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Relationship between PET/CT images and *KRAS* gene mutations in colorectal cancer in Vietnamese patients

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Abstract. – OBJECTIVE: We conducted this study to determine the relationship among standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) indexes of Flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography18 (FDG-PET/CT) imaging and Kirsten rat sarcoma (KRAS) gene mutations in colorectal cancer (CRC).

PATIENTS AND METHODS: This cross-sectional study was conducted in Bach Mai Hospital from 2020 to 2022. It included newly diagnosed CRC patients who underwent PET/CT examination prior to primary tumor resection. The maximum SUV (SUVmax – SUVmean), MTV, and TLG were considered. All pathologically confirmed CRC patients were accepted with further *KRAS* mutation status analysis.

RESULTS: We enrolled 63 newly diagnosed CRC patients who underwent PET/CT examination prior to primary tumor resection. Among them, 31 (49.2%) patients had *KRAS* gene mutation. Patients with *KRAS* mutation status showed significantly different and higher SUVmax (*p*-value = 0.025), SUVmax t/b (*p*-value = 0.013), SUVmax t-b (*p*-value = 0.014), MTV (*p*-value = 0.023), and TLG (*p*-value = 0.011) than patients with WT *KRAS*. Other characteristics, including age, gender, tumor location, SUVb, SUVmean, SUVmax of lymph nodes, and SUVmax of liver metastasis, were insignificantly different between the two groups of patients with *KRAS* mutation status. Receiver operating curve analysis showed that the area under the curve was 0.672 for SUVmax (*p*-value = 0.019), SUVt/b (*p*-value = 0.045), and SUVt-b (*p*-value = 0.020).

CONCLUSIONS: We observed a relationship, considering the quantitative parameters (SUVmax, SUVmax, SUVmax t-b, MTV, and TLG), between ^{18}FDG-PET/CT images and the *KRAS* gene mutation in CRC by analyzing 63 patients prior to treatment.

Key Words:
^{18}FDG-PET/CT images, KRAS Gene Mutations, Colorectal Cancer, Vietnamese patients.

Introduction

Colorectal cancer (CRC) is a common global cancer, including in Vietnam[1]. The fast-rising burden in low- and middle-SDI nations in Asia and Africa requires CRC prevention techniques, improved awareness, and cost-effective screening and therapy alternatives in these regions[2]. In Vietnam, the incidence and mortality of CRC have increased significantly, and the yearly economic cost of CRC is $132.9 million[3]. Multiple criteria, including staging, tumor location, and histopathology, influence the treatment decision. In Vietnam, available treatment options include surgery, radiation, and chemotherapy (systemic and targeted)[4].

New insights into the molecular pathophysiology of CRC reveal that it is caused by the accumulation of genetic mutation[5]. The location and phenotype of *RAS* and *BRAF* oncogene mutations are different. Human *RAS* genes include *KRAS*, *NRAS*, and *HRAS*, with mutations in the *KRAS* gene occurring in approximately 40% of CRC cases, on the average. *NRAS* gene mutations occur in approximately 2%-10% of CRC cases, but *HRAS* gene mutations nearly never occur. In CRC patients with *RAS* and *BRAF* mutations, epidermal growth factor receptor (EGFR)-targeted medications are ineffective[6-8]. Determining the mutation status of the *RAS* genes has become a crucial test indication for CRC patients prior to EGFR-targeted drug therapy.

Clinical symptoms and paraclinical testing are mainly used to diagnose CRC stage. In recent years, Flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG-PET/CT) with the combination of PET metabolic images and anatomical images on CT has proven to play an excellent role in the accu-

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rate staging, evaluation of treatment response, monitoring for recurrence, and planning of radiotherapy for CRC patients. Numerous studies on ^{18}FDG-PET/CT in CRC patients have been conducted worldwide. Some studies suggest that SUVmax and SUVmean are correlated with *RAS* mutation status in CRC[9-11]. SUVmax cutoff value of 13 or 14 can predict *KRAS* status with 75% precision[11]. However, some authors[12] suggest that *KRAS* mutations and ^{18}FDG-PET/CT in patients with metastatic CRC have no relationship, but others believe otherwise.

In Vietnam, the frequency of KRAS mutations in Vietnamese CRC was 41.0%, and the relationship between genetics showed that the distribution of KRAS mutation was mutually exclusive against that of NRAS and BRAF mutations in CRC[13]. Determining the significance of the association among standardized uptake value (SUV) max, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) indexes on ^{18}FDG-PET/CT and *KRAS* gene mutation status will aid in predicting gene mutation status using ^{18}FDG-PET/CT imaging. In addition, defining the role of ^{18}FDG-PET/CT in CRC highlights the relevance of ^{18}FDG-PET/CT in clinical settings and the therapy of CRC. We conducted this study to determine the relationship among SUV, MTV, and TLG indexes of ^{18}FDG-PET/CT imaging and *KRAS* gene mutations in CRC.

Patients and Methods

This cross-sectional study was conducted in Bach Mai Hospital from 2020 to 2022. It included newly diagnosed CRC patients who underwent PET/CT examination prior to primary tumor resection, including maximum SUV (SUVmax - SUVmean), MTV, and TLG. No patients received preoperative chemotherapy. All pathologically confirmed CRC patients were accepted with further *KRAS* mutation status analysis. Inclusion criteria: (1) newly diagnosed patients who had not received radiotherapy or chemotherapy prior to PET/CT examination; (2) adenocarcinoma or adenocarcinoma confirmed by pathology, with KRAS gene detection performed; (3) consent to participate in the study. Exclusion criteria: (1) multiple primary cancers; (2) other pathological types: pregnant patients; patients with severe comorbidities, such as heart failure, renal failure, severe diabetes, and exacerbation of chronic obstructive pulmonary disease; patients with acute bacterial infection, tuberculosis; patients with blood glucose level ≥ 150 mg/dl; (3) incomplete case data.

PET Imaging and Analysis

^{18}FFDG PET/CT examination

PET/CT scan (Bach Mai Hospital) was conducted on the Siemens Biography Sensation 16 PET/CT imager (Knoxville, TN, USA). ^{18}F-FDG was used with 109.7 minutes of T1/2. Following the standard protocol, tumor PET/CT graphics were analyzed in Nuclear Medicine and Oncology Center, Bach Mai Hospital. The ^{18}FDG-PET/CT results were examined using two nuclear medicine specialists with at least two years of experience in evaluating PET/CT results.

Software AW workstation version 4.7 (GE Healthcare, Milwaukee, WI, USA) was used to establish the volume of interest (VOI) to measure the lesion's traditional metabolic parameters. ^{18}F-FDG PET/CT-derived parameters were computed by PETVCAR software (version 4.7, GE Healthcare, Milwaukee, WI, USA[14]), including SUVmax (the maximum value of SUV in the tumor volume) and SUVmean (the mean value of SUV in the tumor volume). The MTV was calculated as the tumor volume. TLG was computed by multiplying SUVmean by MTV; the SUVmax of tumor-to-background ratio (SUVmax t/b) and SUVmax t-b were also included (SUVmax of tumor minus SUVmax of background).

Pretreatment Staging Based on PET/CT

The staging was performed based on the tumor-node-metastasis (TNM) staging system for CRC following the American Joint Committee on Cancer Guidelines (AJCC) 2018 (AJCC 8th).

KRAS Mutational Analysis

Pathological samples were obtained following tumor resection for analyzing the *KRAS* mutation status. The pathologists used the commercially available kit *KRAS* StripAssay® (Vienna Lab Diagnostics, Vienna, Austria). PCR amplification was performed using amplification products that were hybridized to nitrocellulose test. In our study, this procedure can be divided into four stages. Stage 1: DNA extraction, where the pathologists select the tumor area in tissue blocks and extract DNA from formalin-fixed, paraffin-embedded tumor tissue slides; Stages 2 and 3: DNA amplification and hybridization, where *KRAS* analysis was performed using polymerase

Table I. General characteristics of study population.

Factors		n (63)	(%)
Age	< 60	23	36.5
	>= 60	40	63.5
Gender	Male	37	41.3
	Female	26	58.7
Types of cancer	Colon cancer	40	63.5
	Rectal cancer	23	36.5
KRAS	Wild type	32	50.8
	Mutant	31	49.2
Tumor	T1	0	0
	T2	13	20.6
	T3	41	65.1
	T4	9	14.3
Nodes	N0	26	41.3
	N1	14	22.2
	N2	23	36.5
Metastases	M0	29	46.0
	M1	34	54.0
Stage (PET/CT)	I	3	4.8
	II	10	15.9
	III	16	25.4
	IV	34	54.0

chain reaction (PCR) hybridization StripAssay® (ViennaLab, Vienna, Austria); Stage 4: Mutation analysis, where the analyzed mutations further use StripAssay Evaluator® software (ViennaLab).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 20.0 (IBM, Corp., Armonk, NY, USA). Continuous data were represented by mean±standard deviation (SD), and categorical data were expressed as proportions. Chi-square test, *t*-test, and Mann–Whitney U test were used to compare clinicopathological and PET indicators between *KRAS* mutant and *KRAS* wild type (WT). The PET parameter-predicted KRAS mutation status was obtained using the receiver operating characteristic (ROC), and the area under the curve (AUC) was calculated. All analyses were two-sided, and $p<0.05$ was considered statistically significant.

Results

Study Population

We enrolled 63 newly diagnosed CRC patients who underwent PET/CT examination prior to primary tumor resection, and pathological samples were obtained to examine the *KRAS* mutation status. Among the 63 patients, 31 (49.2%) had *KRAS* gene mutation. The clinical characteristics of the 63 patients are shown in Table I. PET/CT characteristics are shown in Table II, and Figure 1 shows the typical PET/CT images in our study. Patients with *KRAS* mutation status showed significantly different and higher SUVmax (p-value = 0.025), SUVmax t/b (p-value = 0.013), SUVmax t-b (p-value = 0.014), MTV (p-value = 0.023), and TLG (p-value =0.011) than patients with WT *KRAS*. Other characteristics, including age, gender, tumor location, SUVb, SUVmean, SUVmax of lymph nodes, and SUVmax of liver metastasis, were insignificantly different between the two groups (Table III).

Table II. PET/CT images characteristics of study population.

Factors		N	Min – Max	Mean ± SD
Tumor	SUVmaxT	63	3.09 - 22.91	11.08 ± 4.61
	SUVb	63	1.90 - 4.10	2.61 ± .37
	SUVmax t/b	63	1.34 - 8.81	4.25 ± 1.76
	SUVmax t-b	63	.79 - 20.31	8.46 ± 4.54
	SUVmean	63	2.72 - 7.92	5.10 ± 1.27
	MTV	63	1.84 - 191.94	38.35 ± 36.83
	TLG	63	5.00 - 1368.53	220.63 ± 249.98
Location of distant metastasis	Liver	21	3.53 - 13.00	8.12 ± 2.62
	Lung	10	1.08 - 10.00	4.17 ± 3.30
	Bone	6	2.30 - 8.1	6.53 ± 2.15
	The peritoneum, the mesentery	4	3.10 - 8.60	5.95 ± 2.40
	Abdominal lymph nodes	11	3.50 - 9.90	6.17 ± 2.00
	Inguinal lymph nodes	2	3.18 - 9.10	6.14 ± 4.18
	Mediastinal ganglion	5	3.20 - 13.09	7.70 ± 3.66
	Neck lymph nodes	35	1.00 - 15.86	4.66 ± 3.52
	Other metastasis	4	3.00 - 10.35	6.55 ± 3.86

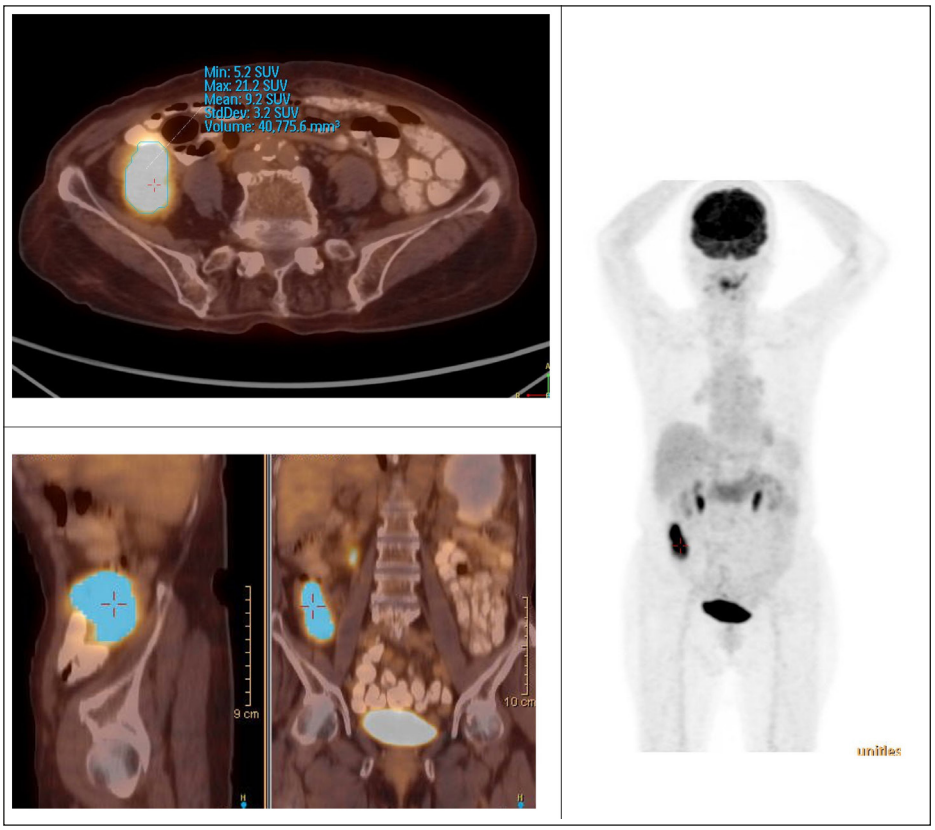


Figure 1. ^{18}FDG-PET/CT imaging in colorectal cancer.

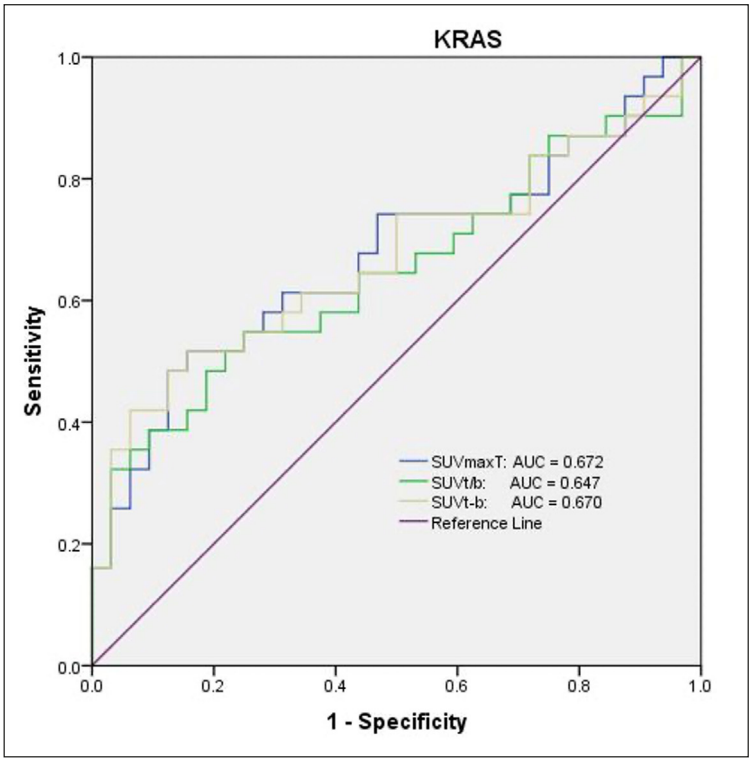
Predictive Value of SUVmax and MTV for KRAS Mutation Status

ROC curve analysis was performed (Figure 2): the AUC for SUVmax was 0.672 (95% CI: 0.537-0.808) *p*-value = 0.019. The AUC for MTV was 0.578 (95% CI: 0.435-0.720) *p*-value = 0.290. The AUC for TLG was 0.631 (95% CI: 0.494-0.769) *p*-value = 0.074. The AUC for SUVt/b was 0.647 (95% CI: 0.508–0.786), *p*-value = 0.045. The AUC for SUVt-b was 0.670 (95% CI: 0.533-0.807), *p*-value = 0.020.

Table III. Relationship between PET/CT images and KRAS gene mutations in colorectal cancer.

Factors		Wild Type	Mutated KRAS	*p*-value
Age		61.19 ± 15.05	59.90 ± 14.87	0.908
Gender	Male	21	16	0.259
	Female	11	15	
Tumor location	Colon	20	20	0.868
	Rectal	12	11	
Tumor	SUVmax	9.59 ± 3.45	12.62 ± 5.17	0.025
	SUVb	2.57 ± 0.44	2.66 ± 0.28	0.199
	SUVmean	4.67 ± 1.03	5.54 ± 1.36	0.060
	SUVmax t/b	3.74 ± 1.29	4.78 ± 2.02	0.013
	SUVmax t-b	7.02 ± 3.32	9.95 ± 5.18	0.014
	MTV	30.97 ± 23.17	45.98 ± 46.16	0.023
	TLG	156.84 ± 126.73	286.48 ± 322.07	0.011
Lymph Nodes	SUVmax	4.33 ± 2.57	4.91 ± 4.15	0.130
		(n = 15)	(n = 20)	
Liver metastasis	SUVmax	8.98 ± 2.19	7.33 ± 2.82	0.155
		(n = 10)	(n = 11)	

Figure 2. ROC of KRAS.



Discussion

Petersen et al[15] examined the clinical impact of FDG-PET/CT on CRC staging and treatment strategy in 67 CRC patients and found that in 30% of cases, ^{18}FDG-PET/CT influenced the treatment plan. Changes from radical to palliative or vice versa are among these influences. However, the SUVmax at the primary tumor reveals whether glucose consumption is high or low, and the SUVmax t-b and SUVmax t/b represent the level of ^{18}FDG uptake in the tumor after considering other potential causes. The factors include increased absorption of FDG in the colon due to inflammation or increased intestinal motility. These indices were more significant in the group with mutations. After ROC analysis, the SUVmax, SUVmax t-b, and SUVmax t/b were statistically significant. Therefore, we believe that ^{18}FDG-PET/CT can be used to evaluate the presence of *KRAS* gene mutations in CRC. Our study was not limited to SUVmax, the same as that in the majority of comparative research. In addition, we investigated the volume-based measures (MTV and TLG) that are predictive variables for various cancer types, including CRC. In this study, most individuals have an advanced-stage colon and rectal cancer. Our findings showed that the mutation rate of the *KRAS* gene was 49.2%. In the group of CRC patients with *KRAS* mutation, glucose metabolism (SUVmax and SUVmax t/b, SUVmax t-b) was significantly higher in the primary tumor than in the group without mutation. SUVmax indices at the regional lymph nodes and distant metastases did not differ between the gene-mutated and unmutated groups.

Kawada et al[16] performed a retrospective analysis on 55 metastatic CRC tumors diagnosed by ^{18}F-FDG PET/CT prior to surgery and found that SUVmax was still substantially correlated with *KRAS* mutations. The *KRAS* status may be predicted with 71.4% precision using a SUVmax cut-off value of 6.0. Lee et al[17] suggested that in CRC patients with CRP 6.0 mg/L, *KRAS* mutations were associated with SUVmax and SUVpeak values that were substantially greater than those expressing wild-type *KRAS* mutations (p-value< 0.05). Moreover, He et al[18] indicated that SUVmax and SUVmax t/b were included in the analysis to predict the efficacy of *KRAS*/*NRAS*/*BRAF* mutations in CRC. SUVmax t/b and SUVmax may be potential surrogate imaging markers for predicting *KRAS*/*NRAS*/*BRAF* mutation status in CRC patients[18]. Lovinfosse et al[9] conducted a ^{18}FDG-PET/CT imaging research on rectal cancer. They found the association with *RAS* mutant status in 151 newly diagnosed patients with rectal cancer:

83 patients had *RAS* mutations (55%), including 74 *KRAS* and 9 *NRAS*. SUVmax and SUVmean are correlated with *RAS* mutation status (p-value = 0.002) and *RAS* mutation status (p-value = 0.006). With a sensitivity of 69% and a specificity of 52%, SUVmax demonstrated AUC = 0.65 with a sensitivity (69%) and specificity (52%). With *RAS* mutations, no association is found between tumor volume with SUV uptake (MTV) and total glucose metabolism (TLG).

Some studies[12,19,20] contradict the previous studies. Krikelis et al[19] indicated that no statistically significant association exists between SUVmax ^{18}FDG-PET/CT levels and *KRAS* mutation status. Krikelis et al[12] investigated the *KRAS* codon 12 and 13 mutation status of 44 primary CRCs and compared it with the usual maximum uptake value of ^{18}FDG PET/CT (SUVmax) of the lesions. No statistically significant connection was found between SUVmax ^{18}FDG PET/CT values and the presence or absence of *KRAS* mutations. According to Oner et al[20] no statistically significant difference exists between the wild-type *KRAS* group and the SUVmax, SUVmean, MTV, and TLG value mutants. The ability of SUVmax, SUVmean, MTV, and TLG values to predict *KRAS* oncogene mutations was tested using the ROC curve. The AUC for SUVmax was 0.543 (p-value = 0.60), 0.543 (p-value = 0.600) for SUVmean, 0.591 (p-value = 0.263) for MTV, and 0.601 (p-value = 0.0.214) for TLG.

Conclusions

We observed a relationship between the quantitative parameters (SUVmax, SUVmax, SUVmax t-b, MTV, and TLG) on ^{18}FDG-PET/CT images and the *KRAS* gene mutation in CRC by analyzing 63 patients prior to treatment.

Conflict of Interests
The authors have no conflict of interest to declare.

Data Availability Statement
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval
The Ethics Committee of Hanoi Medical University approved the study and authorized its conduct (Approval No.: 97/GCN/ HĐĐĐNCYSH-ĐHYHN). The study was in accordance with the Declaration of Helsinki.

Informed Consent
Individual patient consent for inclusion in the study was obtained. Before the operation, written informed consent was provided to all participants after a thorough explanation of the purpose of this study. Patients had the right to discontinue at any time during the study.

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Authors' Contributions
All authors made substantial contributions to conceptualization and design, data acquisition, data analysis, and interpretation, took part in the drafting of the initial manuscript and revising it critically, gave final approval of the version to be published, agreed to submit to the current journal, and agreed to be accountable for all aspects of the work.

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