



Retrospective Study

# Value of glucose transport protein 1 expression in detecting lymph node metastasis in patients with colorectal cancer

Hongsik Kim, Song-Yi Choi, Tae-Young Heo, Kyeong-Rok Kim, Jisun Lee, Min Young Yoo, Taek-Gu Lee, Joung-Ho Han

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**Hongsik Kim**, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju 28644, South Korea

**Song-Yi Choi**, Department of Pathology, Chungnam National University College of Medicine, Daejeon 35015, South Korea

**Tae-Young Heo, Kyeong-Rok Kim**, Information and Statistics, Chungbuk National University, Cheongju 28644, South Korea

**Jisun Lee**, Department of Radiology, College of Medicine, Chungbuk National University, Chungbuk National University Hospital, Cheongju-si 28644, South Korea

**Min Young Yoo**, Department of Nuclear Medicine, School of Medicine, Inha University, Incheon 22332, South Korea

**Taek-Gu Lee**, Department of Surgery, Chungbuk National University, College of Medicine, Cheongju-si 28644, South Korea

**Joung-Ho Han**, Department of Internal Medicine, Chungbuk National University, College of Medicine, Cheongju-si 28644, South Korea

**Corresponding author:** Joung-Ho Han, MD, PhD, Professor, Department of Internal Medicine, Chungbuk National University, College of Medicine, No. 1 Chungdae-ro, Seowon-gu, Cheongju-si 28644, South Korea. [joungcho@chungbuk.ac.kr](mailto:joungcho@chungbuk.ac.kr)

## Abstract

### BACKGROUND

There are limited data on the use of glucose transport protein 1 (GLUT-1) expression as a biomarker for predicting lymph node metastasis in patients with colorectal cancer. GLUT-1 and GLUT-3, hexokinase (HK)-II, and hypoxia-induced factor (HIF)-1 expressions may be useful biomarkers for detecting primary tumors and lymph node metastasis when combined with fluorodeoxyglucose (FDG) uptake on positron emission tomography/computed tomography (PET/CT).

### AIM

To evaluate GLUT-1, GLUT-3, HK-II, and HIF-1 expressions as biomarkers for detecting primary tumors and lymph node metastasis with 18F-FDG-PET/CT.

## METHODS

This retrospective study included 169 patients with colorectal cancer who underwent colectomy and preoperative 18F-FDG-PET/CT at Chungbuk National University Hospital between January 2009 and May 2012. Two tissue cores from the central and peripheral areas of the tumors were obtained and were examined by a dedicated pathologist, and the expressions of GLUT-1, GLUT-3, HK-II, and HIF-1 were determined using immunohistochemical staining. We analyzed the correlations among their expressions, various clinicopathological factors, and the maximum standardized uptake value (SUVmax) of PET/CT.

## RESULTS

GLUT-1 was found at the center or periphery of the tumors in 109 (64.5%) of the 169 patients. GLUT-1 positivity was significantly correlated with the SUVmax of the primary tumor and lymph nodes, regardless of the biopsy site (tumor center,  $P < 0.001$  and  $P = 0.012$ ; tumor periphery,  $P = 0.030$  and  $P = 0.010$ , respectively). GLUT-1 positivity and negativity were associated with higher and lower sensitivities of PET/CT, respectively, for the detection of lymph node metastasis, regardless of the biopsy site. GLUT3, HK-II, and HIF-1 expressions were not significantly correlated with the SUVmax of the primary tumor and lymph nodes.

## CONCLUSION

GLUT-1 expression was significantly correlated with the SUVmax of 18F-FDG-PET/CT for primary tumors and lymph nodes. Clinicians should consider GLUT-1 expression in preoperative endoscopic biopsy in interpreting PET/CT findings.

**Key Words:** 18F-FDG-PET-CT; Biomarker; Colorectal neoplasms; Glucose transporter type 1; Lymph node

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**Core Tip:** Glucose transport protein 1 (GLUT-1) expression is a significant predictor of lymph node metastasis in patients with colorectal cancer. Positron emission tomography/computed tomography showed a higher sensitivity for detecting lymph node metastasis for GLUT-1-positive tumors, suggesting that GLUT-1 expression can be used to improve the accuracy of preoperative staging and guide treatment planning in patients with colorectal cancer.

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## INTRODUCTION

Colorectal cancer is the third most common malignant tumor globally, with a high incidence in developed countries[1]. Preoperative staging is important for predicting prognosis and determining appropriate treatment modalities. Although various imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT are used, the diagnostic accuracy for lymph node metastasis varies from 54% to 80% [2, 3]. Several studies have suggested the importance of PET/CT in patients with colorectal cancer; however, the extent of its contribution has not been well-established [4, 5]. Its sensitivity for diagnosing the primary site is as high as 95%-100%, while its sensitivity for diagnosing lymph node metastasis remains low (29%-37%), although a high specificity of 83%-96% has been reported [6-9].

18F-fluorodeoxyglucose (18F-FDG)-PET/CT is widely used to detect primary tumors and metastasis, monitor recurrence, and evaluate therapeutic response [10]. It is based on the enhanced glucose metabolism of malignant tumors. Malignant tumors increase glucose utilization *via* increasing the expression of glucose transporter (GLUT) and upregulating intracellular enzymes such as hexokinase (HK) that promote glycolysis and result in the accumulation of FDG [11, 12]. Further, malignant tumors grow abnormally and become hypoxic, which induces the expression of hypoxia induced factor-1 (HIF-1). HIF-1 is a transcription factor that promotes the expression of several genes involved in glucose utilization, including glucose transporters and glycolytic enzymes such as GLUT and HK-II [13]. Some studies have evaluated the relationship between the expression of several proteins, including GLUT, HK-II, and HIF-1, and FDG uptake on PET/CT to increase the accuracy of PET/CT in detecting various malignancies [14-16]. However, the correlation between protein expression and FDG uptake in various malignancies remains controversial [11]. While FDG uptake in colorectal cancer has been reported, its correlation with protein expression has not been established [17, 18].

Previous studies have shown that low GLUT expression at the tumor center (tissue obtained by surgery) is correlated with a false-negative diagnosis based on PET/CT [19, 20]. Therefore, further studies investigating whether PET/CT findings in combination with GLUT expression in preoperative endoscopic biopsy of colorectal cancer can help provide a more accurate assessment of lymph node staging are in demand. Studies assessing GLUT expressions in relation to

biopsy sites (tumor center with the tissue being obtained by surgery *vs* tumor periphery with the sample being obtained by endoscopy) are also needed.

In this study, we used immunohistochemistry (IHC) to determine the correlation between GLUT-1, GLUT-3, HK-II, and HIF-1 expressions in the central and peripheral areas of a primary tumor and investigated their values as biomarkers for detecting primary colorectal cancer and lymph node metastasis in combination with FDG uptake on PET/CT.

## MATERIALS AND METHODS

### Patients

We retrospectively analyzed 240 patients with colorectal cancer who had undergone colectomy and were diagnosed with adenocarcinoma at Chungbuk National University Hospital between January 2009 and May 2012. The histologic findings were interpreted based on the World Health Organization classification. The colon cancer stage evaluation was based on the American Joint Committee on Cancer 7<sup>th</sup> Edition Cancer Staging Manual. A total of 71 patients were excluded from this study: 66 patients were not examined with 18F-FDG-PET/CT, and 5 patients were not followed up. None of the patients had received neoadjuvant chemotherapy or radiotherapy.

Two tissue cores from the central and peripheral areas of the tumor were obtained from the 169 included patients for pathological examination, and GLUT-1 expression was evaluated using IHC staining. The samples were examined by a dedicated pathologist (SYC). All clinical, laboratory, and radiological data were collected from the electronic medical records. The Institutional Review Board (IRB No. 2013-03-003) of Chungbuk National University Hospital approved this study, and the requirement for informed consent was waived due to the retrospective nature of the study.

### Immunohistochemical staining

All cases were reviewed, and 3 mm-sized tissue microarrays (TMA) were reconstructed. Two cores (tumor center and periphery) were obtained for each case. The core obtained from the center of the tumor close to the mucosa was indicated as "tumor center," and the core obtained from the deep invasive front was designated as "periphery." Sections of 4- $\mu$ m thickness were cut and placed on SuperfrostPlus microscope slides (Fisher Scientific). IHC staining was performed using the BenchMark XT automated immunohistochemistry stainer (Ventana Medical Systems, Inc., United States) and signal was detected using a Ventana Ultraview DAB Kit (Ventana Medical Systems). Briefly, sections were deparaffinized using the EZ Prep solution. Antigen retrieval was performed using the CC1 standard automated process (pH 8.4 buffer contained Tris/Borate/EDTA). A DAB inhibitor (3% H<sub>2</sub>O<sub>2</sub> endogenous peroxidase) was blocked for 4 min at 37 °C temperature. The slides were incubated with primary antibodies specific to GLUT-1 (1:100, Thermo Fisher Scientific, USA), GLUT-3 (1:50, Thermo Fisher Scientific, USA), HK-II (1:100, Cell Signaling Technology, United States), and HIF-1 (1:50, Thermo Fisher Scientific) for 30 min at 37 °C followed by incubation with a secondary antibody (Universal HRP Multimer) for 8 min at 37 °C. The slides were incubated with DAB (chromogen) + H<sub>2</sub>O<sub>2</sub> (substrate) for 8 min, followed by counterstaining using hematoxylin and DAPI at 37 °C. Tris buffer (pH 7.6) was used as the washing solution.

GLUT-1, GLUT-3, HK-II, and HIF-1 expressions were considered positive when > 5% of tumor cells demonstrated cytoplasmic or membranous staining. The immunoreactive score was rated as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong) based on the average staining intensity. A score of 2 or higher indicated positivity. HIF-1 expression was considered positive when > 5% of tumor cells demonstrated nuclear staining (Figures 1 and 2).

### Statistics

Descriptive statistics were used to summarize the patient and tumor characteristics, and the data are reported as proportions and medians for continuous variables. The categorical data are presented as numbers (%). The continuous variables were compared using the Student's *t*-test, and the categorical variables were compared using the chi-squared or Fisher's exact test. Statistical significance was set at  $P < 0.05$ . Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY, United States).

## RESULTS

### Relationship between GLUT-1 expression and clinicopathologic parameters

Table 1 presents the relationship between GLUT-1 expression and clinicopathological parameters. Among the 169 patients, 86 (50.9%) and 91 (53.8%) patients showed GLUT-1 positivity in the tumor center and periphery, respectively. GLUT-1 positivity was significantly correlated with the SUVmax of the primary tumor and lymph nodes, regardless of the biopsy site (tumor center,  $P < 0.001$  and  $P = 0.012$ ; tumor periphery  $P = 0.030$  and  $P = 0.010$ , respectively).

### Lymph node metastasis prediction based on PET/CT findings combined with GLUT-1 expression

We analyzed the predictive values of PET/CT, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for lymph node metastasis (Table 2).

Among the 169 patients, 53 were classified as positive for lymph node metastasis on PET/CT, and 35 were histologically confirmed positive, with a sensitivity of 50.0% and a PPV of 66.0%. A total of 116 patients were classified as negative for lymph node metastasis on PET/CT, and 81 patients were histologically confirmed as negative with a specificity of 81.8% and an NPV of 69.8%.

**Table 1 Correlation between glucose transport protein 1 expression and clinicopathological parameters**

|                                     | GLUT-1 (center) |              | P value | GLUT-1 (periphery) |              | P value |
|-------------------------------------|-----------------|--------------|---------|--------------------|--------------|---------|
|                                     | (-) (n = 83)    | (+) (n = 86) |         | (-) (n = 78)       | (+) (n = 91) |         |
| Age (yr ± SD)                       | 64.0 ± 11.4     | 64.7 ± 12.6  | 0.740   | 64.0 ± 11.6        | 64.7 ± 12.4  | 0.718   |
| Sex                                 |                 |              |         |                    |              |         |
| Male                                | 52              | 54           | 0.985   | 51                 | 55           | 0.507   |
| Female                              | 31              | 32           |         | 27                 | 36           |         |
| Tumor size (mean ± SD)              | 4.9 ± 1.8       | 5.2 ± 2.0    | 0.277   | 5.1 ± 1.7          | 5.1 ± 2.1    | 0.932   |
| T stage                             |                 |              |         |                    |              |         |
| T1, 2                               | 16              | 7            | 0.035   | 11                 | 12           | 0.836   |
| T3, 4                               | 67              | 79           |         | 67                 | 79           |         |
| N stage                             |                 |              |         |                    |              |         |
| N0                                  | 51              | 48           | 0.457   | 48                 | 51           | 0.47    |
| N1-2                                | 32              | 38           |         | 30                 | 40           |         |
| AJCC stage                          |                 |              |         |                    |              |         |
| I, II                               | 49              | 48           | 0.672   | 47                 | 50           | 0.486   |
| III, IV                             | 34              | 38           |         | 31                 | 41           |         |
| Lymphatic invasion                  |                 |              |         |                    |              |         |
| Negative                            | 70              | 72           | 0.913   | 64                 | 78           | 0.517   |
| Positive                            | 13              | 14           |         | 14                 | 13           |         |
| Perineural invasion                 |                 |              |         |                    |              |         |
| Negative                            | 66              | 73           | 0.361   | 68                 | 71           | 0.12    |
| Positive                            | 17              | 13           |         | 10                 | 20           |         |
| Blood glucose level (mean ± SD)     | 110.5 ± 36.2    | 111.6 ± 25.8 | 0.818   | 112.4 ± 38.8       | 109.9 ± 23.2 | 0.612   |
| SUVmax of primary tumor (mean ± SD) | 12.3 ± 5.9      | 16.1 ± 7.4   | <0.001  | 13.0 ± 6.4         | 15.3 ± 7.3   | 0.030   |
| SUVmax of lymph node (mean ± SD)    | 1.04 ± 2.6      | 2.15 ± 3.1   | 0.012   | 0.99 ± 2.6         | 2.13 ± 3.0   | 0.010   |

GLUT-1: Glucose transport protein 1; SD: Standard deviation; AJCC: American Joint Committee on Cancer; SUV: Standardized uptake value.

We investigated whether GLUT-1 expression in peripheral and central sites of the primary tumor could facilitate a more accurate assessment of lymph node staging based on FDG uptake on PET/CT (Table 2). Patients with GLUT-1 positivity demonstrated higher sensitivity of lymph node metastasis prediction by PET/CT than all patients considered together (overall patients, 50.0%; tumor center, 60.5%; tumor periphery, 65.0%). In contrast, patients with GLUT-1 negativity demonstrated overall lower sensitivity for the prediction of lymph node metastasis by PET/CT than all patients considered together (overall patients, 50.0%; tumor center, 37.5%; tumor periphery, 29.0%).

### **Relationship between GLUT-3, HK-II, and HIF-1 expressions and clinicopathologic parameters**

We investigated the expressions of other proteins associated with glucose metabolism that could be associated with false-negative prediction of lymph node metastasis by PET/CT. Due to the staining of TMA slides, a few tissue cores were lost; therefore, different cases were analyzed using each antibody. The GLUT3, HK-II, and HIF-1 expressions did not significantly correlate with the SUVmax of the primary tumor and lymph nodes, other than for GLUT-3 in the tumor periphery ( $P = 0.013$ ) (Tables 3-5).

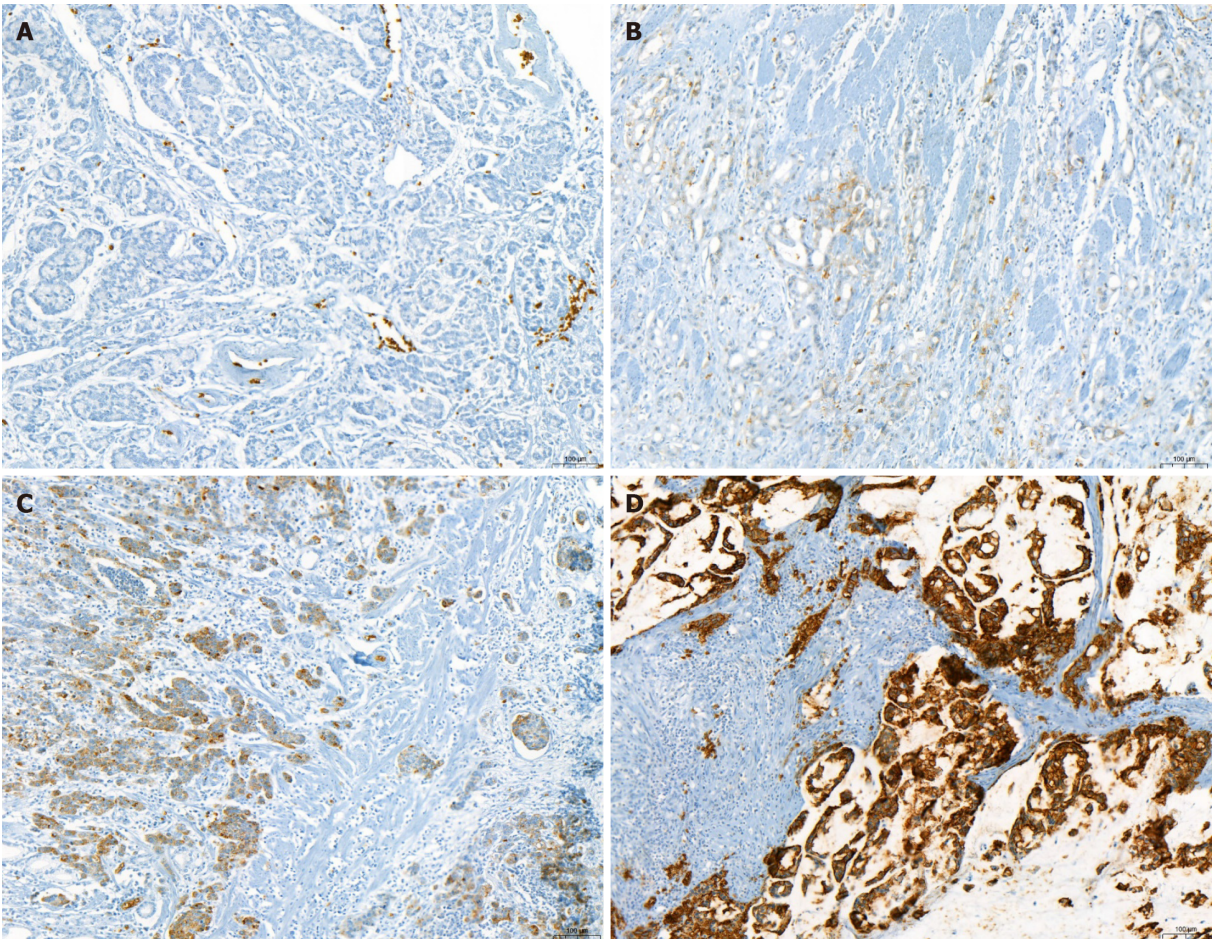
## **DISCUSSION**

In this study, we analyzed the role of GLUT-1 expression as a biomarker for lymph node metastasis detected by FDG uptake on PET/CT and assessed whether GLUT-1 expression differed in the peripheral and central areas of the tumor. We discovered that 109/169 patients (64.5%) exhibited GLUT-1 positivity in the center or periphery of the primary tumor. The expression of GLUT-1 was significantly correlated with the SUVmax of the primary tumor and lymph node,

Table 2 Predictive value of fluorodeoxyglucose-positron emission tomography/computed tomography based on glucose transport protein 1 expression

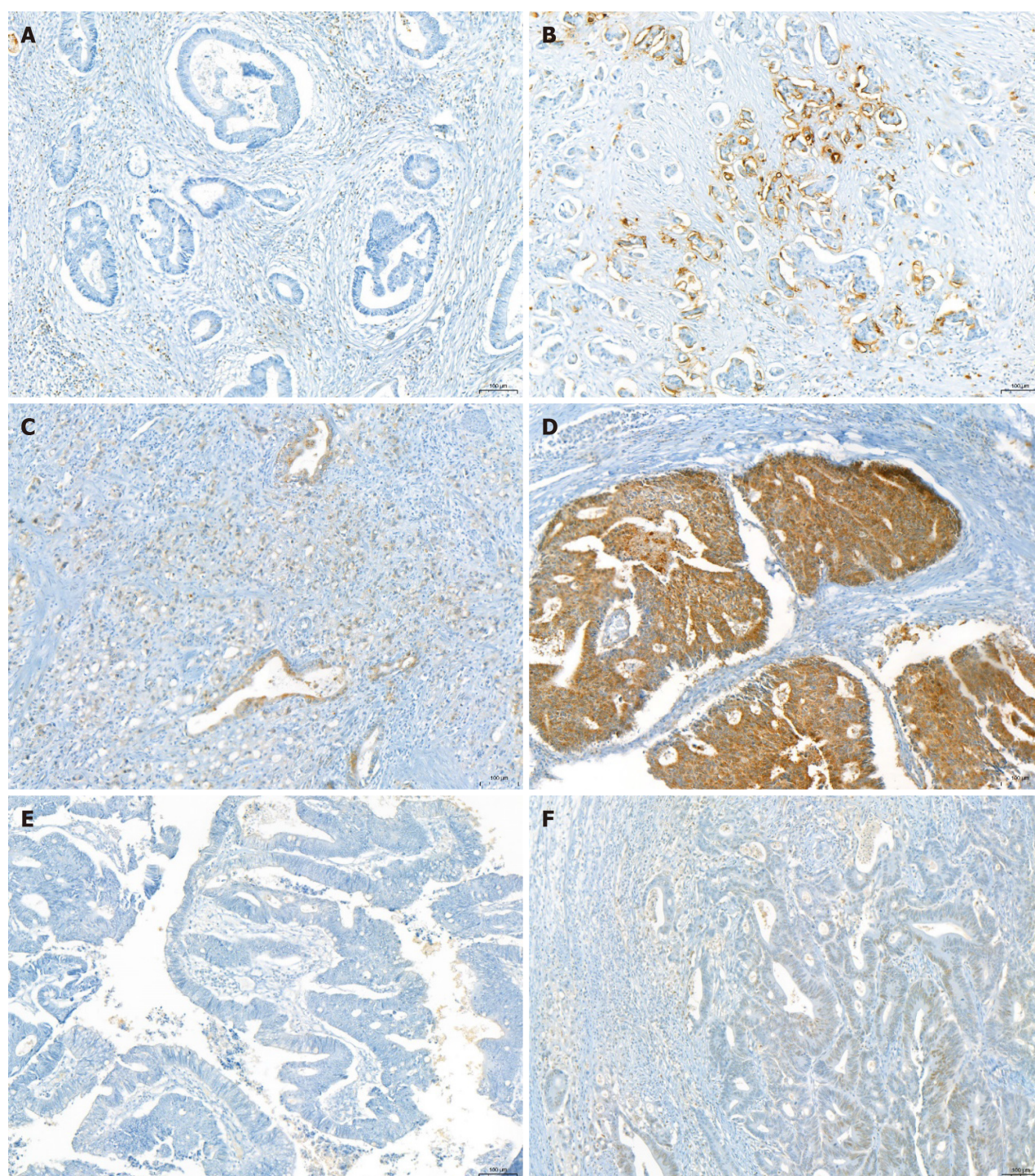
| Pathology              |                          | PET/CT diagnosis |            | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|------------------------|--------------------------|------------------|------------|-----------------|-----------------|---------|---------|
|                        |                          | PET LN (+)       | PET LN (-) |                 |                 |         |         |
| All patients (n = 169) |                          | LN (+)           | 35         | 35              | 50              | 81.8    | 66.03   |
|                        |                          | LN (-)           | 18         | 81              |                 |         | 69.82   |
| Tumor center           | GLUT-1 negative (n = 83) | LN (+)           | 12         | 20              | 37.5            | 88.2    | 66.6    |
|                        |                          | LN (-)           | 6          | 45              |                 |         | 69.2    |
|                        | GLUT-1 positive (n = 86) | LN (+)           | 23         | 15              | 60.5            | 75      | 65.7    |
|                        |                          | LN (-)           | 12         | 36              |                 |         | 70.6    |
| Tumor periphery        | GLUT-1 negative (n = 78) | LN (+)           | 9          | 21              | 29              | 87.5    | 60      |
|                        |                          | LN (-)           | 6          | 42              |                 |         | 66.6    |
|                        | GLUT-1 positive (n = 91) | LN (+)           | 26         | 14              | 65              | 76.5    | 68.4    |
|                        |                          | LN (-)           | 12         | 39              |                 |         | 73.6    |

GLUT-1: Glucose transport protein 1; FDG: Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; LN: Lymph node; PPV: Positive predictive value; NPV: Negative predictive value



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Figure 1 Immunohistochemical staining for glucose transport protein 1 in colorectal cancer. Glucose transport protein 1 expression was demonstrated as cytoplasmic or membranous staining. A-D: The score was assessed according to the intensity [0 = negative (A), 1 = weak (B), 2 = moderate (C), 3 = strong (D); × 100]. A score of 2 or higher was considered as positive.



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**Figure 2** Immunohistochemical staining for glucose transport protein 3, hexokinase-II, and hypoxia-inducible factor-1 in colorectal cancer. Glucose transport protein 3 (GLUT-3) and hexokinase-II expressions were demonstrated as cytoplasmic or membranous staining. A: GLUT-3 negative; B: GLUT-3 positive; C: Hexokinase-II negative; D: Hexokinase-II positive; E and F: Hypoxia-inducible factor-1 (HIF-1) expression was demonstrated as nuclear staining (E: HIF-1 negative, F: HIF-1 positive).

regardless of the biopsy site. In addition, patients with GLUT-1 positivity demonstrated overall higher sensitivity for the prediction of lymph node metastasis by PET/CT. These findings suggest that GLUT-1 expression is a useful biomarker for predicting lymph node metastasis when combined with PET/CT. In this study, the tumor periphery was regarded as the edge of the tumor close to the mucosa; this is the part of the tumor that can be reached during preoperative endoscopic biopsy, which suggests that the measurement of GLUT-1 expression in endoscopic tumor biopsy specimens can predict lymph node metastasis. Therefore, we recommend that clinicians evaluate GLUT-1 expression in preoperative endoscopic biopsy specimens and consider interpreting PET/CT results according to GLUT-1 expression. Since lymph node metastasis is underestimated in patients with colorectal cancer with GLUT-1 negativity, clinicians should be cautious when interpreting PET/CT results in preoperative patients, because of the possibility of false negative findings.

**Table 3** The correlation between glucose transport protein 3 expression and clinicopathologic parameters

|                                          | GLUT-3 (center)  |                  | P value | GLUT-3 (periphery) |                  | P value |
|------------------------------------------|------------------|------------------|---------|--------------------|------------------|---------|
|                                          | (-) (n = 153)    | (+) (n = 12)     |         | (-) (n = 78)       | (+) (n = 91)     |         |
| Age (yr), mean $\pm$ SD                  | 64.5 $\pm$ 11.8  | 63.0 $\pm$ 14.6  | 0.729   | 64.1 $\pm$ 11.9    | 67.8 $\pm$ 13.0  | 0.194   |
| Sex                                      |                  |                  |         |                    |                  |         |
| Male                                     | 98               | 5                | 0.135   | 93                 | 7                | 0.013   |
| Female                                   | 55               | 7                |         | 49                 | 13               |         |
| Tumor size (mean $\pm$ SD)               | 5.07 $\pm$ 2.0   | 5.02 $\pm$ 2.0   | 0.931   | 5.05 $\pm$ 2.0     | 5.20 $\pm$ 1.6   | 0.743   |
| T stage                                  |                  |                  |         |                    |                  |         |
| T1, 2                                    | 20               | 2                | 0.663   | 20                 | 1                | 0.475   |
| T3, 4                                    | 133              | 10               |         | 122                | 19               |         |
| N stage                                  |                  |                  |         |                    |                  |         |
| N0                                       | 93               | 4                | 0.074   | 89                 | 6                | 0.007   |
| N1-2                                     | 60               | 8                |         | 53                 | 14               |         |
| AJCC stage                               |                  |                  |         |                    |                  |         |
| I, II                                    | 91               | 4                | 0.127   | 87                 | 6                | 0.014   |
| III, IV                                  | 62               | 8                |         | 53                 | 14               |         |
| Lymphatic invasion                       |                  |                  |         |                    |                  |         |
| Negative                                 | 128              | 11               | 0.693   | 120                | 17               | 1.000   |
| Positive                                 | 25               | 1                |         | 22                 | 33               |         |
| Perineural invasion                      |                  |                  |         |                    |                  |         |
| Negative                                 | 127              | 8                | 0.234   | 117                | 17               | 1.000   |
| Positive                                 | 26               | 4                |         | 25                 | 3                |         |
| Blood sugar level (mean $\pm$ SD)        | 111.3 $\pm$ 32.0 | 109.2 $\pm$ 26.9 | 0.803   | 112.7 $\pm$ 33.0   | 101.8 $\pm$ 20.3 | 0.150   |
| SUV max of primary tumor (mean $\pm$ SD) | 14.1 $\pm$ 7.5   | 13.5 $\pm$ 4.7   | 0.678   | 14.3 $\pm$ 7.6     | 12.9 $\pm$ 4.8   | 0.433   |
| SUV max of lymph node (mean $\pm$ SD)    | 1.6 $\pm$ 2.8    | 2.8 $\pm$ 4.0    | 0.328   | 1.4 $\pm$ 2.7      | 3.8 $\pm$ 4.0    | 0.013   |

GLUT-3: Glucose transport protein 3; SD: Standard deviation; AJCC: American Joint Committee on Cancer; SUV: Standardized uptake value.

Previous studies have reported a correlation between GLUT-1 expression and SUVmax in various carcinomas; however, discordant findings were reported[21-23]. Meyer *et al*[11] conducted a meta-analysis and reported that GLUT-1 and SUVmax were highly correlated in patients with pancreatic cancer and cervical cancer but not in those with colorectal cancer and endometrial cancer. However, Zhang *et al*[23] and Gu *et al*[24] reported a significant correlation between GLUT-1 expression and SUVmax in patients with colorectal cancer, which is consistent with our results. However, both studies included a small number of patients ( $n < 40$ ), and the correlation between GLUT-1 expression and the SUVmax of the primary tumor remains unclear. In addition, few studies have reported an association between GLUT-1 expression and the prediction of lymph node metastasis by PET/CT in patients with non-small cell lung cancer. Taira *et al*[22] demonstrated that the predictive accuracy of lymph node metastasis by PET/CT differed from that obtained when GLUT-1 expression in patient samples was incorporated in the assessment, which is consistent with our results. However, to date, the exact reasons underlying these controversial results remains unclear. Probably, the complex glucose metabolism of malignant tumors differ between tumor types and might affect the association between GLUT-1 expression and SUVmax. In addition, GLUT-1 expression is not only specific for tumor cells, as GLUT-1 is also expressed on erythrocytes and immune cells. Moreover, a low burden of tumors and some good differentiated tumor types might reduce GLUT-1 expression, which could be the reason for false-negativity on PET/CT[25].

We analyzed the expression of other proteins (including GLUT3, HK-II, and HIF-1) associated with glucose metabolism, which could influence false-negative identification of lymph node metastasis on PET/CT. Our results revealed that GLUT-3, HK-II, and HIF-1 expressions did not significantly correlate with the SUVmax of the primary tumor and lymph nodes. This suggests that the expressions of these proteins are less useful than that of GLUT-1 when determining lymph node staging before surgery. However, further studies are needed to evaluate more biomarkers to increase the effectiveness of PET/CT.

**Table 4** The correlation between hexokinase-II expression and clinicopathologic parameters

|                                     | Hexokinase-II (center) |              | P value | Hexokinase-II (periphery) |              | P value |
|-------------------------------------|------------------------|--------------|---------|---------------------------|--------------|---------|
|                                     | (-) (n = 94)           | (+) (n = 70) |         | (-) (n = 114)             | (+) (n = 48) |         |
| Age (yr ± SD)                       | 65.1 ± 12.3            | 63.5 ± 11.6  | 0.403   | 64.3 ± 12.3               | 64.8 ± 11.5  | 0.806   |
| Sex                                 |                        |              |         |                           |              |         |
| Male                                | 61                     | 41           | 0.409   | 73                        | 27           | 0.352   |
| Female                              | 33                     | 29           |         | 41                        | 21           |         |
| Tumor size (mean ± SD)              | 5.1 ± 1.8              | 5.1 ± 2.2    | 0.976   | 5.1 ± 2.0                 | 5.1 ± 1.9    | 0.977   |
| T stage                             |                        |              |         |                           |              |         |
| T1, 2                               | 15                     | 7            | 0.268   | 16                        | 5            | 0.531   |
| T3, 4                               | 79                     | 63           |         | 98                        | 43           |         |
| N stage                             |                        |              |         |                           |              |         |
| N0                                  | 54                     | 42           | 0.743   | 68                        | 28           | 0.876   |
| N1-2                                | 40                     | 28           |         | 46                        | 20           |         |
| AJCC stage                          |                        |              |         |                           |              |         |
| I, II                               | 53                     | 41           | 0.779   | 67                        | 27           | 0.766   |
| III, IV                             | 41                     | 29           |         | 47                        | 21           |         |
| Lymphatic invasion                  |                        |              |         |                           |              |         |
| Negative                            | 77                     | 61           | 0.365   | 97                        | 40           | 0.778   |
| Positive                            | 17                     | 9            |         | 17                        | 8            |         |
| Perineural invasion                 |                        |              |         |                           |              |         |
| Negative                            | 75                     | 60           | 0.325   | 95                        | 38           | 0.528   |
| Positive                            | 19                     | 10           |         | 19                        | 10           |         |
| Blood glucose level (mean ± SD)     | 105.2 ± 22.8           | 116.8 ± 35.1 | 0.017   | 110.2 ± 32.0              | 113.9 ± 31.3 | 0.493   |
| SUVmax of primary tumor (mean ± SD) | 14.0 ± 7.1             | 14.2 ± 7.7   | 0.874   | 14.3 ± 7.2                | 13.9 ± 7.7   | 0.786   |
| SUVmax of lymph node (mean ± SD)    | 1.6 ± 2.8              | 1.8 ± 3.2    | 0.712   | 1.5 ± 2.6                 | 2.0 ± 3.7    | 0.450   |

SD: Standard deviation; AJCC: American Joint Committee on Cancer; SUV: Standardized uptake value.

To the best of our knowledge, this is the first study to evaluate the relationship between GLUT-1 expression and the SUVmax of primary tumors and lymph node metastasis in patients with colorectal cancer, as well as its role in detecting lymph node metastasis using 18F-FDG-PET/CT according to biopsy sites. We discovered that GLUT-1 expression was significantly correlated with the SUVmax of primary tumors and facilitated the prediction of lymph node metastasis using 18F-FDG-PET/CT. Moreover, GLUT-1 expression did not differ based on whether it was measured in either central or peripheral primary tumor biopsy sites in patients with colorectal cancer.

Our study has several limitations. First, it was retrospective, and our results should be confirmed in a prospective study. Second, only Asian patients with colorectal cancer were analyzed in this study, limiting the generalizability of our results as molecular profiles and clinical features of Western and Eastern populations differ significantly. Third, IHC cannot differentiate membranous from cytoplasmic GLUT-1 expressions. Cytoplasmic GLUT-1 is known to be inactive. Thus, to determine the clinical effects of GLUT-1, it is necessary to measure the expression of membranous GLUT-1. However, this distinction is presently challenging and limits the application of our findings[21].

## CONCLUSION

GLUT-3, HK-II, and HIF-1 expressions were not significantly correlated with the SUVmax of the primary tumor and lymph nodes. GLUT-1 expression, on the other hand, demonstrated a significant correlation and may be a useful biomarker to be used in conjunction with PET/CT to diagnose colorectal cancers. Clinicians should consider GLUT-1 expression during preoperative endoscopic biopsy in interpreting PET/CT findings for the diagnosis of colorectal cancers and lymph node metastases.

**Table 5** The correlation between hypoxia-induced factor-1 expression and clinicopathologic parameters

|                                         | HIF-1 (center)    |                   | P value | HIF-1 (periphery) |                   | P value |
|-----------------------------------------|-------------------|-------------------|---------|-------------------|-------------------|---------|
|                                         | (-) (n = 94)      | (+) (n = 72)      |         | (-) (n = 89)      | (+) (n = 75)      |         |
| Age (yr), mean $\pm$ SD                 | 64.0 $\pm$ 12.4   | 65.1 $\pm$ 11.5   | 0.576   | 63.5 $\pm$ 12.6   | 65.6 $\pm$ 11.3   | 0.246   |
| Sex                                     |                   |                   |         |                   |                   |         |
| Male                                    | 59                | 45                | 0.972   | 58                | 45                | 0.495   |
| Female                                  | 35                | 27                |         | 31                | 30                |         |
| Tumor size (mean $\pm$ SD)              | 4.7 $\pm$ 1.7     | 5.5 $\pm$ 2.2     | 0.014   | 4.8 $\pm$ 1.7     | 5.3 $\pm$ 2.2     | 0.082   |
| T stage                                 |                   |                   |         |                   |                   |         |
| T1, 2                                   | 17                | 6                 | 0.071   | 16                | 7                 | 0.112   |
| T3, 4                                   | 77                | 66                |         | 73                | 68                |         |
| N stage                                 |                   |                   |         |                   |                   |         |
| N0                                      | 59                | 38                | 0.196   | 57                | 40                | 0.164   |
| N1-2                                    | 35                | 34                |         | 32                | 35                |         |
| AJCC stage                              |                   |                   |         |                   |                   |         |
| I, II                                   | 57                | 38                | 0.310   | 55                | 40                | 0.274   |
| III, IV                                 | 37                | 34                |         | 34                | 35                |         |
| Lymphatic invasion                      |                   |                   |         |                   |                   |         |
| Negative                                | 80                | 60                | 0.755   | 76                | 62                | 0.634   |
| Positive                                | 14                | 12                |         | 13                | 13                |         |
| Perineural invasion                     |                   |                   |         |                   |                   |         |
| Negative                                | 77                | 59                | 0.996   | 73                | 61                | 0.909   |
| Positive                                | 17                | 13                |         | 16                | 14                |         |
| Blood glucose level (mean $\pm$ SD)     | 109.91 $\pm$ 30.8 | 112.29 $\pm$ 32.6 | 0.632   | 108.97 $\pm$ 32.2 | 113.69 $\pm$ 31.1 | 0.342   |
| SUVmax of primary tumor (mean $\pm$ SD) | 14.0 $\pm$ 7.1    | 14.0 $\pm$ 7.6    | 0.979   | 14.2 $\pm$ 7.0    | 13.8 $\pm$ 7.9    | 0.754   |
| SUVmax of lymph node (mean $\pm$ SD)    | 1.4 $\pm$ 2.9     | 2.0 $\pm$ 2.9     | 0.229   | 1.6 $\pm$ 2.9     | 1.8 $\pm$ 2.9     | 0.713   |

HIF-1: Hypoxia-inducible factor-1; SD: Standard deviation; AJCC: American Joint Committee on Cancer; SUV: Standardized uptake value.

## ARTICLE HIGHLIGHTS

### Research perspectives

Further studies are needed to evaluate clinical benefit of glucose transport protein 1 (GLUT-1) expression as biomarkers for detecting primary tumors and lymph node metastasis *via* fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT).

### Research conclusions

GLUT-1 expression was significantly correlated with the maximum standardized uptake value (SUVmax) of 18F-FDG-PET/CT for primary tumors and lymph nodes. Clinicians should consider GLUT-1 expression in preoperative endoscopic biopsy when interpreting PET/CT findings.

### Research results

GLUT-1 positivity was significantly correlated with the SUVmax of the primary tumor and lymph nodes, regardless of biopsy site (tumor center,  $P < 0.001$  and  $P = 0.012$ ; tumor periphery,  $P = 0.030$  and  $P = 0.010$ , respectively). GLUT-1 positivity and negativity were associated with higher and lower sensitivities of PET/CT, respectively, for the detection of lymph node metastasis, regardless of biopsy site. GLUT3, HK-II, and HIF-1 expressions were not significantly associated with the SUVmax of the primary tumor and lymph nodes.

### Research methods

Two tissue cores from the central and peripheral areas of the tumors were examined and the expressions of GLUT-1,

GLUT-3, HK-II, and HIF-1 were determined *via* immunohistochemical staining. We analyzed the correlations among their expressions, various clinicopathological factors, and the SUVmax of PET/CT.

### Research objectives

The research objective was to investigate the role of GLUT-1 expression as a biomarker for lymph node metastasis detected by FDG uptake on PET/CT; in addition, we aimed to assess whether GLUT-1 expression differed in the peripheral and central areas of the tumor.

### Research motivation

The research motivation was to evaluate GLUT-1, GLUT-3, HK-II, and HIF-1 expressions as biomarkers for detecting primary tumors and lymph node metastasis with 18F-FDG-PET/CT.

### Research background

There are limited data on the use of GLUT-1 and GLUT-3, HK-II, and HIF-1 expressions as biomarkers for predicting lymph node metastasis when combined with FDG uptake on PET/CT in patients with colorectal cancer.

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## FOOTNOTES

**Co-first authors:** Hongsik Kim and Song-Yi Choi.

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**Country/Territory of origin:** South Korea

**ORCID number:** Hongsik Kim 0000-0002-9469-6699; Jisun Lee 0000-0002-6264-7171; Taek-Gu Lee 0000-0002-3765-5655; Joung-Ho Han 0000-0003-4469-9215.

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