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RESEARCH ARTICLE

Glucose Transporter-1 and Tumor Size Affect Assessment in Gastric Cancer on SPECT

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ABSTRACT

Background: GLUT-1 expression is the crucial parameter affecting gastric cancer 18-FDG absorption is still controversial. This study is to explore the significance of GLUT-1 in gastric cancer 18-FDG SPECT.

Material/Methods: The gastric cancer samples of 134 patients with preoperative 18-FDG SPECT were assessed by GLUT-1 immunohistochemical staining. The clinicopathological information of enrolled patients were analyzed with univariate and regression analyses.

Results: The SUVmax in positive GLUT-1 expression was significantly higher than that in negative expression (5.136±3.088 vs 4.003±3.604, p=0.004). Tumor diameter (OR 1.415, p=0.005) and GLUT-1 expression level(OR 1.683, p=0.041) were the factors associated with imaging results by visual assessment, independently. Tumor diameter was independent factor associated with SUVmax in positive imaging cases (p=0.029). Tumor diameter(p=0.003) and tumor differentiation(p=0.026) were independent factors related to SUVmax in differentiated carcinoma cases.

Conclusions: GLUT-1 expression level is major factor determining 18-FDG uptake of gastric cancer on SPECT. It is necessary to verify the result with PET/CT. Further investigation on analysis GLUT-1 expression in lesions of gastric cancer metastases and recurrences is required.

Keywords: Glucose Transporter Type 1, Gastric cancer, FDG, SPECT

Introduction

Gastric cancer incidence rates are highest in Eastern Asia though a steady decline in the rates has been noted in recent years[1]. Surgical resection has been proved to be the most effective treatment for improving poorer prognosis and reducing higher mortality of the cancer[2]. The optimized therapeutic strategies depend on comprehensive preoperative assessment with the development of medical imaging equipment[3].

PET/CT (positron emission tomography/ computerized tomography) has become a routine imaging modality for gastrointestinal cancers[4], which has stretched knowledge on cancer metabolism[5]. The device was employed in not only detecting cancer but also monitoring recurrence and metastases[6]. However, the cost-effective of the imaging remains luxury especially in developing countries[6]. Though SPECT/CT (single photon emission computerized tomography/computerized tomography) has been limited due to lower resolution than PET/CT[7-9], the modality also is valuable and favorable on staging gastric cancer in developing countries such as China with the cost advantage[10], which has advanced with hardware-updating and software- upgrading[8,11].

Glucose transporter-1(GLUT-1) is overexpressed in a variety of cancers, which is supposed to be major rate-limiting step for tumor 18-FDG (18F-fluoro deoxyglucose) absorption[12]. Theoretically speculation and several clinical researches proposed that expression level of GLUT-1 determined 18-FDG uptake in gastric cancer[13,14], but other studies addressed contrary conclusion[15,16]. Whether GLUT-1 expression is the crucial parameter affecting gastric cancer 18-FDG absorption is still controversial. Our previous works suggested that tumor size and depth of invasion were clinicopathological parameters influencing 18-FDG SPECT assessment in gastric cancer independently[17]. Moreover, GLUT-1 is higher expressed in advanced gastric cancer[16]. Accordingly, the study is to explore the significance of GLUT-1 in gastric cancer 18-FDG SPECT.

Methods

Gastric cancer patients undergoing preoperative SPECT between January 2008 and January 2015 at the Fifth People's Hospital of Shanghai were reviewed for this study. The patients with preoperative chemotherapy or radiotherapy and without gastrectomy were eliminated. 134 available patients were included in this study.
The American Joint Committee on Cancer (6th edition) was applied in staging gastric cancer. The histology is referred to World Health Organization classification[18]. The study has been approved by the local Research Ethics Commission.

SPECT and image assessment

Image acquisition equipment of the study was SPECT (Infinia VC Hawkeye, General Electric Medical Systems, Israel). Fasting for at least 6 hours was necessary before examination. 45 min after the intravenous injection of 370MBq FDG, patients were scanned in the supine position. Xeleris workstation (General Electric Medical System) was used to reconstructed images with ordered subset expectation maximization with attenuation correction.

The evaluation of images was independently finished by two experienced nuclear medicine physicians with visual assessment. The determination of results was based on consensus of the two physicians. Focally increased activity higher than surrounding tissue was considered as positive FDG uptake. SUVmax calculation was obtained from the software in workstation after location of regions of interest (ROI) in the section with maximum uptake of radioactivity.

Immunohistochemistry and Assessment

4μm-thick tissue slides were cut from the paraffin-embedded samples. 3% H_2O_2 was used to treat slides for 10min at room temperature after deparaffinization and hydration. The antigen retrieval was 0.01M sodium citrate buffer (pH 6.0) at 100 °C for 1min. Monoclonal GLUT-1 antibody (ab40084, Abcam, UK, 1:100) was the primary antibody for incubating specimens. Staining system was EnVision Detection Systems (Peroxidase/DAB, Rabbit/Mouse, DAKO). The slides were counterstained by Mayer's hematoxylin after staining. Dehydration with gradient ethanol and seal with neutral balsam were essential for interpretation and conservation. Quality controls were routine in the processes.

Experienced pathologists blinded to clinical details analyzed the sections. The staining of tumor cell membrane was regarded as positive cell. Semiquantitative evaluation was used to assess the expression level of GLUT-1 [13,14]. The scoring criteria were: score 0, <1% positive tumor cells; score 1, 1%~30% positive tumor cells; score 2, >30% positive tumor cells.

Statistical analysis

The relation between imaging assessment and clinicopathological parameters such as gender, tumor localization were analyzed with the Chi-squared or Fisher's exact test if necessary. Mann-Whitney U test was performed to compare

age, tumor diameter between imaging, GLUT-1 positive and negative group. The differences of SUVmax in tumor localization, GLUT-1 expression, pT stage, pN stage, histological type, adenocarcinoma differentiation was test by Kruskal-Wallis one-way analysis variance. The Spearman's rank correlation test was applied to analyze the association between imaging and clinicopathological parameters including GLUT-1 expression. The multivariate analyses of imaging assessment and potentially significant factors ($p<0.10$) was finished with the logistic regression analysis for visual assessment and multiple linear regression for SUVmax. $p<0.05$ was regarded as statistically significant. Stata 7.0 was used for all statistical analyses.

Results

The characteristics of the patients was shown in Table 1.

Table 1. The characteristics of 134 gastric cancer patients

Clinicopathological Parameters	
Gender	
Male	89
Female	45
Age(yr)	67(32~87)
Tumor diameter(cm)	4.76±2.54(1~14)
Tumor localization	
Upper	28
Middle	20
Lower	86
pT stage	
T1	21
T2	18
T3	89
T4	6
pN stage	
N0	41
N1	51
N2	31
N3	11
M stage	
M0	127
M1	7
TNM stage	
IA	17
IB	11
II	25
IIIA	37
IIIB	25
IV	19
Histology	
Well differentiated	25
Moderately differentiated	47
Poorly differentiated	54
Signet-ring cell	6
Mucinous	2
Lauren	
Intestinal	72
Diffuse	62
Venous invasion	
Positive	90
Negative	44
Perineural invasion	
Positive	74
Negative	60

Figure 1 showed ROI with maximum uptake of radioactivity of gastric cancer lesion on SPECT software.

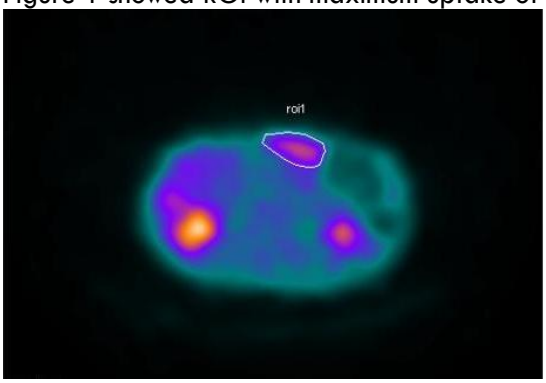

Figure 1. Regions of interest (ROI) of gastric lesion on SPECT of patient (male, 54yrs, lower gastric cancer, SUVmax 5.51)

The GLUT-1 positive staining was shown in Figure 2.

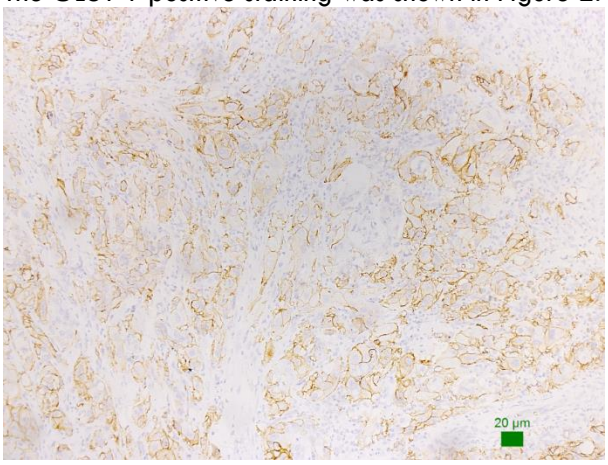

Figure 2. Glucose transporter-1 (GLUT-1) staining in gastric adenocarcinoma(100×) of patient (male, 54yrs, lower gastric cancer, Grade 3)

The sensitivity of the imaging was 64.93% (87/134) in this study. The SUVmax of positive imaging group was 4.719±3.312 (1.25~16.19). The results of imaging visual assessment were associated with tumor diameter, pT stage, pN stage, TNM stage, clinical stage, histology, venous invasion and GLUT-1 expression (Table 2).

Table 2. The relation between imaging results and clinicopathological parameters including GLUT-1 exfpression in 134 patients with gastric cancer

Clinicopathological Parameters	**Imaging results (visual assessment)**		***p* value**
	negative	**positive**	
Gender			0.641
Male	30	59	
Female	17	28	
Age(yr)	63.19±10.11	66.30±11.88	0.050[a]
Tumor diameter(cm)	3.51±1.88	5.44±2.59	<0.001[a,*]
Tumor localization			0.085
Upper	5	23	
Middle	9	11	
Lower	33	53	
pT stage			<0.001*
T1	16	5	
T2	5	13	
T3	23	66	
T4	3	3	

Clinicopathological Parameters	Imaging results (visual assessment)		*p* value
	negative	**positive**	
pN stage			
N0	20	21	0.034*
N1	19	32	
N2	5	26	
N3	3	8	
M stage			0.696[b]
M0	44	83	
M1	3	4	
TNM stage			0.003*
IA、IB	18	10	
II	7	18	
IIIA、IIIB	15	47	
IV	7	12	
Clinical stage			<0.001*
Early	16	5	
Advanced	31	82	
Histology			0.014*
Well differentiated	13	12	0.071[c]
Moderately differentiated	12	35	
Poorly differentiated	17	37	
Signet-ring cell	5	1	
Mucinous	0	2	
Lauren			0.927
Intestinal	25	47	
Diffuse	22	40	
Venous invasion			0.004*
Positive	24	66	
Negative	23	21	
Perineural invasion			0.150
Positive	22	52	
Negative	25	35	
GLUT-1 expression			0.042*
0	27	32	
1	6	10	
2	14	45	

a . Mann-Whitney U test; b. Fisher's exact test; c. Comparison in differentiated adenocarcinoma
*$p<0.05$

Table 3 showed the correlation between imaging results (visual assessment) and clinicopathological parameters.

Table 3 The correlation between imaging results (visual assessment) and clinicopathological parameters

Parameters	ρ	*p* value
Tumor diameter	0.383	<0.001
pT stage	0.250	0.004
pN stage	0.235	0.006
TNM stage	0.207	0.016
GLUT-1 expression	0.217	0.012

The association between GLUT-1 expression and clinicopathological parameters, SUVmax in positive imaging was exhibit in Table 4, and that in negative imaging was done in Table 5.

Table 4 The relation between GLUT-1 expression and clinicopathological parameters, SUVmax in positive imaging

Clinicopathological Parameters	GLUT-1 expression		*p* value
	Negative (score 0)	Positive (score 1~2)	
Gender			0.739
Male	21	38	
Female	11	17	
Age(yr)	65.22±14.21	66.93±10.37	0.919[a]
Tumor diameter(cm)	4.94±2.23	5.73±2.76	0.262[a]
Tumor localization			0.079
Upper	4	19	
Middle	5	6	
Lower	23	30	
pT stage			0.321
T1	2	3	
T2	7	6	
T3	23	43	
T4	0	3	
pN stage			
N0	5	16	0.473
N1	12	20	
N2	12	14	
N3	3	5	
M stage			1.000[b]
M0	31	52	
M1	1	3	
TNM stage			0.952
IA、IB	3	7	
II	7	11	
IIIA、IIIB	18	29	
IV	4	8	
Clinical stage			1.000[b]
Early	2	3	
Advanced	30	52	
Histology			0.049*
Well differentiated	4	8	0.021[c,]*
Moderately differentiated	7	28	
Poorly differentiated	19	18	
Signet-ring cell	1	0	
Mucinous	1	1	
Lauren			0.005*
Intestinal	11	36	
Diffuse	21	19	
Venous invasion			0.507
Positive	23	43	
Negative	9	12	
Perineural invasion			0.610
Positive	18	34	
Negative	14	21	
SUVmax	4.003±3.604	5.136±3.088	0.004[a,]*

a . Mann-Whitney U test; b. Fisher's exact test; c. Comparison in differentiated adenocarcinoma
*$p<0.05$

Table 5 The relation between GLUT-1 expression and clinicopathological parameters in negative imaging

Clinicopathological Parameters	GLUT-1 expression		*p* value
	negative(score 0)	positive(score 1~2)	

Gender			0.047*
Male	14	16	
Female	13	4	
Age(yr)	61.22±9.71	65.85±10.27	0.178[a]
Tumor diameter(cm)	3.70±2.02	3.25±1.69	0.442[a]
Tumor localization			0.626
Upper	2	3	
Middle	6	3	
Lower	19	14	
pT stage			0.535
T1	10	6	
T2	4	1	
T3	12	11	
T4	1	2	
pN stage			0.983
N0	11	9	
N1	11	8	
N2	3	2	
N3	2	1	
M stage			0.070[b]
M0	27	17	
M1	0	3	
TNM stage			0.535
IA、IB	10	6	
II	4	1	
IIIA、IIIB	12	11	
IV	1	2	
Clinical stage			0.615
Early	10	6	
Advanced	17	14	
Histology			0.004*
Well differentiated	7	6	0.002*
Moderately differentiated	2	10	
Poorly differentiated	14	3	
Signet-ring cell	4	1	
Mucinous	/	/	
Lauren			0.002*
Intestinal	9	16	
Diffuse	18	4	
Venous invasion			0.642
Positive	13	11	
Negative	14	9	
Perineural invasion			0.706
Positive	12	10	
Negative	15	10	

a . Mann-Whitney U test; b. Fisher's exact test; c. Comparison in differentiated adenocarcinoma
*$p<0.05$

Moreover, the SUVmax in positive GLUT-1 expression was significantly higher than that in negative expression. Tumor diameter and GLUT-1 expression level were the factors associated with imaging results by visual assessment, independently (Table 6).

Table 6 The logistic regression analysis of imaging results (visual assessment) with the clinicopathological parameters in 134 gastric cancer cases

Regression	Coefficient	Odds Ratio	*p* value

Clinicopathological Parameters	(95% CI)	(95% CI)	
Age	0.008(-0.030~0.045)	1.008(0.970~1.046)	0.691
Tumor diameter	0.347(0.103~0.591)	1.415(1.109~1.806)	0.005*
Tumor localization	-0.045(-0.591~0.501)	0.956(0.554~1.650)	0.872
pT stage	0.003(-0.645~0.650)	1.003(0.525~1.916)	0.994
pN stage	0.213(-0.354~0.781)	1.238(0.702~2.183)	0.461
Histology	0.163(-0.372~0.698)	1.177(0.690~2.010)	0.549
Venous invasion	0.501(-0.471~1.473)	1.651(0.625~4.364)	0.312
GLUT-1 expression level	0.521(0.021~1.021)	1.683(1.021~2.775)	0.041*

*$p<0.05$

The SUVmax was related to histology type, Lauren classification and GLUT-1 expression level in 87 positive imaging cases (Table 7). The SUVmax was positively correlated with age ($\gamma=0.262$, $p=0.014$), tumor diameter ($\gamma=0.328$, $p=0.002$) and GLUT-1 expression ($\rho=0.309$, $p=0.004$) in these cases.

Table 7 The relation between SUVmax and clinicopathological parameters including GLUT-1 expression in 87 positive imaging cases

Clinicopathological Parameters	n	SUVmax ($\bar{x}\pm SD$)	*p* value
Gender			0.095
Male	59	5.014±3.514	
Female	28	4.099±2.799	
Tumor localization			0.468[a]
Upper	23	4.943±3.484	
Middle	11	5.059±2.908	
Lower	53	4.552±3.363	
pT stage			0.095[a]
T1	5	2.744±0.868	
T2	13	4.608±2.631	
T3	66	4.696±3.445	
T4	3	9.000±2.376	
pN stage			0.161[a]
N0	21	4.932±3.050	
N1	32	5.507±4.187	
N2	26	3.451±1.857	
N3	8	5.136±3.021	
M stage			0.384
M0	83	4.667±3.323	
M1	4	5.800±3.237	
TNM stage			0.589[a]
IA、IB	10	3.554±1.647	
II	18	5.073±3.119	
IIIA、IIIB	47	4.707±3.757	
IV	12	5.208±2.791	
Clinical stage			0.189
Early	5	2.744±0.868	
Advanced	82	4.840±3.370	
Histology			0.024[a,*]
Well differentiated	12	6.851±4.417	0.020[a,b,*]
Moderately differentiated	35	4.818±2.337	
Poorly differentiated	37	4.127±3.554	
Signet-ring cell	1	1.400	
Mucinous	2	2.825±1.549	

Clinicopathological Parameters	n	SUVmax ($\bar{x}$±SD)	*p* value
Lauren			0.003*
Intestinal	47	5.337±3.083	
Diffuse	40	3.994±3.462	
Venous invasion			0.901
Positive	66	4.727±3.377	
Negative	21	4.695±3.180	
Perineural invasion			0.955
Positive	52	4.606±3.221	
Negative	35	4.888±3.485	
GLUT-1 expression			0.015[a,]*
0	32	4.003±3.604	
1	10	4.936±3.130	
2	45	5.181±3.113	

a . Kruskal-Wallis test; b. Comparison in differentiated adenocarcinoma
*p<0.05

Tumor diameter was independent factor associated with SUVmax in positive imaging cases(Table 8).

Table 8 The multiple linear regression analysis of SUVmax with the clinicopathological parameters in 87 positive imaging cases

Clinicopathological Parameters	Regression Coefficient (95% CI)	standard error	*p* value
Age	0.040(-0.021~0.102)	0.031	0.198
Tumor diameter	0.310(0.033~0.587)	0.139	0.029*
Lauren classification	0.847(-0.610~2.305)	0.733	0.251
GLUT-1 expression level	0.318(-0.451~1.088)	0.387	0.413

*p<0.05

There were 84 differentiated carcinoma cases among 87 positive imaging cases. Tumor diameter and tumor differentiation were independent factors related to SUVmax in these differentiated carcinoma cases (Table 9).

Table 9 The multiple linear regression analysis of SUVmax with the clinicopathological parameters in 84 differentiated cases with positive imaging

Clinicopathological Parameters	Regression Coefficient (95% CI)	standard error	*p* value
Tumor diameter	0.414(0.149~0.680)	0.134	0.003*
Differentiated	-1.086(-2.041~-0.131)	0.480	0.026*

*p<0.05

Discussion

Although 18-FDG imaging was useful in monitoring recurrence and metastases in post-operative gastric cancer patients[19,20], the sensitivity for detecting of gastric cancer in the early stage was poor[21,22]. Thus, the imaging has not been routine modality for gastric cancer screening. However, the role of 18-FDG imaging in assessing locally advanced gastric cancer has been recognized[23].

With the development of concepts of surgical treatment on gastric cancer, optimal therapy is based on precise staging, which is one of hotspots of gastric cancer research[24]. Prospective study showed that FDG-PET/CT indentified occult metastases in approximately 10% of locally advanced gastric cancer patients, suggesting that PET/CT should be included in the standard staging algorithm for localized gastric cancer[23]. A meta-analysis affirmed the value of FDG-PET/CT in preoperative staging of gastric cancer[25]. Moreover, prognosis of patients with metastatic advanced gastric cancer could be predicted with the pretreatment maximal SUV of the stomach[26].

Kaneko et al. proposed that large tumor size(>3cm), non-signet ring cell carcinoma type and GLUT-1 positive expression were significant clinicopathological parameters of predicting FDG avidity[27]. Our previous work suggested that tumor size and depth of invasion was independent factors affecting assessment of FDG imaging (including SUVmax) without the evaluation of GLUT-1 expression.[17] Therefore, tumor size was the key clinicopathological parameter associated with FDG uptaking in gastric cancer before analyzing molecular factors (e.g. GLUT-1).

Previous researchers focused on the relation between GLUT-1 expression and gastric cancer FDG uptake[13,14,16,27,28]. There were controversial conclusions on the relationship. Most studies supposed that FDG uptake in gastric cancer was based on GLUT-1 expression[13,14,27,28], which accorded with theoretical prediction. This study also demonstrated that GLUT-1 was an independent factor associated with FDG imaging results by visual assessment. However, the independent factors included tumor diameter and Lauren classification in positive imaging cases. Although it had not been confirmed that GLUT-1 expression level was the independent factor related to SUVmax with multivariate analyses, the SUVmax was positively correlated with GLUT-1 expression. The GLUT-1 expression level is major factor affected 18-FDG uptake in not only visual assessment but also quantitative evaluation (e.g. SUVmax). Therefore, GLUT-1 in gastric cancer played an important role in FDG absorption.

FDG imaging result in gastric cancer was related to GLUT-1 expression, owing to absorption of FDG depending on gastric cancer GLUT-1 expression level. Nevertheless, a few cases of higher GLUT-1 expression lever had negative imaging result. The reasons are as follows; First, shorter tumor diameter was the primary cause of negative imaging result. Mean tumor diameter of cases that had GLUT-1 high expression level and negative imaging results was shorter than that of not only negative imaging but also positive imaging results. It is harder to find the smaller gastric cancer lesion in CT scanning. In addition, inadequate FDG absorption due to limited GLUT-1 expression level of smaller lesion might not be detected as positive in device. Second, not only the system resolution and sensitivity of SPECT/CT in this study inferior to PET/CT[29] but also different reconstruct methods leads to difference in imaging quality[30]. It is necessary to verify the result with PET/CT.

There were 32 GLUT-1-negative cases showing positive imaging in this work, which indicated that GLUT-1 expression level was not sole factor leading to tracer concentration in image. These cases had greater tumor diameter (4.94±2.23cm) and higher SUVmax (4.003±3.604). It was found that more capillaries and intravascular erythrocyte gathering in gastric cancer tissue of some cases with the microscope. Tumor tissue consists of tumor cells and stroma, which absorbed ^{18}F-FDG resulting in uptake of tumor tissue displayed in image, especially for SUVmax. SUV calculation is : SUV= radioactivity concentration of the pixel/(injection dose/body weight) [31]. The radioactivity concentration of tissue from tumor cells and stroma determine the SUV within corresponding pixel area. Therefore, the reasons of GLUT-1 negative gastrice cancer exhibiting positive imaging with higher SUVmax may be as follow: First, other subtype GLUT (e.g GLUT-3[32]) or protein with transporting glucose exist within cancer cell membrane. Second, HK-II increasing within cell results in ^{18}F-FDG absorption independence of GLUT-1 overexpression. HK-II overexpression in gastric cancer has been demonstrated [33]. Third, neovascularizaition in tumor stromal contain erythrocyte which uptake ^{18}F-FDG efficiently with expressing GLUT-1. The organs with better blood supply and more erythrocyte (e.g heart, brain, kidney) absorb more ^{18}F-FDG. This may be intrinsic reason why tumor size is only independent factor influencing imaging within visual assessment and SUVmax.

Lee et al. suggested that ^{18}F-FDG uptake and SUVmax were significantly independent prognosis factor of gastric cancer recurrence in studying the relation between preoperative PET/CT, SUVmax and recurrence after curative surgical resection[34]. Our previous work and other researchers' studies show that GLUT-1 is a prognosis factor of postoperative recurrence and metastases within most digestive malignant tumor including gastric cancer[35-38]. Therefore, with the result of this study, it is supposed that GLUT-1 is intrinsic factor of ^{18}F-FDG imaging predicting gastric cancer recurrence. However, further investigation on analysis GLUT-1 expression in lesions of gastric cancer metastases and recurrences is required.

Conclusion

In conclusion, GLUT-1 expression level is major factor determining ^{18}F-FDG uptake of gastric cancer. ^{18}F-FDG imaging monitoring gastric cancer metastases and recurrence is possibly associated with GLUT-1 expression on lesions of metastases and recurrence.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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No

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