

World Journal of *Clinical Cases*

World J Clin Cases 2024 February 16; 12(5): 872-1038



Contents

Thrice Monthly Volume 12 Number 5 February 16, 2024

EDITORIAL

- 872 Is it possible to anchor a tooth with photobiomodulation?
Dominguez A
- 875 Strengthening pharmacotherapy research for COVID-19-induced pulmonary fibrosis
Liu YM, Zhang J, Wu JJ, Guo WW, Tang FS

ORIGINAL ARTICLE

Clinical and Translational Research

- 880 Causal associations between gastroesophageal reflux disease and essential hypertension: A bidirectional Mendelian randomization study
Wei N, Liu MH, Song YH
- 891 Serum urate is associated with an increased risk of inflammatory bowel disease: A bidirectional Mendelian randomization study
Zhang S, Fang X, Kang L, Sui XY, Liu M, Luo YJ, Fu S, Li ZS, Zhao SB, Bai Y

Retrospective Cohort Study

- 903 Effect of health education based on information-motivation-behavioral skills model on patients with unilateral vestibular dysfunction
Shi Q, Wu RJ, Liu J

Retrospective Study

- 913 Removal of intrahepatic bile duct stone could reduce the risk of cholangiocarcinoma: A single-center retrospective study in South Korea
Kim TI, Han SY, Lee J, Kim DU
- 922 Effect of nursing on postoperative respiratory function and mental health of lung cancer patients
Yang X, Yin D, Chen SQ
- 931 Value of glucose transport protein 1 expression in detecting lymph node metastasis in patients with colorectal cancer
Kim H, Choi SY, Heo TY, Kim KR, Lee J, Yoo MY, Lee TG, Han JH

Observational Study

- 942 Clinical efficacy and mechanism study of mid-frequency anti-snoring device in treating moderate obstructive sleep apnea-hypopnea syndrome
Qian B, Chen ZJ, Wang YS, Hu XY, Hu XB, Zheng YH
- 951 Urinary metabolic profiles during *Helicobacter pylori* eradication in chronic gastritis
An WT, Hao YX, Li HX, Wu XK

- 966 Clinical significance of platelet mononuclear cell aggregates in patients with sepsis and acute respiratory distress syndrome

Huang CM, Li JJ, Wei WK

CASE REPORT

- 973 Left ventricular thrombosis caused cerebral embolism during venoarterial extracorporeal membrane oxygenation support: A case report

Bai YB, Zhao F, Wu ZH, Shi GN, Jiang N

- 980 Abnormal uterine bleeding successfully treated *via* ultrasound-guided microwave ablation of uterine myoma lesions: Three case reports

Kakinuma T, Kakinuma K, Okamoto R, Yanagida K, Ohwada M, Takeshima N

- 988 Omental fibroma combined with right indirect inguinal hernia masquerades as a scrotal tumor: A case report

Zhou P, Jin CH, Shi Y, Ma GQ, Wu WH, Wang Y, Cai K, Fan WF, Wang TB

- 995 Imaging, pathology, and diagnosis of solitary fibrous tumor of the pancreas: A case report and review of literature

Wang WW, Zhou SP, Wu X, Wang LL, Ruan Y, Lu J, Li HL, Ni XL, Qiu LL, Zhou XH

- 1004 Neuroimaging features in a patient with non-ketotic hyperglycaemic seizures: A case report

Wu J, Feng H, Zhao Y, Li J, Li T, Li K

- 1010 Novel approach of ultrasound-guided lateral recess block for a patient with lateral recess stenosis: A case report

Yang J, Li XL, Li QB

- 1018 Ankylosing spondylitis coexisting with *Clonorchis sinensis* infection: A case report

Yi TX, Liu W, Leng WF, Wang XC, Luo L

- 1025 Hematuria after nocturnal exercise of a man: A case report

Bai MJ, Yang ST, Liu XK

LETTER TO THE EDITOR

- 1029 Response letter to "Acute cholangitis: Does malignant biliary obstruction *vs* choledocholithiasis etiology change the outcomes?" with imaging aspects

Aydin S, Irgul B

- 1033 Exploring multifaceted factors in chronic kidney disease risk: A comprehensive analysis of biochemistry, lifestyle, and inflammation in elderly Chinese individuals

Cardona F

- 1036 Transcranial direct current stimulation efficacy in trigeminal neuralgia

Fasilis T, Gatzonis S, Patrikelis P, Korfiatis S, Alexoudi A

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Abdulkarim Hasan, MD, MSc, Consultant Physician-Scientist, Doctor, Lecturer, Department of Pathology, Al-Azhar University, Faculty of Medicine, Cairo 11884, Egypt. doctorabdulkarim7@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJCC as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

February 16, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



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

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Shah SIA, Pakistan; Yan B, China

Received: November 9, 2023

Peer-review started: November 9, 2023

First decision: December 21, 2023

Revised: January 4, 2024

Accepted: January 22, 2024

Article in press: January 22, 2024

Published online: February 16, 2024



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

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

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Kim H, Choi SY, Heo TY, Kim KR, Lee J, Yoo MY, Lee TG, Han JH. Value of glucose transport protein 1 expression in detecting lymph node metastasis in patients with colorectal cancer. *World J Clin Cases* 2024; 12(5): 931-941

URL: <https://www.wjgnet.com/2307-8960/full/v12/i5/931.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v12.i5.931>

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 7th 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- μ 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% H₂O₂ 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) + H₂O₂ (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).

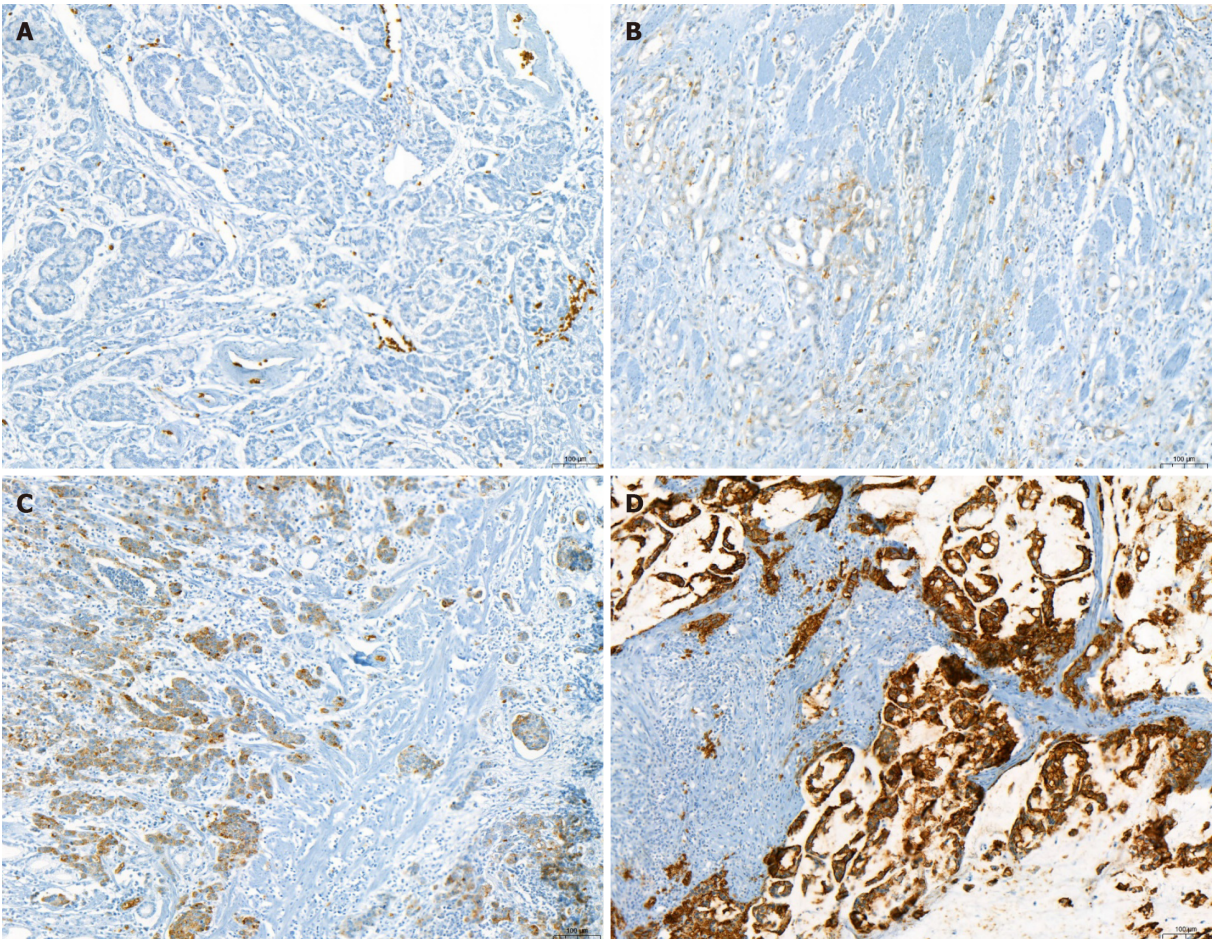
DISCUSSION

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

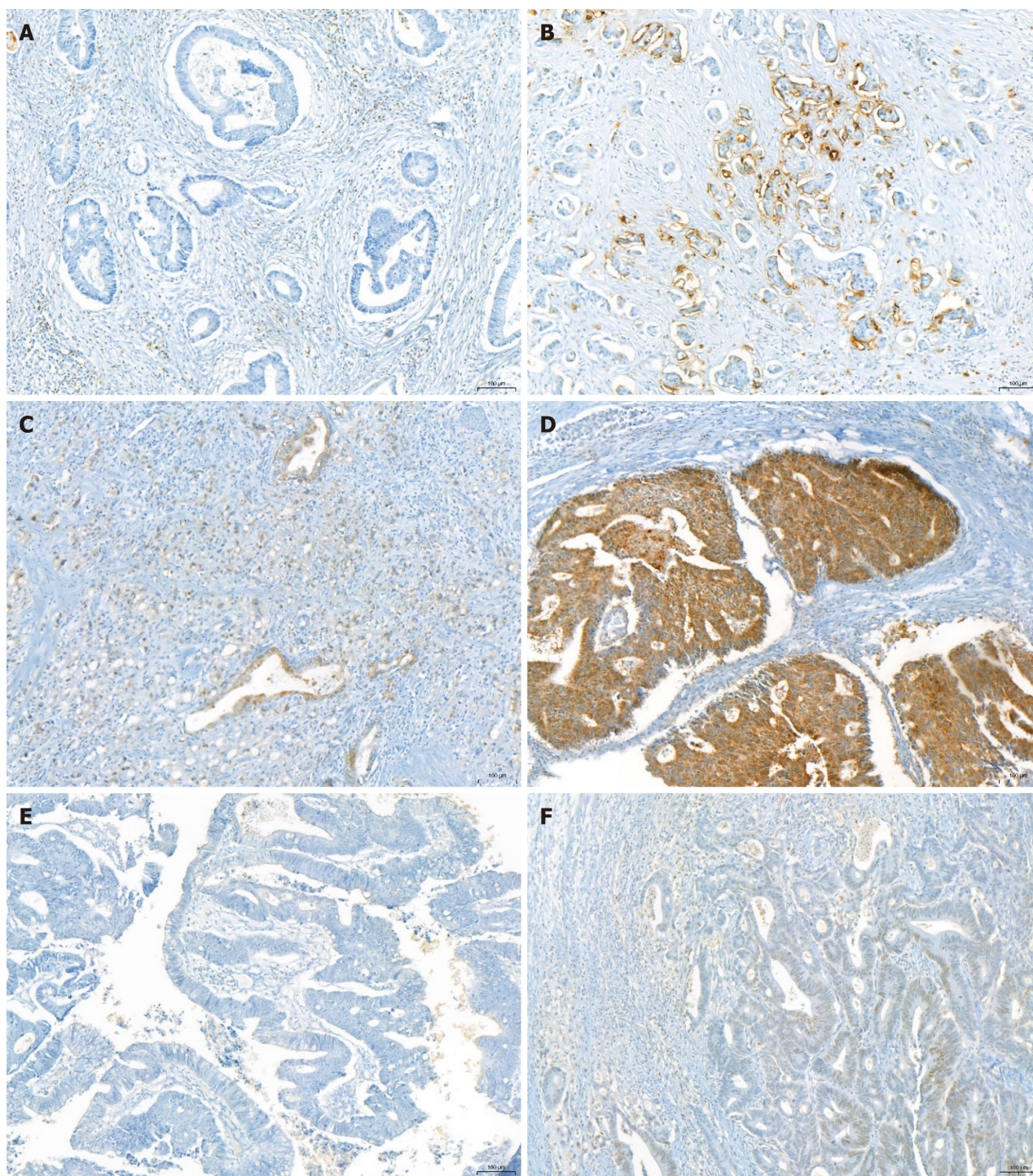
Pathology		PET/CT diagnosis		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		PET LN (+)	PET LN (-)				
All patients (n = 169)		LN (+)	35	35	50	81.8	66.03
		LN (-)	18	81			69.82
Tumor center	GLUT-1 negative (n = 83)	LN (+)	12	20	37.5	88.2	66.6
		LN (-)	6	45			69.2
	GLUT-1 positive (n = 86)	LN (+)	23	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



DOI: 10.12998/wjcc.v12.i5.931 Copyright ©The Author(s) 2024.

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.



DOI: 10.12998/wjcc.v12.i5.931 Copyright ©The Author(s) 2024.

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.

FOOTNOTES

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

Author contributions: contributed to Kim H, Choi SY, Heo TY, Kim KR, Lee J, Yoo MY, Lee TG, and Han JH conceptualization, data curation, writing—review & editing; Heo TY and Kim KR contributed to formal analysis, software; Han JH contributed to funding acquisition, project administration, supervision; Kim H, Choi SY, Heo TY, Kim KR, and Han JH contributed to investigation, methodology, validation; Kim H and Choi SY contributed to visualization; Kim H, Choi SY, and Han JH contributed to writing - original draft.

Institutional review board statement: The Institutional Review Board (IRB No. 2013-03-003) of Chungbuk National University Hospital approved this study.

Informed consent statement: The requirement for written informed consent was waived due to retrospective design of the study.

Conflict-of-interest statement: The authors have no conflict of interest to declare regarding the publication of this work.

Data sharing statement: IRB of CBNUH did not permit sharing the raw data of patients without consent.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

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.

S-Editor: Liu JH

L-Editor: A

P-Editor: Zheng XM

REFERENCES

- 1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
- 2 Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmoeker S, Brown G, McLeod R, Kennedy E. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2012; **19**: 2212-2223 [PMID: 22271205 DOI: 10.1245/s10434-011-2210-5]
- 3 Dighe S, Purkayastha S, Swift I, Tekkis PP, Darzi A, A'Hern R, Brown G. Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. *Clin Radiol* 2010; **65**: 708-719 [PMID: 20696298 DOI: 10.1016/j.crad.2010.01.024]
- 4 Nasseri Y, Langenfeld SJ. Imaging for Colorectal Cancer. *Surg Clin North Am* 2017; **97**: 503-513 [PMID: 28501243 DOI: 10.1016/j.suc.2017.01.002]
- 5 Park IJ, Kim HC, Yu CS, Ryu MH, Chang HM, Kim JH, Ryu JS, Yeo JS, Kim JC. Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. *Eur J Surg Oncol* 2006; **32**: 941-947 [PMID: 16843635 DOI: 10.1016/j.ejso.2006.05.019]
- 6 Abdel-Nabi H, Doerr RJ, Lamonica DM, Cronin VR, Galantowicz PJ, Carbone GM, Spaulding MB. Staging of primary colorectal carcinomas

- with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. *Radiology* 1998; **206**: 755-760 [PMID: 9494497 DOI: 10.1148/radiology.206.3.9494497]
- 7 **Kijima S**, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. *World J Gastroenterol* 2014; **20**: 16964-16975 [PMID: 25493009 DOI: 10.3748/wjg.v20.i45.16964]
- 8 **Kantorová I**, Lipská L, Bělohávek O, Visokai V, Trubač M, Schneiderová M. Routine (18)F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. *J Nucl Med* 2003; **44**: 1784-1788 [PMID: 14602860]
- 9 **Mukai M**, Sadahiro S, Yasuda S, Ishida H, Tokunaga N, Tajima T, Makuuchi H. Preoperative evaluation by whole-body 18F-fluorodeoxyglucose positron emission tomography in patients with primary colorectal cancer. *Oncol Rep* 2000; **7**: 85-87 [PMID: 10601597]
- 10 **Boellaard R**, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke J, Bockisch A, Beyer T, Chiti A, Krause BJ; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging* 2015; **42**: 328-354 [PMID: 25452219 DOI: 10.1007/s00259-014-2961-x]
- 11 **Meyer HJ**, Wienke A, Surov A. Associations between GLUT expression and SUV values derived from FDG-PET in different tumors-A systematic review and meta analysis. *PLoS One* 2019; **14**: e0217781 [PMID: 31206524 DOI: 10.1371/journal.pone.0217781]
- 12 **van Berkel A**, Rao JU, Kusters B, Demir T, Visser E, Mensenkamp AR, van der Laak JA, Oosterwijk E, Lenders JW, Sweep FC, Wevers RA, Hermus AR, Langenhuijsen JF, Kunst DP, Pacak K, Gotthardt M, Timmers HJ. Correlation between *in vivo* 18F-FDG PET and immunohistochemical markers of glucose uptake and metabolism in pheochromocytoma and paraganglioma. *J Nucl Med* 2014; **55**: 1253-1259 [PMID: 24925884 DOI: 10.2967/jnumed.114.137034]
- 13 **Busk M**, Horsman MR, Jakobsen S, Bussink J, van der Kogel A, Overgaard J. Cellular uptake of PET tracers of glucose metabolism and hypoxia and their linkage. *Eur J Nucl Med Mol Imaging* 2008; **35**: 2294-2303 [PMID: 18682937 DOI: 10.1007/s00259-008-0888-9]
- 14 **Yang HJ**, Xu WJ, Guan YH, Zhang HW, Ding WQ, Rong L, Qiu ZB, Zhong L. Expression of Glut-1 and HK-II in Pancreatic Cancer and Their Impact on Prognosis and FDG Accumulation. *Transl Oncol* 2016; **9**: 583-591 [PMID: 27916293 DOI: 10.1016/j.tranon.2016.08.004]
- 15 **Krzeslak A**, Wojcik-Krowiranda K, Forma E, Jozwiak P, Romanowicz H, Bienkiewicz A, Brys M. Expression of GLUT1 and GLUT3 glucose transporters in endometrial and breast cancers. *Pathol Oncol Res* 2012; **18**: 721-728 [PMID: 22270867 DOI: 10.1007/s12253-012-9500-5]
- 16 **Krishnamachary B**, Berg-Dixon S, Kelly B, Agani F, Feldser D, Ferreira G, Iyer N, LaRusch J, Pak B, Taghavi P, Semenza GL. Regulation of colon carcinoma cell invasion by hypoxia-inducible factor 1. *Cancer Res* 2003; **63**: 1138-1143 [PMID: 12615733]
- 17 **Saigusa S**, Toiyama Y, Tanaka K, Okugawa Y, Fujikawa H, Matsushita K, Uchida K, Inoue Y, Kusunoki M. Prognostic significance of glucose transporter-1 (GLUT1) gene expression in rectal cancer after preoperative chemoradiotherapy. *Surg Today* 2012; **42**: 460-469 [PMID: 22072148 DOI: 10.1007/s00595-011-0027-2]
- 18 **Yang J**, Wen J, Tian T, Lu Z, Wang Y, Wang Z, Wang X, Yang Y. GLUT-1 overexpression as an unfavorable prognostic biomarker in patients with colorectal cancer. *Oncotarget* 2017; **8**: 11788-11796 [PMID: 28052033 DOI: 10.18632/oncotarget.14352]
- 19 **Carvalho KC**, Cunha IW, Rocha RM, Ayala FR, Cajaiba MM, Begnami MD, Vilela RS, Paiva GR, Andrade RG, Soares FA. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. *Clinics (Sao Paulo)* 2011; **66**: 965-972 [PMID: 21808860 DOI: 10.1590/s1807-59322011000600008]
- 20 **Hong R**, Lim SC. ¹⁸F-fluoro-2-deoxyglucose uptake on PET CT and glucose transporter 1 expression in colorectal adenocarcinoma. *World J Gastroenterol* 2012; **18**: 168-174 [PMID: 22253523 DOI: 10.3748/wjg.v18.i2.168]
- 21 **Choi WH**, Yoo IeR, O JH, Kim TJ, Lee KY, Kim YK. Is the Glut expression related to FDG uptake in PET/CT of non-small cell lung cancer patients? *Technol Health Care* 2015; **23** Suppl 2: S311-S318 [PMID: 26410497 DOI: 10.3233/THC-150967]
- 22 **Taira N**, Atsumi E, Nakachi S, Takamatsu R, Yohena T, Kawasaki H, Kawabata T, Yoshimi N. Comparison of GLUT-1, SGLT-1, and SGLT-2 expression in false-negative and true-positive lymph nodes during the (18)F-FDG PET/CT mediastinal nodal staging of non-small cell lung cancer. *Lung Cancer* 2018; **123**: 30-35 [PMID: 30089592 DOI: 10.1016/j.lungcan.2018.06.004]
- 23 **Zhang M**, Yang J, Jiang H, Wang Z. Correlation between glucose metabolism parameters derived from FDG and tumor TNM stages and metastasis-associated proteins in colorectal carcinoma patients. *BMC Cancer* 2021; **21**: 258 [PMID: 33750337 DOI: 10.1186/s12885-021-07944-z]
- 24 **Gu J**, Yamamoto H, Fukunaga H, Danno K, Takemasa I, Ikeda M, Tatsumi M, Sekimoto M, Hatazawa J, Nishimura T, Monden M. Correlation of GLUT-1 overexpression, tumor size, and depth of invasion with 18F-2-fluoro-2-deoxy-D-glucose uptake by positron emission tomography in colorectal cancer. *Dig Dis Sci* 2006; **51**: 2198-2205 [PMID: 17080242 DOI: 10.1007/s10620-006-9428-2]
- 25 **Baek HJ**, Chung JH, Park JH, Zo JI, Cheon GJ, Choi CW, Lim SM, Choi SY, Hong JM, Hong JS. FDG-PET in Mediastinal Nodal Staging of Non-small Cell Lung Cancer: Correlation of False Results with Histopathologic Finding. *Cancer Res Treat* 2003; **35**: 232-238 [PMID: 26680941 DOI: 10.4143/crt.2003.35.3.232]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

