Glucose Transporter-1 (GLUT-1) Expression is Associated with Tumor Size and Poor Prognosis in Locally Advanced Gastric Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Chenqing Yin*
EF 1 Bin Gao*
BD 2 Ju Yang
BD 2 Jingbo Wu

1 Department of General Surgery, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, P.R. China
2 Department of Pathology, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, P.R. China

Corresponding Author:
Source of support:

* These authors contributed equally to this work
Chenqing Yin, e-mail: catcherlk@126.com
Nature Science Foundation of Minhang District, 2014MHZ032 and 2013MHZ017

Background:
The clinicopathological parameters associated with glucose transporter-1 (GLUT-1) expression in advanced gastric cancer are still controversial. This study aimed to determine the clinicopathological parameters and prognosis associated with GLUT-1 expression in advanced gastric cancer.

Material/Methods:
The GLUT-1 expression level of 234 consecutive gastric cancer samples was detected by immunohistochemical staining and evaluated by semiquantitative analysis. The clinicopathological data and expression level of GLUT-1 of enrolled patients were retrospectively analyzed with univariate and multivariate analyses.

Results:
Tumor size, depth of invasion, and Lauren classification were independent factors related to GLUT-1 expression ($P<0.05$). Within advanced gastric cancer, tumor size and Lauren type were independent factors associated with GLUT-1 ($P=0.011$, $P<0.001$, respectively). The mean survival time of GLUT-1-positive patients with stage M0 advanced gastric cancer who had undergone radical gastrectomy was shorter than that of GLUT-1-negative patients (61.26 ± 6.12 versus 80.88 ± 7.38, $P=0.044$). GLUT-1 was an independent prognosis factor in locally advanced gastric cancer patients who had undergone radical gastrectomy (hazard ratio [HR] 1.769, $P=0.046$). The mean survival time of adjuvant chemotherapy was significantly better than no adjuvant chemotherapy in the GLUT-1-positive group (71.10 ± 6.88 versus 24.65 ± 8.69, $P<0.001$) and in the GLUT-1 negative group (87.48 ± 7.99 versus 49.39 ± 11.71, $P<0.001$).

Conclusions:
Tumor size and Lauren type independently affected GLUT-1 expression in advanced gastric cancer. GLUT-1 was not only related to poor prognosis but also predicted to be a metabolic biomarker for intestinal type in locally advanced gastric cancer. The relationship among GLUT-1, hepatic metastasis and chemotherapy regimens, and mechanism of chemotherapy responses related to GLUT-1 should be further investigated.

MeSH Keywords:
Chemotherapy, Adjuvant • Glucose Transporter Type 1 • Prognosis • Stomach Neoplasms

Full-text PDF:
https://www.basic.medscimonit.com/abstract/index/idArt/920778

📄 1984   ⊞ 5   ᴧ 4   📖 45

Background

Gastric cancer is the second most common cancer in Eastern Asia [1]. In Japan, mortality from gastric cancer may be reduced due to screening, although the incidence remains high [2,3]. A reduction in the incidence of gastric cancer has been reported in the Shanghai urban area [4]. However, mortality in this region has not decreased, resulting in a high rate of individuals with advanced gastric cancer [5]. The characteristics of advanced gastric cancer should be investigated to improve survival.

Glucose transporter-1 (GLUT-1) is a member of the major transporter superfamily [6] and regulates glucose distribution by controlling the direction of movement of glucose [7]. The transporter is expressed in numerous cell types, such as erythrocytes, brain cells, and muscle cells, at varying levels [8]. It is significant that for tissues depending on glucose for energy production that GLUT-1 is a highly expressed protein [9]. In addition, a variety of cancers, including lung cancer and colorectal carcinoma, overexpress GLUT-1 [10,11].

GLUT-1 positivity in gastric cancer is not high among malignant tumors and is only 19~29.5% in Japan [12,13], 16.9~43.0% in Korea [14–16], and 22.0~50.0% in Germany [17,18]. Depth of invasion, lymphatic permeation, venous invasion, lymph node metastasis, and hepatic metastasis were associated with s positive rate in Japan, where early gastric cancer is predominant among all gastric cancer cases [13]. The clinicopathological parameters associated with GLUT-1 expression in advanced gastric cancer in the Chinese population are still controversial. Therefore, this study aimed to explore the clinicopathological parameters and prognosis related to GLUT-1 in advanced gastric cancer.

Material and Methods

Patients

A total of 234 consecutive patients who did not undergo preoperative chemotherapy or radiotherapy between January 2008 and January 2014 at the Fifth People's Hospital of Shanghai were enrolled in this study. All of them had pathologically confirmed disease after gastrectomy and lymph node dissection. All advanced stage cases underwent radical gastrectomy and D2 dissection. Adjuvant chemotherapy has been employed according to NCCN clinical practice guidelines. Advanced gastric cancer patients underwent chemotherapy protocol including mFOLFOX and SOX. All enrolled patients had an over 5-years follow-up period and examinations at regular intervals. The local Research Ethics Commission approved this study.

The staging system used in of this study was the American Joint Committee on Cancer, 8th edition. Histology was scored according to the World Health Organization (WHO) classification [19]. The characteristics of the patients are shown in Table 1.

Experimental procedures

Paraffin-embedded samples of tumors were sliced into 4 μm-thick specimens. After deparaffinization and hydration, the slides were treated with 3% H_2O_2 for 10 minutes at room temperature. We used 0.01 M sodium citrate buffer (pH 6.0) at 100°C for 1 minute for antigen retrieval. The slides were incubated with primary monoclonal GLUT-1 antibody (ab40084, Abcam, UK, 1: 100). EnVision detection systems (Peroxidase/DAB, Rabbit/Mouse, DAKO) were used for staining. After treatment with the kits, the sections were counterstained with Mayer's hematoxylin. Then, the specimens were dehydrated with gradient ethanol series and sealed with neutral balsam. For quality control, omission of the GLUT-1 antibody and use of isotype controls (ab18413, Abcam, UK) were performed.

The analyses were conducted by experienced pathologists blinded to the patients' clinical information. Positive tumor cells were identified by staining of the cell membrane (Figure 1). The GLUT-1 expression level was evaluated by semiquantitative assessment [20,21]. The scoring system criteria were as follows: 0 as <1% positive tumor cells; 1 as 1~30% positive tumor cells; and 2 as >30% positive tumor cells.

Statistical analysis

Continuous variables are expressed as mean values with standard deviation or range. Chi-squared test or Fisher's exact test was performed to determine the relationship between GLUT-1 expression and clinicopathological parameters such as gender and tumor localization. Age and tumor diameter of the GLUT-1-positive and GLUT-1-negative groups were compared with the Mann-Whitney U test. Multivariate analyses of GLUT-1 expression and potentially significant factors ($P<0.10$) were performed with logistic regression analysis, which was verified by stepwise regression of all clinicopathological parameters. The 132 patients with stage M0 advanced gastric cancer who had undergone radical gastrectomy (dissected lymph nodes ≥20, R0 resection) were included in the survival analysis with the Kaplan-Meier method and log-rank test. Cox regression multivariate analysis included the clinicopathological parameters for survival analysis. $P<0.05$ was considered to be statistically significant. SPSS software, version 16.0, was used for all statistical analyses.

Table 1. The relation between GLUT-1 expression and clinicopathological parameters in 234 gastric cancer cases.

Clinicopathological parameters	GLUT-1 expression		P-value
	Negative (score 0) n=99	Positive (score 1~2) n=135	
Gender			0.086
Male	63 (63.6%)	100 (74.1%)	
Female	36 (36.4%)	35 (25.9%)	
Age (year)	63±13	65±11	0.219a
Tumor diameter(cm)	4.31±2.30	5.24±2.60	0.002a,*
Tumor localization			0.013*
Upper	10 (10.1%)	34 (25.2%)	
Middle	18 (18.2%)	18 (13.3%)	
Lower	71 (71.7%)	83 (61.5%)	
pT			0.088b
T1 (T1a, T1b)	25 (25.3%)	19 (14.1%)	
T2	14 (14.1%)	14 (10.4%)	
T3	1 (1.0%)	3 (2.2%)	
T4 (T4a, T4b)	59 (59.6%)	99 (73.3%)	
pN			0.936
N0	29 (29.3%)	41 (30.4%)	
N1	15 (15.2%)	24 (17.8%)	
N2	23 (23.2%)	30 (22.2%)	
N3 (N3a, N3b)	32 (32.3%)	40 (29.6%)	
M			0.009b,*
M0	97 (98.0%)	120 (88.9%)	
M1	2 (2.0%)	15 (11.1%)	
TNM stage			0.133b
IA, IB	25 (25.3%)	25 (18.5%)	
IIA, IIB	18 (18.2%)	24 (17.8%)	
IIIA, IIIB, IIIC	54 (54.5%)	75 (55.6%)	
IV	2 (2.0%)	11 (8.1%)	
Clinical stage			0.031*
Early	25 (25.3%)	19 (14.1%)	
Advanced	74 (74.7%)	116 (85.9%)	
Histology			<0.001b,*
Well differentiated	18 (18.2%)	32 (23.7%)	<0.001c,*
Moderately differentiated	22 (22.2%)	60 (44.4%)	
Poorly differentiated	49 (49.5%)	36 (26.7%)	
Signet-ring cell	9 (9.1%)	5 (3.7%)	
Mucinous	1 (1.0%)	2 (1.5%)	

Table 1 continued. The relation between GLUT-1 expression and clinicopathological parameters in 234 gastric cancer cases.

Clinicopathological parameters	GLUT-1 expression		P-value
	Negative (score 0) n=99	Positive (score 1~2) n=135	
Lauren type			<0.001*
Intestinal	40 (40.4%)	92 (68.1%)	
Diffuse	59 (59.6%)	43 (31.9%)	
Venous invasion			0.061
Positive	62 (62.6%)	100 (74.1%)	
Negative	37 (37.4%)	35 (25.9%)	
Lymphatic invasion			0.919
Positive	71 (71.7%)	96 (71.1%)	
Negative	28 (28.3%)	39 (28.9%)	
Perineural invasion			0.047*
Positive	51 (51.5%)	87 (64.4%)	
Negative	48 (48.5%)	48 (35.6%)	

[a] Mann-Whitney U test; [b] Fisher's exact test; [c] Comparison of different grade in adenocarcinoma. * $P<0.05$. GLUT-1 – glucose transporter-1.
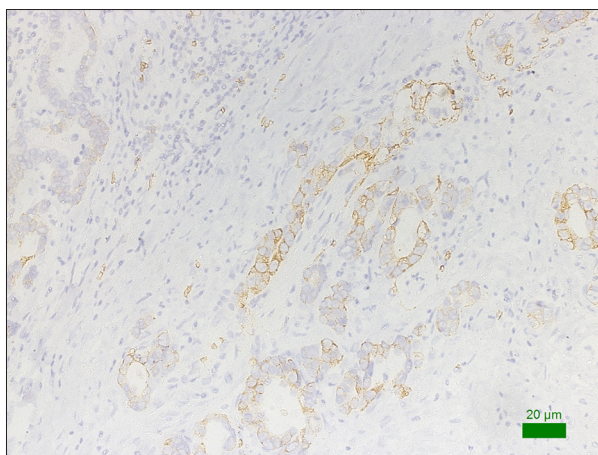

Figure 1. Glucose transporter-1 (GLUT-1) positive staining in gastric adenocarcinoma cell membrane (200×).

Results

In these gastric cancer patients, the overall positive rate of GLUT-1 expression was 57.69% (135 out of 234 patients). The relationship between GLUT-1 and clinicopathological parameters is shown in Table 1. Tumor diameter, localization, M stage, and histology/Lauren type were associated with GLUT-1 expression in advanced gastric cancer (Table 2). Tumor diameter, M stage, and Lauren type were also independent factors (Table 3).

The median follow-up period was 48.45 months. The mean survival time of GLUT-1-positive patients with stage M0 advanced gastric cancer who had undergone radical gastrectomy was shorter than that of GLUT-1-negative patients (61.26±6.12 versus 80.88±7.38, P=0.044) (Figure 2). The hepatic metastasis hazard curve of GLUT-1-positive patients was higher than that of negative patients (Figure 3). Age, tumor diameter, pT, pN, GLUT-1, and adjuvant chemotherapy were related to survival time in our univariate analysis (Table 4). GLUT-1 was an independent prognosis factor in locally advanced gastric cancer undergone radical gastrectomy (hazard ratio [HR] 1.769, P=0.046) (Table 5).

The mean survival time of the adjuvant chemotherapy group was significantly better than the no adjuvant chemotherapy group in the GLUT-1-positive and negative groups (Figure 4). The mean survival time for patients in the adjuvant chemotherapy and no adjuvant chemotherapy groups in the GLUT-1-positive group was 71.10±6.88 and 24.65±8.69 months, respectively; whereas in the GLUT-1-negative the mean survival time was 87.48±7.99 and 49.39±11.71 months, respectively.

Discussion

Reprogramming energy metabolism is one of the canonical hallmarks of cancer [22]. Glucose metabolism is not only essential for human survival but also associated with carcinogenesis [23].

Table 2. The relation between GLUT-1 expression and clinicopathological parameters in 190 advanced gastric cancer cases.

Clinicopathological parameters	GLUT-1 expression		P-value
	Negative (score 0) n=74	Positive (score 1~2) n=116	
Gender			0.191
Male	49 (66.2%)	87 (75.0%)	
Female	25 (33.8%)	29 (25.0%)	
Age (year)	63±14	66±11	0.099[a]
Tumor diameter (cm)	4.78±2.35	5.68±2.48	0.007[a,*]
Tumor localization			0.039*
Upper	9 (12.2%)	32 (27.6%)	
Middle	14 (18.9%)	16 (13.8%)	
Lower	51 (68.9%)	68 (58.6%)	
pT			0.382[b]
T2	14 (18.9%)	14 (12.1%)	
T3	1 (1.4%)	3 (2.6%)	
T4 (T4a, T4b)	59 (79.7%)	99 (85.3%)	
pN			0.328
N0	9 (12.2%)	26 (22.4%)	
N1	13 (17.5%)	21 (18.1%)	
N2	21 (28.4%)	29 (25.0%)	
N3 (N3a, N3b)	31 (41.9%)	40 (34.5%)	
M			0.012[b,*]
M0	72 (97.3%)	101 (87.1%)	
M1	2 (2.7%)	15 (12.9%)	
TNM stage			0.233[b]
IB	3 (4.0%)	7 (6.0%)	
IIA, IIB	15 (20.3%)	23 (19.8%)	
IIIA, IIIB, IIIC	54 (73.0%)	75 (64.7%)	
IV	2 (2.7%)	11 (9.5%)	
Histology			<0.001[b,*]
Well differentiated	8 (10.8%)	20 (17.3%)	<0.001[b,c,*]
Moderately differentiated	16 (21.6%)	57 (49.1%)	
Poorly differentiated	43 (58.1%)	34 (29.3%)	
Signet-ring cell	6 (8.1%)	3 (2.6%)	
Mucinous	1 (1.4%)	2 (1.7%)	

Table 2 continued. The relation between GLUT-1 expression and clinicopathological parameters in 190 advanced gastric cancer cases.

Clinicopathological parameters	GLUT-1 expression		P-value
	Negative (score 0) n=74	Positive (score 1~2) n=116	
Lauren type			<0.001*
Intestinal	24 (32.4%)	77 (66.4%)	
Diffuse	50 (67.6%)	39 (33.6%)	
Venous invasion			0.085
Positive	55 (74.3%)	98 (84.5%)	
Negative	19 (25.7%)	18 (15.5%)	
Lymphatic invasion			0.100
Positive	65 (87.8%)	91 (78.4%)	
Negative	9 (12.2%)	25 (21.6%)	
Perineural invasion			0.265
Positive	50 (67.6%)	87 (75.0%)	
Negative	24 (32.4%)	29 (25.0%)	

[a] Mann-Whitney U test; [b] Fisher's exact test; [c] Comparison of different grade in adenocarcinoma. * $P<0.05$. GLUT-1 – glucose transporter-1.

GLUT-1 is a typical transporter involved in metabolism and has been further elucidated with xyIE reporter analyses [24]. Gastric cancer and other malignant tumors have been found to be related to GLUT-1 [11,13,25–28]. The Warburg phenotype, which is GLUT-1 positive, is the most common phenotype in triple-negative breast cancer and corresponds to a poor prognosis [29]. The GLUT-1 positive rate of other digestive tract neoplasms, such as colorectal and esophageal carcinoma, is higher (90~100%) [11,30]. However, there have been discrepancies among several studies on GLUT-1 expression in gastric cancer. Therefore, we analyzed its expression in various situation in our study.

In our study, the positive rate of GLUT-1 expression in gastric cancer samples was similar to that reported in previous studies [12–16,31–38]. Moreover, the positive rate in the advanced stage group was significantly higher than that in the early stage group. The difference in the ratio of advanced to early stage cancer patients among studies may result in a higher positive rate found in Chinese studies, including ours, than found in studies from other East Asian countries [12–16,31–38]. The ratio in our study was significantly higher than that of other large case studies [13]. The differences in the epidemiological characteristics are likely caused by the varying strategies for diagnosing and treating gastric cancer. For example, an advanced screening system for gastric cancer in Japan may lead to a lower proportion of individuals with advanced gastric cancer than found in other East Asian countries [2,3].

Tumor diameter and pT stage were independent factors associated with GLUT-1 expression in all gastric cancer cases, and they were positively correlated with each other. The growth of gastric lesions in perpendicular directions determined the independence of these variables [39]. Tumor diameter was also an independent factor in advanced stage gastric cancer, which suggested that GLUT-1 expression was associated with further tumor enlargement.

Korean studies have suggested that the intestinal type of gastric cancer is related to GLUT-1 [14,16,40]. Our study also obtained a similar result: multivariate analysis of overall or advanced stage gastric cancer revealed that the positive rate of GLUT-1 in intestinal gastric cancer was higher than that in the diffuse type. Lauren proposed his classification of gastric carcinoma in 1965 [41]. This histological classification is simplified, accessible, and reproducible to the benefit of research [42]. Both the Lauren classification and the WHO classification have been commonly used in gastric cancer studies, which can be correlated to each other [42]. The mucinous and signet-ring cell types in the WHO classification are mostly categorized as diffuse type in the Lauren classification. The positive rate of GLUT-1 expression in the 2 types was lower than that in the differentiated type [13,31]. Therefore, the lower rate in the diffuse type was probably the result of the characteristics of mucinous and signet-ring cell gastric cancer. GLUT-1 might be a potential metabolic biomarker for the intestinal type in advanced gastric cancer.

Table 3. The logistic regression analysis of GLUT-1 expression with clinicopathological parameters in 190 advanced gastric cancer cases.

Parameters	Regression coefficient (95% CI)	OR (95% CI)	*P*-value
Gender	−0.310 (−0.709~0.089)	0.734 (0.336~1.602)	0.437
Age	0.012 (−0.003~0.027)	1.012 (0.982~1.043)	0.453
Tumor diameter	0.198 (0.120~0.276)	1.220 (1.047~1.420)	0.011*
Tumor localization	−0.272 (−0.494~−0.050)	0.762 (0.493~1.177)	0.221
pT	0.306 (0.051~0.561)	1.358 (0.825~2.236)	0.229
pN	−0.369 (−0.621~−0.117)	0.691 (0.422~1.133)	0.143
M	2.168 (1.280~3.056)	8.744 (1.535~49.819)	0.015*
Lauren type (intestinal =. diffuse)	1.338 (0.980~1.696)	3.810 (1.888~7.687)	<0.001*
Venous invasion	−0.682 (−1.230~−0.134)	0.506 (0.173~1.481)	0.214
Lymphatic invasion	0.356 (−0.358~1.070)	1.427 (0.352~5.790)	0.618
Perineural invasion	−0.079 (−0.555~0.397)	0.924 (0.364~2.349)	0.869

* *P*<0.05. OR – odds ratio; CI – confidence interval; GLUT-1 – glucose transporter-1.
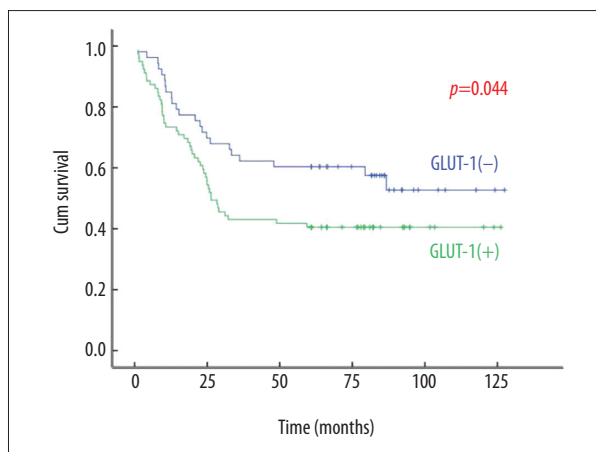

Figure 2. The survival curves of the stage M0 advanced gastric cancer patients who had undergone radical gastrectomy (dissecting lymph nodes ≥20, R0 resection), glucose transporter-1 (GLUT-1) positive and negative.
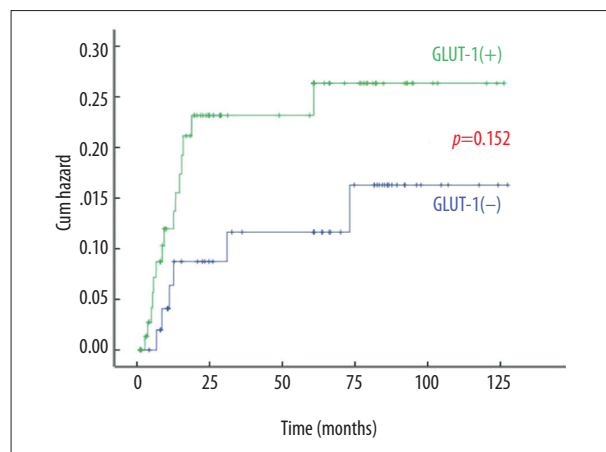

Figure 3. The hepatic metastasis hazard curves of the stage M0 advanced gastric cancer patients who had undergone radical gastrectomy (dissecting lymph nodes ≥20, R0 resection), glucose transporter-1 (GLUT-1) positive and negative.

Table 4. Kaplan-Meier survival analysis in stage M0 advanced gastric cancer after radical gastrectomy (dissected lymph nodes ≥20, R0 resection).

Parameters	Mean survival time, months (95%CI)	P-value
Gender		0.793
Male	68.39 (57.516~79.265)	
Female	67.96 (50.524~85.393)	
Age (year)		<0.001*
<65	91.08 (78.064~104.100)	
≥65	51.37 (39.539~63.202)	
Tumor diameter (cm)		0.003*
<5	81.28 (68.810~93.754)	
≥5	56.26 (43.277~69.233)	
Tumor localization		0.073
Upper	36.67 (21.558~51.772)	
Middle	74.96 (52.284~97.628)	
Lower	72.83 (61.413~84.251)	
pT		0.006*
T2	101.73 (84.760~118.691)	
T3~4 (T4a, T4b)	62.65 (52.27~73.02)	
pN		0.002*
N0	77.86 (59.137~96.587)	
N1	99.64 (80.68~118.61)	
N2	63.72 (47.12~80.33)	
N3 (N3a, N3b)	43.59 (30.21~59.96)	

Parameters	Mean survival time, months (95%CI)	P-value
Lauren type		0.763
Intestinal	69.39 (56.784~81.993)	
Diffuse	68.74 (54.751~82.735)	
Venous invasion		0.059
Positive	64.72 (54.178~75.261)	
Negative	69.86 (55.660~84.068)	
Lymphatic invasion		0.363
Positive	74.77 (56.08~93.45)	
Negative	67.23 (56.46~78.00)	
Perineural invasion		0.052
Positive	63.77 (52.674~74.857)	
Negative	69.07 (56.085~82.064)	
GLUT-1		0.044*
Positive	61.26 (49.256~73.256)	
Negative	80.88 (66.418~95.348)	
Adjuvant chemotherapy		<0.001*
Yes	78.16 (67.763~88.563)	
No	35.74 (19.779~51.692)	

* $P<0.05$. CI – confidence interval; GLUT-1 – glucose transporter-1.

There have been different results from previous Chinese studies on the relationship between GLUT-1 expression and differentiated type in gastric cancer [31-35]. Wei et al. found that the GLUT-1 positive rate in well-differentiated types of gastric cancers was higher than that in moderately and poorly differentiated types [31]. Nevertheless, other researchers presented distinct results that showed the rate of poorly differentiated and undifferentiated type was higher [33–35]. Our study demonstrated that GLUT-1 expression was positively correlated with differentiation grade. The positive rate of moderately differentiated type was the highest of all the types, which was in line with the results reported by Yu et al. [32]. Such contradictory results suggest that GLUT-1 is probably a molecular factor that is not dependent on differentiation.

Kawamura et al. found that GLUT-1 expression was associated with poor survival in gastric cancer patients using multivariate

Table 5. Cox regression multivariate analysis in stage M0 advanced gastric cancer after radical gastrectomy (dissected lymph nodes ≥20, R0 resection).

Parameters	HR (95% CI)	P-value
Gender	1.065 (0.605~1.876)	0.826
Age	1.043 (1.016~1.071)	0.001*
Tumor diameter	1.094 (0.994~1.205)	0.067
Tumor localization	0.641 (0.452~0.910)	0.013*
pT	1.408 (0.901~2.201)	0.133
pN	2.840 (1.755~4.597)	<0.001*
Lauren type	0.778 (0.467~1.296)	0.335
Venous invasion	0.644 (0.226~1.839)	0.411
Lymphatic invasion	0.171 (0.051~0.576)	0.004*
Perineural invasion	1.404 (0.646~3.052)	0.392
GLUT-1	1.769 (1.010~3.096)	0.046*
Adjuvant chemotherapy	0.468 (0.253~0.866)	0.016*

* $P<0.05$. GLUT-1 – glucose transporter-1.

Figure 4. The survival curves of the stage M0 advanced gastric cancer patients who had undergone radical gastrectomy (dissecting lymph nodes ≥20, R0 resection), glucose transporter-1 (GLUT-1) positive and negative, adjuvant chemotherapy (CT(+)) and no adjuvant chemotherapy (CT(–)).

analyses [13]. Jung et al. in Korea also affirmed that GLUT-1-positive gastric cancer patients had a shorter mean survival time [16]. Nevertheless, studies in China have not clearly shown that GLUT-1 expression is related to poor prognosis [31,35]. This inconsistency may be associated with differences in the epidemiological characteristics of gastric cancer between patients in China and those in other East Asian countries. Patients with advanced stage gastric cancer are predominant in China due to the country's strategy on diagnosing and treating cancer. Moreover, the development of multi-disciplinary treatments with new drugs, devices, and techniques has improved the survival of advanced gastric cancer [43]. This study only showed that GLUT-1 positivity was associated with poor survival in stage M0 advanced gastric cancer patients who had undergone radical gastrectomy. Therefore, the epidemiological characteristics limited the application of our work in overall stages of gastric cancer. The hepatic metastasis hazard curve of GLUT-1-positive stage M0 advanced gastric cancer after radical gastrectomy was higher than that of the GLUT-1-negative
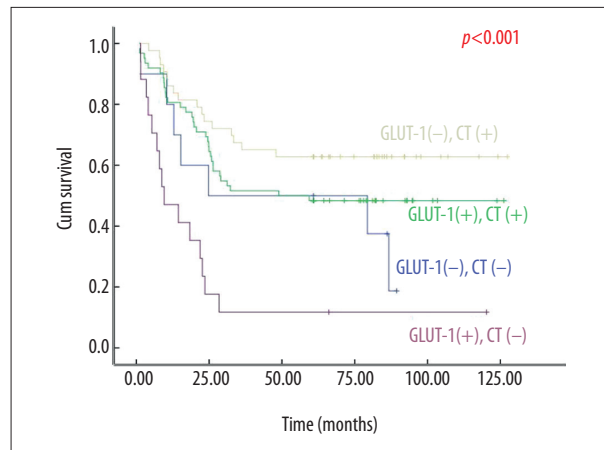
group, and GLUT-1 expression was associated with the intestinal type of advanced gastric cancer.

The chemotherapy regime 5-fluorouracil (5-FU) has been shown to affect GLUT-1 on gastric cancer cell *in vitro,* which indicates that GLUT-1 may be partly associated with responses to 5-FU chemotherapy in gastric cancer [44]. Lu et al. suggested that GLUT-1 may be a marker for gastric cancer sensitivity to ascorbate in chemotherapy with *in vitro* and *in vivo* experiments [45]. Our work indicated that GLUT-1-positive patients might be subject to benefit from chemotherapy based on clinical data.

Although our work suggested that GLUT-1 might be associated with hepatic metastasis from gastric cancer and chemotherapy responses, there were a few limitations to our study, including the study was a small single center retrospective study and advanced gastric cancer was the predominantly patient diagnosis (especially pT4 staging). The relationship between GLUT-1, hepatic metastasis and chemotherapy, and mechanism of chemotherapy responses related to GLUT-1 should be further investigated.

Conclusions

GLUT-1 expression in advanced stage gastric cancer was significantly higher than that in early stage gastric cancer. Tumor size and Lauren type independently affected GLUT-1 expression in advanced gastric cancer. GLUT-1 was not only related to poor prognosis but also predicted to be a metabolic biomarker for the Lauren classification in locally advanced gastric cancer.

Conflict of interest

None.

References:

1. Jemal A, Bray F, Center MM et al: Global cancer statistics. Cancer J Clin, 2011; 61(2): 69–90

2. Lee KJ, Inoue M, Otani T et al: Gastric cancer screening and subsequent risk of gastric cancer: A large-scale population-based cohort study, with a 13-year follow-up in Japan. Int J Cancer, 2006; 118(9): 2315–21

3. Hamashima C, Shibuya D, Yamazaki H et al: The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol, 2008; 38(4): 259–67

4. Fei SJ, Xiao SD: Diet and gastric cancer: A case-control study in Shanghai urban districts. Chin J Dig Dis, 2006; 7(2): 83–8

5. Wang X, Wu C, Zheng Y et al: [Time trends and characteristics of gastric cancer incidence in urban Shanghai.] Zhonghua Liu Xing Bing Xue Za Zhi, 2007; 28(9): 875–80 [in Chinese]

6. Pao SS, Paulsen IT, Saier MH Jr: Major facilitator superfamily. Microbiol Mol Biol Rev, 1998; 62(1): 1–34

7. Medina RA, Owen GI: Glucose transporters: Expression, regulation and cancer. Biol Res, 2002; 35(1): 9–26

8. Wood IS, Trayhurn P: Glucose transporters (GLUT and SGLT): Expanded families of sugar transport proteins. Br J Nutr, 2003; 89(1): 3–9

9. Adekola K, Rosen ST, Shanmugam M: Glucose transporters in cancer metabolism. Curr Opin Oncol, 2012; 24(6): 650–54

10. Younes M, Brown RW, Stephenson M et al: Overexpression of GLUT1 and GLUT3 in stage I non-small cell lung carcinoma is associated with poor survival. Cancer, 1997; 80(6): 1046–51

11. Haber RS, Rathan A, Weiser KR et al: GLUT1 glucose transporter expression in colorectal carcinoma: A marker for poor prognosis. Cancer, 1998; 83(1): 34–40

12. Noguchi Y, Marat D, Saito A et al: Expression of facilitative glucose transporters in gastric tumors. Hepatogastroenterology, 1999; 46(28): 2683–89

13. Kawamura T, Kusakabe T, Sugino T et al: Expression of glucose transporter-1 in human gastric carcinoma: Association with tumor aggressiveness, metastasis, and patient survival. Cancer, 2001; 92(3): 634–41

14. Kim WS, Kim YY, Jang SJ et al: Glucose transporter 1 (GLUT1) expression is associated with intestinal type of gastric carcinoma. J Korean Med Sci, 2000; 15(4): 420–24

15. Hur H, Xuan Y, Kim YB et al: Expression of pyruvate dehydrogenase kinase-1 in gastric cancer as a potential therapeutic target. Int J Oncol, 2013; 42(1): 44–54

16. Jung JH, Im S, Jung ES et al: Clinicopathological implications of the expression of hypoxia-related proteins in gastric cancer. Int J Med Sci, 2013; 10(9): 1217–23

17. Schlosser HA, Drebber U, Urbanski A et al: Glucose transporters 1, 3, 6, and 10 are expressed in gastric cancer and glucose transporter 3 is associated with UICC stage and survival. Gastric Cancer, 2017; 20(1): 83–91

18. Berlth F, Monig S, Pinther B et al: Both GLUT-1 and GLUT-14 are independent prognostic factors in gastric adenocarcinoma. Ann Surg Oncol, 2015; Suppl 3: S822–31

19. Hamilton S, Aaltonen L: Pathology and genetics of tumours of the digestive system. IARCP, 2000

20. Yamada A, Oguchi K, Fukushima M et al: Evaluation of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography in gastric carcinoma: Relation to histological subtypes, depth of tumor invasion, and glucose transporter-1 expression. Ann Nucl Med, 2006; 20(9): 597–604

21. Alakus H, Batur M, Schmidt M et al: Variable 18F-fluorodeoxyglucose uptake in gastric cancer is associated with different levels of GLUT-1 expression. Nucl Med Commun, 2010; 31(6): 532–38

22. Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell, 2011; 144(5): 646–74

23. Shaw RJ: Glucose metabolism and cancer. Curr Opin Cell Biol, 2006; 18(6): 598–608

24. Sun L, Zeng X, Yan C et al: Crystal structure of a bacterial homologue of glucose transporters GLUT1-4. Nature, 2012; 490(7420): 361–66

25. Kobayashi M, Kaida H, Kawahara A et al: The relationship between GLUT-1 and vascular endothelial growth factor expression and 18F-FDG uptake in esophageal squamous cell cancer patients. Clin Nucl Med, 2012; 37(5): 447–52

26. Shim BY, Jung JH, Lee KM et al: Glucose transporter 1 (GLUT1) of anaerobic glycolysis as predictive and prognostic values in neoadjuvant chemoradiotherapy and laparoscopic surgery for locally advanced rectal cancer. Int J Colorectal Dis, 2013; 28(3): 375–83

27. Zimmerman RL, Fogt F, Burke M et al: Assessment of GLUT-1 expression in cholangiocarcinoma, benign biliary lesions and hepatocellular carcinoma. Oncol Rep, 2002; 9(4): 689–92

28. Hussein YR, Bandyopadhyay S, Semaan A et al: GLUT-1 expression correlates with basal-like breast cancer. Transl Oncol, 2011; 4(6): 321–27

29. Kim S, Kim DH, Jung WH et al: Metabolic phenotypes in triple-negative breast cancer. Tumour Biol, 2013; 34(3): 1699–1712

30. Tohma T, Okazumi S, Makino H et al: Overexpression of glucose transporter 1 in esophageal squamous cell carcinomas: A marker for poor prognosis. Dis Esophagus, 2005; 18(3): 185–89

31. Wei B, Chen L, Li J: [Expression of glucose transporter 1 in gastric carcinoma and metastatic lymph nodes and its association with prognosis]. Zhonghua Wei Chang Wai Ke Za Zhi, 2009; 12(3): 277–80 [in Chinese]

32. Yu Y, Hu J, Fang Y: Clinical pathological significance of GLUT-1 protein expression in gastric carcinoma. China Medicine, 2009; 4(11): 845–46

33. Chen Y, Liu Q, Huang J et al: GLUT1 expression and clinicopathological significance in gastric cancer. Clinical Focus, 2012; 27(8): 694–95

34. Li W, Song X, Sun S, et al: Expressions of HIF-1α, GLUT1 and PCNA in gastric cancer and clinical significance. Chinese Journal of Gastroenterology and Hepatology, 2008; 17(3): 223–25

35. Qian Y, Shi H: HIF-1α and GLUT1 expression and significance in gastric cancer. Zhejiang Clinical Medical Journal, 2013(10): 1444–47

36. Zhang P, Wu J, Zhang H et al: HIF-1α, VEGF and GLUT1 protein expression in gastric carcinoma. Acta Universitatis Medicinalis Anhui, 2010; 45(1): 86–89

37. Sun J: Expression and clinical significance of Survivin and Glut 1 protein in gastric carcinoma. Clinical Medicine of China, 2013; 29(2): 176–78

38. Xu Q: The interaction between glucose transporter-1(GLUT-1) and expression of Hrd-1 and Derlin-1 in gastric cancer [Master Degree]. Southeast University, 2013

39. Yin C, Nan Y, Lu T et al: Clinicopathological parameters influence assessment of FDG SPECT in gastric cancer. Hepatogastroenterology, 2015; 62(139): 762–65

40. Choi BH, Song HS, An YS et al: Relation between fluorodeoxyglucose uptake and glucose transporter-1 expression in gastric signet ring cell carcinoma. Nucl Med Mol Imaging, 2011; 45(1): 30–35

41. Lauren P: The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand, 1965; 64: 31–49

42. Yu Y: [Evaluation of traditional pathological classification at molecular classification era for gastric cancer.] Zhonghua Wei Chang Wai Ke Za Zhi, 2014; 17(1): 18–20 [in Chinese]

43. Ji J, Li Z, Shen L et al: Attaching importance to the effect of multidisciplinary team in the standardized treatment of gastric cancer. Chinese Journal of Practical Surgery, 2014(7): 592–94

44. Won HJ, Ha TK, Kwon SJ et al: Differential effects of 5-fluorouracil on glucose transport and expressions of glucose transporter proteins in gastric cancer cells. Anticancer Drugs, 2010; 21(3): 270–76

45. Lu YX, Wu QN, Chen DL et al: Pharmacological ascorbate suppresses growth of gastric cancer cells with GLUT1 overexpression and enhances the efficacy of oxaliplatin through redox modulation. Theranostics, 2018; 8(5): 1312–26