cohesive gastric carcinoma (ANGC), 4) advanced cohesive gastric carcinoma (ACGC). Early gastric carcinoma (EGC) is defined as a lesion in which the depth of invasion is limited to the mucosa, submucosa, or both, regardless of whether regional lymph node metastasis is evident on histological examination.[21] This is equivalent to the pT1 category in the pTNM (pathologic tumor/node/metastasis) system of the UICC (International Union Against Cancer) classification. The others were classified as advanced gastric carcinoma (AGC).

Immunohistochemical analysis

GLUT-1 transporters were detected by immunohistochemistry using the labeled streptavidin biotin (LSAB) procedure. Three micrometer sections were cut from paraffin-embedded tissue blocks in the middle of the tumor area

Table 1 Results of GLUT-1 expression and FDG uptake in 40 gastric carcinomas

Patient	Age	Gender	Histology[a]	ly[a]	v[a]	T[a]	Size [mm]	GLUT-1 expression	FDG uptake
1	71	M	Tub2	1	1	2	35	–	–
2	74	M	Tub2	2	1	2	50	–	±
3	63	M	Tub2	0	0	1	15	–	±
4	53	M	Tub2	0	0	1	15	–	±
5	73	F	Por2	3	1	3	115	–	+
6	60	M	Por2	1	1	2	95	–	+
7	58	F	Por2	0	0	1	55	–	±
8	73	F	Sig	0	0	1	25	–	±
9	69	F	Sig	0	0	1	25	–	±
10[b]	66	F	Sig	0	0	1	55	–	–
			Sig	0	0	1	33	–	–
11	50	F	Sig	0	0	1	5	–	–
12	45	M	Sig	1	0	1	25	–	–
13	42	M	Sig	0	0	1	35	–	±
14[b]	76	M	Sig	2	3	3	210	–	±
			Pap	2	3	1	80	+	++
15	77	M	Pap	1	3	2	95	+	++
16	83	F	Tub1	0	1	1	60	++	++
17	79	M	Tub1	0	0	1	27	+	±
18	69	M	Tub1	0	0	1	17	+	±
19	67	M	Tub1	3	1	2	37	+	+
20	83	M	Tub2	3	3	3	51	++	++
21	72	M	Tub2	2	2	2	65	++	++
22	83	M	Tub2	2	3	2	90	++	++
23[b]	77	M	Tub2	3	1	2	40	++	+
			Tub2	0	0	1	30	+	±
			Tub1	0	0	1	7	+	±
24	57	F	Tub2	3	0	3	20	+	+
25	72	F	Tub2	1	1	4	85	+	++
26	81	M	Tub2	2	2	2	75	+	+
27	49	M	Tub2	1	1	2	20	+	±
28	80	M	Por1	2	2	3	80	++	++
29	74	F	Por1	2	1	2	55	+	++
30	54	F	Por1	3	2	2	35	+	+
31	79	M	Por1	3	2	3	80	+	+
32	58	M	Por1	3	3	2	65	+	++
33	75	M	Por1	2	2	2	25	+	++
34	73	M	Sig	2	1	2	25	+	±
35[b]	56	M	Sig	1	2	2	140	+	±
			Sig	0	1	1	35	–	±

[a] According to the General Rules for the Clinical and Pathological Recording of Gastric Carcinoma by the Japanese Gastric Carcinoma Society. Pap = papillary adenocarcinoma; Tub1 = well-differentiated tubular adenocarcinoma; Tub2 = moderately-differentiated tubular adenocarcinoma; Por1 = solid type poorly differentiated adenocarcinoma; Por2 = non-solid type poorly differentiated adenocarcinoma; Sig = signet-ring cell carcinoma; ly = lymphatic permeation; v = venous invasion T = depth of invasion, [b] Multiple lesions coexisted in one specimen.

and deparaffinized. Before the immunohistochemical procedures, all sections were unmasked by the microwave method using a citrate buffer, pH 6.0 for 40 min. Endogenous peroxidase was neutralized with 0.3% hydrogen peroxide for 30 minutes. The samples were then washed and incubated at room temperature for 1 hour in a 1:50 dilution of the polyclonal rabbit antihuman GLUT-1 antibody (A3536; DAKO, Carpinteria, CA) raised against a 12 amino acid synthetic peptide corresponding to the carboxyl terminus of human GLUT-1. Parallel sections were incubated with healthy rabbit immunoglobulin G (Ig G) as negative controls. The samples were then washed off, and biotinylated secondary antibody (DAKO LSAB Kit, biotinylated anti-mouse, anti-rabbit, and anti-goat) was applied to the slides for 45 minutes in a humidity chamber. The slides were again washed and incubated with streptavidin peroxidase for an additional 45 minutes and then submerged in a DAB bath for 5 minutes. Tissues

Table 2 Comparison between histopathological parameters and FDG uptake in gastric carcinoma

Histopathological parameters	FDG uptake				p value
	Undetectable		Detectable		
	No	Unclear	Low positive	High positive	
GLUT-1 expression					< 0.001
Negative	5	9	2	0	
Positive	0	7	6	11	
Histologic subtypes					< 0.01
Non-cohesive type	4	8	2	0	
Cohesive type	1	8	6	11	
Depth of invasion					< 0.001
T1	4	11	0	2	
T2–4	1	5	8	9	
Lymphatic permeation					< 0.001
None	3	11	0	1	
Present	2	5	8	10	
Venous invasion					< 0.001
None	4	10	1	0	
Present	1	6	7	11	
Tumor size					< 0.01
< 10 mm [a]	1	1	0	0	
10–30 mm	1	9	1	1	(< 0.01) [b]
> 30 mm	3	6	7	10	

[a] smaller than double of FWHM, [b] excluding the lesions smaller than double of FWHM

were counterstained with hematoxylin. All slides were examined by light microscopy. We used the erythrocytes in the tissue sections for the positive control of GLUT-1 expression. Staining was considered to be positive only when strong membrane associated immunoreactivity was observed.[18] GLUT-1-immunostaining was evaluated without the clinical information including FDG uptake for each tumor. GLUT-1-immunoreactivity was evaluated for each tumor based on the percentage of tumor cells that expressed GLUT-1 on a subjective semiquantitative scale: no expression (0–1%), low positive expression: (2–30%), and high positive expression (>30%).

Statistical analysis

The nonparametric statistical analysis of FDG uptake and histological parameters were evaluated by chi-square test. The difference in FDG uptake between subgroups (ENGC, ECGC, ANGC, ACGC) was evaluated using the Kruskal Wallis test. The multiple regression analysis of FDG uptake (detectability and the degree) and GLUT-1 expression with the histological parameters (lymphatic permeation, venous invasion, depth of invasion, tumor size, histological subtypes, and GLUT-1 expression) were evaluated by a polytomous universal model using the SPSS software (SPSS Inc., Chicago, IL). The correlation coefficient was evaluated for each parameter, and correlated parameters were represented by one parameter to avoid multicollinearity in multiple regression analysis of GLUT-1 expression and detectable FDG uptake. This representation was not applied in the multiple regression analysis of the degree of FDG uptake to determine the most influential factor. Probability values of less than 0.05 were considered statistically significant.

RESULTS

Table 1 summarizes the tumor characteristics, the results of immunohistochemical findings and the FDG-PET imaging of 35 patients. The correlations between the histological parameters and FDG uptake in gastric carcinoma are shown in Table 2.

Immunohistochemical staining of GLUT-1

Twenty-four of the 40 gastric carcinoma lesions (60%) showed positive GLUT-1 expression. The positive rate of GLUT-1 expression was 85% (22 of 26) in the cohesive type and 14% (2 of 14) in the non-cohesive type. All of the 6 solid type poorly differentiated adenocarcinomas showed positive GLUT-1 expression (Fig. 1). GLUT-1 expression of gastric carcinoma differed significantly between the cohesive and non-cohesive types ($p < 0.0001$) (Fig. 2). Frequency of GLUT-1 expression in each subgroup is shown in Table 3. GLUT-1 expression was seen from an early cancer stage and related to the cohesive type of gastric carcinoma.

FDG-PET imaging

Nineteen of the 40 gastric carcinomas showed detectable FDG uptake (48%), with GLUT-1 overexpression seen in 17 of them (89%). FDG uptake in gastric carcinoma

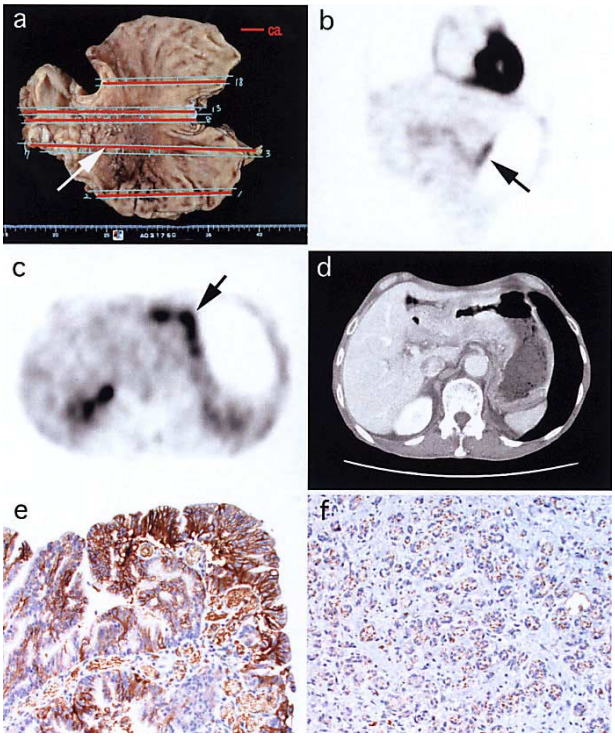

Fig. 1 Patient 14, a case of advanced gastric carcinoma, in which cohesive and non-cohesive types coexisted. a: Macroscopic view of the surgical specimen with distribution of carcinomas. Entire gastric wall thickening by signet ring cell carcinoma infiltration and protruded portion consisting of papillary adenocarcinoma in the lesser curvatures (*arrow*) were observed. b, c: Coronal and transaxial images of FDG PET. Elevated FDG uptake was visualized in the protruded portion (*arrow*). No FDG uptake was seen in the rest of the tumor. d: Corresponding transaxial CT image. e: Immunostaining with antiGLUT-1 showed positive GLUT-1 expression at papillary adenocarcinoma component in the protruded portion. f: No GLUT-1 expression was seen at signet ring cell carcinoma component in the rest of the tumor.

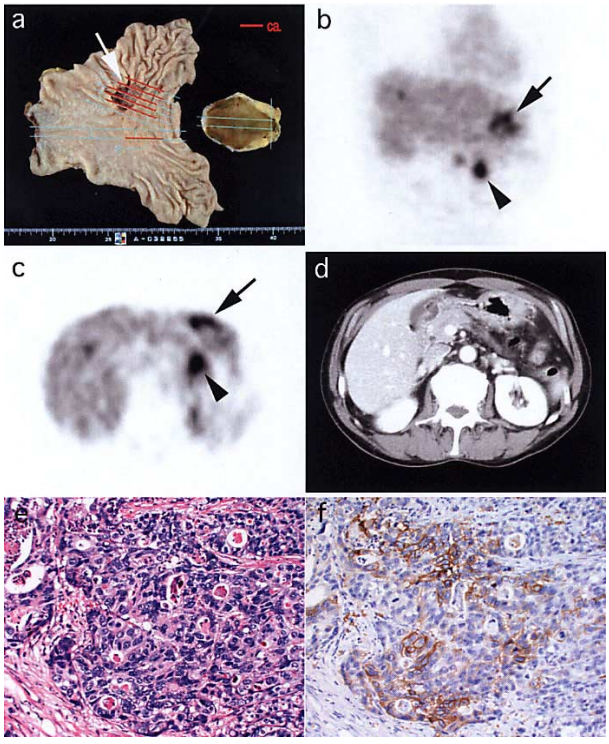

Fig. 2 Patient 31, a case of advanced gastric carcinoma (solid type poorly differentiated adenocarcinoma). a: Macroscopic view of the surgical specimen with distribution of carcinomas. Ulcerated portion consisting of solid type poorly differentiated adenocarcinoma (*arrow*) was observed in anterior wall. b, c: Coronal and transaxial images of FDG PET. Elevated FDG uptake was visualized in the ulcerated portion (*arrow*) and separate lymph node metastases (*arrowhead*). d: Corresponding transaxial CT image. e: Solid type poorly differentiated adenocarcinoma composed of tumor cells with an intimate cohesion, proliferating in solid nests was observed on HE staining. f: Immunostaining with antiGLUT-1 showed positive GLUT-1 expression.

differed significantly depending on GLUT-1 expression ($p < 0.01$). The detectable rate of FDG uptake in the cohesive type was 65% (17 of 26), in contrast to 14% (2 of 14) in the non-cohesive type. All of the 6 solid type poorly differentiated adenocarcinomas showed detectable FDG uptake (Fig. 1). FDG uptake of gastric carcinoma differed significantly between the cohesive and non-cohesive types ($p < 0.01$) (Fig. 2).

Statistical analysis revealed significant associations between FDG uptake and the depth of invasion, lymphatic permeation, and vascular invasion (Table 2). Frequency of detectable FDG uptake in each subgroup is shown in Table 4. FDG uptake was significantly different between subgroups ($p < 0.001$), and higher in ACGC.

Multiple regression analysis of GLUT-1 expression and FDG-PET uptake in gastric carcinoma

The correlation coefficient of histological parameters in gastric carcinoma is shown in Table 5. The correlation coefficient between GLUT-1 expression and histological subtype was higher ($r = 0.71$). The depth of tumor invasion was correlated to lymphatic permeation ($r = 0.82$), venous invasion ($r = 0.66$) and tumor size ($r = 0.58$), but its correlation to GLUT-1 expression was weak ($r = 0.36$). GLUT-1 expression was represented by histological subtype, and the other parameters (lymphatic permeation, venous invasion and tumor size) were represented by the depth of invasion, respectively in multiple regression analysis of GLUT-1 expression and detectable FDG uptake to avoid multicollinearity. Multiple regression analysis revealed that the cohesive type is an independent factor that influences the overexpression of GLUT-1 in gastric

Table 3 Frequency of positive GLUT-1 expression in gastric carcinoma

Histological subtype	Depth of invasion	
	EGC [a]	AGC [b]
Non-cohesive	0% (0/9)	40% (2/5)
Cohesive	75% (6/8)	89% (16/18)

[a] early gastric carcinoma, [b] advanced gastric carcinoma

Table 4 Frequency of detectable positive FDG uptake in gastric carcinoma

Histological subtype	Depth of invasion	
	EGC [a]	AGC [b]
Non-cohesive	0% (0/9)	40% (2/5)
Cohesive	25% (2/8)	83% (15/18)

[a] early gastric carcinoma, [b] advanced gastric carcinoma

Table 5 The correlation coefficient of histological parameters in gastric carcinoma

Parameters	GLUT-1	subtype[a]	T[b]	ly[c]	v[d]	Size
GLUT-1	1.00	0.71	0.37	0.47	0.48	0.01
subtype[a]	0.71	1.00	0.27	0.35	0.33	–0.18
T[b]	0.37	0.27	1.00	0.82	0.66	0.58
ly[c]	0.47	0.35	0.82	1.00	0.69	0.36
v[d]	0.48	0.33	0.66	0.69	1.00	0.64
Size	0.01	–0.18	0.58	0.36	0.64	1.00

[a] cohesive or non-cohesive type, [b] the depth of invasion, [c] lymphatic permeation, [d] venous invasion

Table 6 The multiple regression analysis of GLUT-1 expression with the histological parameters in gastric carcinoma

Parameters	B[a]	p value
Histological subtypes[b]	4.151	0.001
Depth of invasion	1.393	0.164

[a] regression coefficient, [b] cohesive or non-cohesive type

Table 7 The multiple regression analysis of FDG uptake with the histological parameters in gastric carcinoma

Parameters	Detectable FDG uptake		Degree of FDG uptake	
	B[a]	p value	B[a]	p value
GLUT-1 expression			1.866	0.021
Histological subtypes[b]	2.875	0.018	1.492	0.181
Depth of invasion	2.327	0.002	0.385	0.672
Lymphatic permeation			–0.045	0.934
Venous invasion			0.858	0.169
Tumor size			0.013	0.406

[a] regression coefficient, [b] cohesive or non-cohesive type

carcinoma ($p = 0.001$) ($R^2 = 0.66$), but the correlation between the depth of tumor invasion and GLUT-1 expression was weak ($p = 0.164$) (Table 6). Both the depth of invasion ($p = 0.005$) and the cohesive type ($p = 0.005$) were independent factors influencing the detectable FDG uptake in gastric carcinoma ($R^2 = 0.66$) (Table 7). Multiple regression analysis also revealed that the GLUT-1 expression is the most influential factor for the degree of FDG uptake in gastric carcinoma ($p = 0.021$) ($R^2 = 0.68$).

DISCUSSION

The results of this study clarify that the degree of FDG uptake in gastric carcinoma is related to GLUT-1 overexpression. On the other hand, the detectability of gastric carcinoma in FDG-PET depends on histological subtype and the depth of tumor invasion. In other words, the non-cohesive type of gastric carcinoma tends to be undetectable in FDG-PET because GLUT-1 overexpression is related to the cohesive type of gastric carcinoma. And also early gastric carcinoma tends to be undetectable in FDG-PET regardless of histological subtype or GLUT-1 expression.

The association of GLUT-1 overexpression and high FDG uptake has been reported in various malignancies.[2–5] In gastric carcinoma, Kim et al. showed that GLUT-1 expression is associated with the intestinal type of gastric carcinoma.[18] On the other hand, Stahl et al. reported that the intestinal type shows high FDG uptake compared to the non-intestinal type.[16] These studies suggested an association between FDG uptake and GLUT-1 expression in gastric carcinoma, while the present study clarified for the first time that a direct correlation exists between the two. Moreover, the marked differences in FDG uptake and GLUT-1 expression between solid type poorly differentiated adenocarcinoma and the other non-intestinal type of gastric carcinomas described in this study have never been reported before.

The reason for this difference in FDG uptake and GLUT-1 expression between the cohesive and non-cohesive types is unclear, but may be related to oncogenic alterations of glucose metabolism. Uchino et al. classified gastric carcinomas into cohesive and non-cohesive types and showed that p53 alteration occurs selectively in the

former from the intramucosal cancer stage.[22] Solid type poorly differentiated adenocarcinoma is included in the cohesive type and thought to be transformed from the intestinal type.[22–25] The human p53 gene is a tumor suppressor gene, and the alteration is commonly seen in human solid tumors where it plays a role in tumor survival from hypoxic cell death.[26] The mechanism of p53 alteration and GLUT-1 overexpression is not fully clarified; however, the up-regulation of GLUT-1 expression mediated by hypoxia-inducible transcription factor 1 alpha (HIF-1α) activation may be associated.[27] The alteration of p53 is also responsible for activating type-II-hexokinase (HKII), which plays a role in the initiation and maintenance of high rates of glucose catabolism in rapidly growing tumors.[28] The correlation of HKII overexpression and high FDG uptake has been reported in malignant tumors.[29] On the other hand, p53 alteration is rarely seen in the non-cohesive type of gastric carcinoma.[22] Therefore metabolic adaptation including GLUT-1 overexpression may not occur and result in low FDG uptake. The low tumor cell density and rich stroma could be another possible reason of lower FDG uptake of non-cohesive type of gastric carcinoma.

Our results also showed higher FDG uptake in progressive gastric carcinomas represented as the depth of invasion, lymphatic permeation, vascular invasion and the tumor size. Increased glycolysis to maintain cell division and tumor growth is considered to be the cause of higher FDG uptake in advanced carcinoma.[20] In this study group, the size of all tumors was larger than FWHM (4.5 mm), but two of the early gastric carcinomas were smaller than double of FWHM (9.0 mm). Although early carcinoma tended to be smaller than advanced carcinoma ($r = 0.58$), the evaluation of FDG uptake excluding these smaller lesions showed a significant difference depending on the tumor size. Therefore not only the partial volume effect and the physiological mucosal FDG uptake including inflammation but also lower tumor metabolism could be possible reasons for the lower detection rate of FDG-PET study in early gastric carcinoma.[16,20] As our results showed, the degree of FDG uptake is well related to GLUT-1 expression. There were also significant associations between GLUT-1 positivity and adverse tumor features and survival.[19] Therefore the degree of FDG uptake associated with GLUT-1 expression may be a prognostic factor of gastric carcinoma representing tumor metabolism.

A limitation of our study is that the evaluation of FDG uptake was not made by a quantitative way such as standardized uptake value (SUV). But gastric mucosa often shows physiologically higher uptake and sometimes the tumor area is difficult to distinguish from normal mucosa. In this study group, more than half of gastric carcinomas were undetectable making it difficult to determine proper SUV. We decided this effect is not ignorable and chose semiquantitative visual evaluation for this study as a practical way.

In our multiple regression analysis, R^2 was 0.68 for FDG uptake in gastric carcinoma, which means two-thirds of the phenomenon can be explained by the histological parameters considered in this study, but the other third is of unknown factors. Further investigation of the association of p53 alteration and glucose metabolism including the expression of HIF-1α, and HKII is needed to clarify the mechanism of high FDG uptake in gastric carcinoma.

In conclusion, GLUT-1 overexpression is highly correlated to the cohesive type of gastric carcinoma and the most influential factor of higher FDG uptake. On the other hand, the detectability of gastric carcinoma in FDG-PET depends on not only the histological subtype but also the depth of tumor invasion. From these conclusions, this study provided important information on the clinical application of FDG-PET in gastric carcinoma that early or non-cohesive gastric carcinoma may show lower FDG uptake. Therefore, the usefulness of FDG-PET for the detection of gastric carcinoma is limited. But there is a possibility that FDG uptake associated with GLUT-1 expression is a prognostic factor of gastric carcinoma representing tumor metabolism, and further investigation is needed.

ACKNOWLEDGMENTS

The authors are grateful to Drs. Kayoko Higuchi, Katsunori Tauchi, and Kazunobu Miyata for their co-operation; Kouichi Anzai, Muneaki Kimura, and Kentarou Kinoshita for PET operation; and the staff of the PET center, Departments of Radiology and Pathology, Aizawa Hospital for their assistance.

REFERENCES

1. Warburg O. On the origin of cancer cells. *Science* 1956; 123: 309–314.
2. Brown RS, Wahl RL. Over expression of Glut-1 glucose transporter in human breast cancer: an immunohistochemical study. *Cancer* 1993; 72: 2979–2985.
3. Higashi T, Tamaki N, Honda T, Torizuka T, Kimura T, Inokuma T, et al. FDG uptake, GLUT-1 glucose transporter and cellularity in human pancreatic tumors. *J Nucl Med* 1998; 39: 1727–1735.
4. Aloj L, Caraco C, Jagoda E, Eckelman WC, Neumann RD. Glut-1 and hexokinase expression: relationship with 2-fluoro-2-deoxy-D-glucose uptake in A431 and T47D cells in culture. *Cancer Res* 1999; 59: 4709–4714.
5. Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, et al. FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. *J Nucl Med* 2001; 42: 1551–1555.
6. McAteer D, Wallis F, Couper G, Norton M, Welch A, Bruce D, et al. Evaluation of ^{18}F-FDG positron emission tomography in gastric and oesophageal carcinoma. *Br J Radiol* 1999; 72: 525–529.
7. Torizuka T, Tamaki N, Inokuma T, Magata Y, Yonekura Y, Tanaka A, et al. Value of fluorine-18-FDG-PET to monitor

hepatocellular carcinoma after interventional therapy. *J Nucl Med* 1994; 35: 1965–1969.
8. Keiding S, Hansen SB, Rasmussen HH, Gee A, Kruse A, Roelsgaard K, et al. Detection of cholangiocarcinoma in primary sclerosing cholangitis by positron emission tomography. *Hepatology* 1998; 28: 700–706.
9. Bares R, Klever P, Hauptmann S, Hellwig D, Fass J, Cremerius U, et al. F-18 fluorodeoxyglucose PET *in vivo* evaluation of pancreatic glucose metabolism for detection of pancreatic cancer. *Radiology* 1994; 192: 79–86.
10. Gupta NC, Falk PM, Frank AL, Thorson AM, Frick MP, Bowman B. Pre-operative staging of colorectal carcinoma using positron emission tomography. *Nebr Med J* 1993; 78: 30–35.
11. Ishizu K, Sadato N, Yonekura Y, Nishizawa S, Magata Y, Tamaki N, et al. Enhanced detection of brain tumors by [^{18}F]fluorodeoxyglucose PET with glucose loading. *J Comput Assist Tomogr* 1994; 18: 12–15.
12. Kern KA, Brunetti A, Norton JA, Chang AE, Malawer M, Lack E, et al. Metabolic imaging of human extremity musculoskeletal tumors by PET. *J Nucl Med* 1988; 29: 181–186.
13. Kubota K, Matsuzawa T, Fujiwara T, Ito M, Hatazawa J, Ishiwata K, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. *J Nucl Med* 1990; 31: 1927–1932.
14. Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1991; 179: 765–770.
15. Annovazzi A, Peeters M, Maenhout A, Signore A, Dierckx R, Van De Wiele C. 18-fluorodeoxyglucose positron emission tomography in nonendocrine neoplastic disorders of the gastrointestinal tract. *Gastroenterology* 2003; 125: 1235–1245.
16. Stahl A, Ott K, Weber WA, Becker K, Link T, Siewert JR, et al. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med Mol Imaging* 2003; 30: 288–295.
17. Yoshioka T, Yamaguchi K, Kubota K, Saginoya T, Yamazaki T, Ido T, et al. Evaluation of ^{18}F-FDG PET in patients with advanced, metastatic, or recurrent gastric cancer. *J Nucl Med* 2003; 44: 690–699.
18. Kim WS, Kim YY, Jang SJ, Kimm K, Jung MH. Glucose transporter 1 (GLUT1) expression is associated with intestinal type of gastric carcinoma. *J Korean Med Sci* 2000; 15: 420–424.
19. Kawamura T, Kusakabe T, Sugino T, Watanabe K, Fukuda T, Nashimoto A, et al. Expression of glucose transporter-1 in human gastric carcinoma: association with tumor aggressiveness, metastasis, and patient survival. *Cancer* 2001; 92: 634–641.
20. Mochiki E, Kuwano H, Katoh H, Asao T, Oriuchi N, Endo K. Evaluation of ^{18}F-2-deoxy-2-fluoro-D-glucose positron emission tomography for gastric cancer. *World J Surg* 2004; 28 3: 247–253.
21. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition—. *Gastric Cancer* 1998; 1: 10–24.
22. Uchino S, Noguchi M, Ochiai A, Saito T, Kobayashi M, Hirohashi S. p53 Mutation in gastric cancer: a genetic model for carcinogenesis is common to gastric and colorectal cancer. *Int J Cancer* 1993; 54: 759–764.
23. Ueyama T, Tsuneyoshi M. Poorly differentiated solid type adenocarcinomas in the stomach: a clinicopathologic study of 71 cases. *J Surg Oncol* 1992; 51: 81–88.
24. Yokota T, Kunii Y, Saito T, Teshima S, Yamada Y, Takahashi M, et al. Poorly differentiated, solid-type adenocarcinoma of the stomach. *Ups J Med Sci* 1999; 104: 207–216.
25. Fiocca R, Luinetti O, Villani L, Mastracci L, Quilici P, Grillo F, et al. Molecular mechanisms involved in the pathogenesis of gastric carcinoma: interactions between genetic alterations, cellular phenotype and cancer histotype. *Hepato-Gastroenterology* 2001; 48: 1523–1530.
26. Graeber TG, Osmanian C, Jacks T, Housman DE, Koch CJ, Lowe SW, et al. Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. *Nature* 1996; 379: 88–91.
27. Dang CV, Semenza GL. Oncogenic alterations of metabolism. *Trends Biochem Sci* 1999; 2: 68–72.
28. Mathupala SP, Heese C, Pedersen PL. Glucose catabolism in cancer cells. The type II hexokinase promoter contains functionally active response elements for the tumor suppressor p53. *J Biol Chem* 1997; 36: 22776–22780.
29. Smith TA. Mammalian hexokinases and their abnormal expression in cancer. *Br J Biomed Sci* 2000; 2: 170–178.