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ORIGINAL RESEARCH

SUVmax and metabolic tumor volume: surrogate image biomarkers of KRAS mutation status in colorectal cancer

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Purpose: The objective of this study was to explore the association between KRAS mutation status and PET/CT metabolic parameters in colorectal cancer (CRC) patients.

Materials and methods: One hundred and sixty-four CRC patients were enrolled in this study and received PET/CT examination before operation, then KRAS mutation status was analyzed through pathologically confirmed CRC samples. The association between tumor clinical characteristics and PET/CT metabolic parameters, including maximum standardized uptake value (SUVmax), SUVmean, and metabolic tumor volume (MTV), and KRAS mutation status was analyzed using chi-squared tests, Mann–Whitney *U* tests, and logistic regression analysis.

Results: The KRAS mutation type patients exhibited high MTV and high SUVmax using a threshold of 17.8 cm^3 and 8.7 respectively and the predictive accuracy was 0.772 and 0.603 respectively. High MTV (P=0.001; 95% CI: 1.119–1.296) and high SUVmax (P=0.048; 95% CI: 0.564–0.985) were independent predictors for KRAS mutation status.

Conclusion: MTV and SUVmax were associated with KRAS mutation type in CRC patients. PET/CT metabolic parameters can be used for supplementing KRAS mutation status prediction in CRC patients.

Keywords: colorectal cancer, ^{18}F-FDG PET/CT, SUVmax, SUVmean, MTV, KRAS mutation

Introduction

Colorectal cancer (CRC) has high incidence and is the third most common cancer in the worldwide context.[1,2] Over the last 20 years, new molecular insights have indicated the mechanism of tumor initiation and progression for CRC. For instance, adenomatous polyposis coli gene mutation, KRAS gene activation, and P53 gene inhibition are closely related to carcinogenesis, progression, prognosis, and treatment decision of CRC.[3–6] Monoclonal antibody targeting EGFR has made significant breakthrough and great enrichment in the field of colorectal therapy. Nevertheless, KRAS mutation occurs in ~40% of CRC patients and studies have demonstrated that KRAS mutation always predicts a lack of responses to EGFR targeted therapies in metastatic CRC.[7–9]

^{18}F-FDG PET/CT imaging is widely used for early diagnosis, staging, and judgment of recurrence and metastasis after surgery in CRC patients. Exploring the correlation between pretreatment images and genetic alteration is a challenging work to optimize the predictive value of KRAS mutation. CRYSTAL (chemotherapy and cetuximab in metastatic colorectal cancer) and OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) studies have shown that metastatic CRC patients with wild-type (WT) KRAS tumor can benefit from cetuximab treatment, whereas

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the KRAS mutation type patients cannot achieve benefits.[10] Thus, a noninvasive imaging method to predict the KRAS mutation status, especially for patients who cannot undergo an invasive examination, is necessary and valuable. In addition, considering CRC is a heterogeneous disease, the specific location of tumor tissue may not be able to exactly reflect the KRAS mutation status of the entire tumor.[11] Several studies have explored the relationship between PET/CT imaging and KRAS mutation in CRC patients. Cho et al found KRAS mutation patients were inclined to have lung metastasis and had higher ^{18}F-FDG uptake compared to WT KRAS in stage IV CRC patients.[12] Two clinical studies demonstrated that higher ^{18}F-FDG uptake was associated with KRAS mutation in CRC patients.[13,14] One study indicated that the maximum standardized uptake value (SUVmax) for the primary tumor and tumor-to-liver ratio was higher in CRC patients with KRAS mutation. Furthermore, the relationship between different PET/CT metabolic parameters and KRAS mutation status is worth exploring.

In this study, we investigated clinical characteristics and PET/CT metabolic parameters that could potentially predict KRAS mutation status in a cohort of CRC patients and verified the predictive value via receiver operating characteristic (ROC) curve analysis.

Materials and methods

Patient population selection

After obtaining approval from the Ethics Review Board, 164 newly diagnosed CRC patients who underwent PET/CT examination before primary tumor resection from 2012 to 2017 were identified in this study. This retrospective study was approved by the Ethics Committee. All patients provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki. All pathologically confirmed CRC patients accepted with further KRAS mutation status analysis. No patients received preoperative chemotherapy. The median age was 56 years (range: 29–86 years). Ninety-nine patients were men and 65 patients were women. Among them, most of the patients had pathological features, including moderate differentiation, nonmucinous adenocarcinoma, and full thickness invasive depth. Regional lymph node (RLD) metastasis and late stage patients accounted for the majority. All patients were suitable for accepting PET/CT examination. The clinical characteristics of the 164 patients are shown in Table 1. Patient clinical characteristics according to KRAS mutation status are shown in Table 2.

Table 1 Patient clinical characteristics

Characteristics	Number (%)
Patients, n	164
Age, years	
Median (range)	56 (29–86)
Gender	
Male	99 (60.4)
Female	65 (39.6)
Differentiation	
Poor	24 (14.6)
Moderate	125 (76.2)
Well	15 (9.2)
Histologic type	
Nonmucinous adenocarcinoma	140 (85.4)
Mucinous adenocarcinoma	19 (11.6)
Signet-ring cell carcinoma	5 (3.0)
Invasive depth	
Superficial muscle	5 (3.0)
Deep muscle	10 (6.1)
Full thickness	149 (90.9)
RLD metastasis	
Positive	107 (65.2)
Negative	57 (34.8)
Lymphovascular invasion	
Positive	88 (53.7)
Negative	76 (46.3)
Distant metastasis	
Positive	45 (27.4)
Negative	119 (72.6)
Stage, AJCC	
I/II	47 (28.7)
III/IV	117 (71.3)
KRAS mutation status	
Mutation type	72 (43.9)
Wild-type	92 (56.1)
SUVmax (mean±SD)	12.1±6.9
SUVmean (mean±SD)	7.4±4.1
MTV (mean±SD)	22.7±17.0

Abbreviations: AJCC, American Joint Committee on Cancer; MTV, metabolic tumor volume; RLD, regional lymph node; SUVmax, maximum standardized uptake value.

PET/CT imaging acquisition and analysis

All patients fasted for at least 6 hours before receiving PET/CT examination. Their blood glucose levels were then suitable for intravenous injection of ^{18}F-FDG. The PET images were reconstructed by attenuation and iterative reconstruction, then multi-layered, multi-imaged, and merged with the CT images to ensure image clarity. This procedure was conducted by manufacturer review workstation (Xeleris™; GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA). The SUVmax and SUVmean parameters of the primary tumor area were automatically captured and calculated. In our study, MTV was defined as the sum of the primary tumor metabolic volumes using a SUVmax of 2.5 as the threshold.[15,16]

Table 2 Patient clinical characteristics according to KRAS mutation status

Variables	Cases (N=164)	KRAS + (%)	KRAS − (%)	*P*-value
Age, years				0.580
>56	78	36 (46.1)	42 (53.9)	
≤56	86	36 (41.9)	50 (58.1)	
Gender				0.417
Male	99	52 (46.0)	61 (54.0)	
Female	65	20 (39.2)	31 (60.8)	
Differentiation				0.055
Poor	24	10 (41.7)	14 (58.3)	
Moderate	125	51 (40.8)	74 (59.2)	
Well	15	11 (73.3)	4 (26.7)	
Histologic type				0.534
Nonmucinous adenocarcinoma	140	63 (45.0)	77 (55.0)	
Mucinous adenocarcinoma	19	8 (42.1)	11 (57.9)	
Signet-ring cell carcinoma	5	1 (20.0)	4 (80.0)	
Invasive depth				0.508
Superficial muscle	5	2 (40.0)	3 (60.0)	
Deep muscle	10	4 (40.0)	6 (60.0)	
Full thickness	149	83 (55.7)	66 (44.3)	
RLD metastasis				0.504
Positive	107	49 (45.8)	58 (54.2)	
Negative	57	23 (40.3)	34 (59.7)	
Lymphovascular invasion				0.066
Positive	88	45 (51.1)	43 (48.9)	
Negative	76	28 (36.8)	48 (63.2)	
Distant metastasis				0.028
Positive	45	26 (57.8)	19 (42.2)	
Negative	119	46 (38.7)	73 (61.3)	
Stage, AJCC				0.206
I/II	47	17 (36.2)	30 (63.8)	
III/IV	117	55 (47.0)	62 (53.0)	
SUVmax (mean±SD)	164	13.5±7.8	11.0±5.9	0.023
SUVmean (mean±SD)	164	8.2±4.6	6.9±3.6	0.059
MTV (mean±SD)	164	30.8±21.3	16.3±8.4	0.001

Abbreviations: AJCC, American Joint Committee on Cancer; MTV, metabolic tumor volume; RLD, regional lymph node; SUVmax, maximum standardized uptake value.

KRAS mutation analysis

Pathological samples were obtained following tumor resection for analyzing the KRAS mutation status. Pathologists selected the tumor area in tissue blocks and extracted DNA from formalin-fixed, paraffin-embedded tumor tissue slides using FFPE Tissue Kits and DNeasy Blood & Tissue Kits. Polymerase chain reaction was used to amplify the KRAS exon 2 gene and the ABI 3730XL automated DNA analyzer was used to analyze KRAS exon 2 gene using direct sequencing.

Statistical analyses

The categorical variables including clinical characteristics between two or three groups were tested using chi-squared tests. The continuous covariates were expressed as mean ± SD. The differentiations between such PET/CT metabolic parameters and KRAS mutation status were analyzed by Mann-Whitney *U* test. We used ROC analysis to obtain PET/CT metabolic parameters' cutoff values to predict KRAS mutation status. In addition, the multivariate logistic regression analysis was used to confirm the predictive values of PET metabolic parameters for the KRAS mutation status. It is widely known that the area under the ROC curve (AUC) is defined as the predictive value and when the AUC is not <0.7 it represents a good discrimination value.[17] All analyses were two-sided and $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient clinical characteristics

We enrolled 164 newly diagnosed CRC patients who underwent PET/CT examination before primary tumor resection and pathological samples were obtained to examine the

KRAS mutation status. Moderate differentiation (n=125, 76.2%), nonmucinous adenocarcinoma (n=140, 85.4%), and full thickness invasive depth (n=140, 90.9%) account for the vast majority of patients. In addition, 107 patients (65.2%) had RLD metastasis and 117 patients (71.3%) were at stage III/IV. Among the 164 patients, 72 patients had KRAS exon 2 gene mutation type and the mutation rate was 43.9%. The main mutation subtypes were G12D (n=18, 25.0%), G12V (n=17, 23.6%), G13D (n=15, 20.8%), and G12A (n=11, 15.3%). In addition, seven patients (9.7%) had G12S mutation and four patients (5.6%) had G12C mutation. The clinical characteristics of the 164 patients are shown in Table 1. Patient clinical characteristics according to KRAS mutation status are shown in Table 2.

Clinical characteristics and KRAS mutation

Patients at diagnosis had significant correlation between KRAS mutation status and distant metastasis (P=0.028). In addition, patients with KRAS mutation status showed a higher level of differentiation (P=0.055) and higher SUVmean (P=0.059) than patients with WT KRAS, although the differences were not significant. Other clinical characteristics, including gender, histologic type, invasive depth, RLD metastasis, and stages, were not significantly different between the two groups of patients with KRAS mutation status (Table 2).

Association between PET metabolic parameters and KRAS mutation

From Table 2, we found that patients with KRAS mutation status had significantly higher SUVmax (13.5±7.8 vs 11.0±5.9, P=0.023) and MTV (30.8±21.3 vs 16.3±8.4, P=0.001) than those with WT KRAS (Table 2). The quantitative difference of SUVmax and MTV between the two groups of patients with KRAS mutation status are shown in Figure 1. No significant difference of SUVmean was found in the two groups of patients with KRAS mutation status.

Predictive value of SUVmax and MTV for KRAS mutation status

In univariate analysis, KRAS mutation status was significantly correlated with distant metastasis (P=0.029), high SUVmax (P=0.026), high SUVmean (P=0.049), and high MTV (P=0.001). We incorporated these factors into multivariate analyses, and it was revealed that high SUVmax (P=0.048) and high MTV (P=0.001) were independent predictors for KRAS mutation status (Table 3). ROC curve analysis was performed: the AUC for SUVmax was 0.603 (95% CI: 0.516–0.691). A cutoff value of 8.7 was used, which maximized specificity and sensitivity (43.5% and 72.2%, respectively), then the patients were divided into groups of low or high SUVmax. The AUC for MTV was 0.772 (95% CI: 0.698–0.845). A cutoff value of 17.8 was used, which maximizes specificity and sensitivity (69.6% and 76.4%, respectively) then the patients were divided into groups of low or high MTV (Figure 2). Furthermore, KRAS mutation status was more common in patients with high MTV and high SUVmax than in those with low MTV (66.3% vs 21.0%, P=0.001) and low SUVmax (53.7% vs 37.1%, P=0.035).

Discussion

KRAS mutation occurs in ~40% of CRC patients and studies have demonstrated that KRAS mutation always predicts a lack of responses to EGFR targeted therapies in metastatic

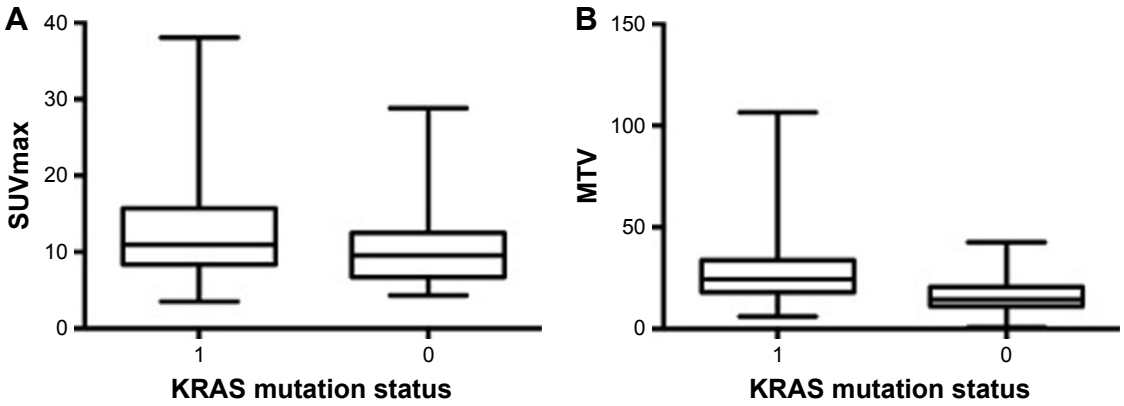

Figure 1 Analysis of SUVmax and MTV according to KRAS mutation status.
Notes: (**A**) SUVmax was significantly higher in patients with KRAS mutation than in those with WT KRAS (P=0.023; Mann–Whitney U test). (**B**) MTV was significantly higher in patients with KRAS mutation than in those with WT KRAS (P=0.001; Mann–Whitney U test).
Abbreviations: MTV, metabolic tumor volume; SUVmax, maximum standardized uptake value; WT, wild-type.

Table 3 Univariate and multivariate regression analyses for predicting KRAS mutation status

Variables	Univariate	OR	95% CI	Multivariate	OR	95% CI
	P-value			*P*-value		
Age	0.968	1.020	0.453–1.558			
Gender	0.725	0.846	0.503–1.778			
Differentiation	0.057	0.275	0.883–3.305			
Histologic type	0.732	1.167	0.348–1.451			
Invasive depth	0.608	0.560	0.524–2.410			
RLD metastasis	0.148	0.676	0.651–2.396			
Lymphovascular invasion	0.066	1.123	0.917–3.206			
Distant metastasis	0.029	2.172	1.081–4.361	0.240	1.645	0.718–3.769
Stage	0.208	1.565	0.780–3.143			
SUVmax	0.026	1.055	1.006–1.106	0.048	0.758	0.564–0.985
SUVmean	0.049	1.081	1.000–1.169	0.597	1.120	0.737–1.702
MTV	0.001	1.097	1.055–1.139	0.001	1.204	1.119–1.296

Abbreviations: MTV, metabolic tumor volume; RLD, regional lymph node; SUVmax, maximum standardized uptake value.

CRC.[7–9] Thus, for patients who cannot undergo an invasive examination, a noninvasive imaging method to predict the KRAS mutation status is necessary and valuable. In addition, considering CRC is a heterogeneous disease, specific location of tumor tissue may not be able to exactly reflect the KRAS mutation status of the entire tumor. In our study, we demonstrated PET/CT metabolic parameters such as MTV (P=0.001) and SUVmax (P=0.048) were independent predictors for KRAS mutation. MTV with the threshold of 17.8 cm^3 achieved higher accuracy in predicting KRAS mutation than SUVmax with a threshold of 8.7 through ROC analysis (0.772 vs 0.603). However, SUVmean (P=0.597) did not show a predictive value for KRAS mutation status.

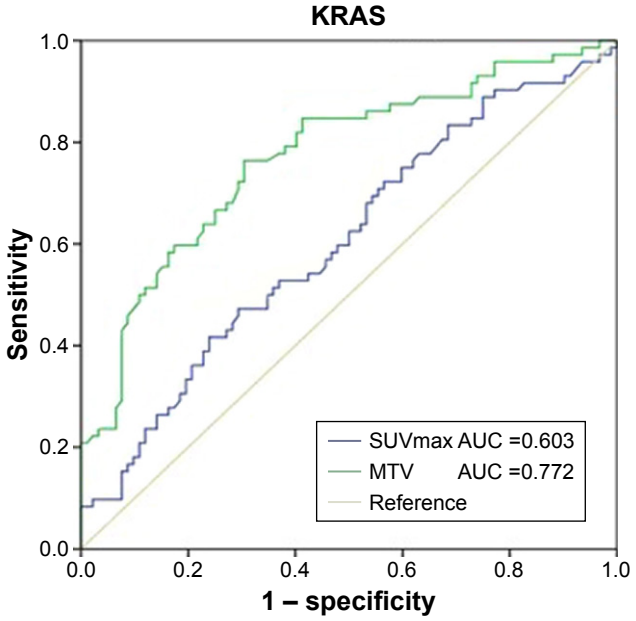

Figure 2 The prediction models consist of two metabolic parameters.
Abbreviations: AUC, area under the curve; MTV, metabolic tumor volume; SUVmax, maximum standardized uptake value.

PET/CT imaging involves the quantitative information of tumor depending on ^{18}F-FDG uptake, which is superior to CT or MRI that rely on the doctor's subjective judgement. Several studies have explored the underlying mechanism of the relationship between glucose accumulation and KRAS mutation status. Yun et al studied the transcriptomes of paired CRC cell lines and found GLUT1 which encodes glucose transporter-1 was upregulated in KRAS or BRAF mutations CRC cell lines. Therefore the KRAS mutant cells exhibited enhanced glucose uptake, whereas the WT cells were subjected to a low glucose environment.[18] Sasaki et al also explored the correlation between the KRAS mutation and glucose accumulation in 283 non-small-cell lung cancer samples and demonstrated GLUT1, as the most common glucose transporter in cells, was highly expressed in cells with KRAS mutation status.[19] All these observations may explain the phenomenon that tumors with KRAS mutation status always had glucose accumulation. Thus, PET/CT metabolic parameters may be theoretically an ideal predictor for KRAS mutation status. Kawada et al conducted a study to verify whether FDG accumulation is associated with KRAS mutation status and its predictive value of KRAS status in metastatic CRC patients.[13] They demonstrated that SUVmax remained significantly associated with KRAS mutations and that it was an ideal predictor of KRAS status with an accuracy of 71.4%.[12] In addition, Lee et al also depicted SUVmax and SUVpeak to be significantly associated with KRAS mutation.[20] However, they did not explore whether these metabolic parameters were predictors for KRAS status. Iwamoto et al investigated the mechanisms that mutated KRAS status increased FDG accumulation and found that upregulation of GLUT1 and additive effect of hypoxia-inducible factor 1α (HIF-1α) in hypoxic lesions could cause FDG accumulation in CRC with KRAS mutation status.[21]

Several studies have reported the correlation between KRAS status and clinical outcomes after topical treatment of CRC liver metastases (CLM).[22–25] Shady et al[22] evaluated the prognostic value of KRAS mutation in patients with CLM who underwent percutaneous radiofrequency ablation (RFA) and found KRAS mutation was a predictor of poor overall survival (OS) (P=0.016), new liver metastases (P=0.037), and peritoneal metastases (P=0.015). Similar results were also demonstrated in two other studies. Calandri et al[23] found 3-year local tumour progression-free survival rates of KRAS mutant subgroups were significantly worse than WT KRAS subgroups ($P<0.001$ and P=0.006). The same result was also verified in the research by Odisio et al, with a P-value of 0.001.[24] In addition to RFA, Yttrium-90 radioembolization therapy is also an important topical treatment option for unresectable CLM. KRAS mutation was verified to be an independent prognostic factor for poor OS in patients with CLM treated with Yttrium-90 radioembolization therapy.[25] Therefore, KRAS status is important for the management of the treatment of patients with CLM.

We explored the association between KRAS mutation status and different clinical characteristics in our study, such as sex, differentiation, histologic type, invasive depth, RLD metastasis, distant metastasis, and stage. We did not find significant association between these characteristics. Nevertheless, the KRAS mutation group was found to have tumors with distant metastasis (P=0.028). Our study demonstrated that a high MTV was significantly associated with KRAS mutation (P=0.001). A high SUVmax was also a good predictor for KRAS mutation (P=0.048). SUVmean was not found to be associated with KRAS mutation (P=0.597). Our study provided evidence that PET/CT metabolic parameters have an important role in the noninvasive prediction of KRAS mutation status. SUVmax was a semiquantitative parameter that could vary with different factors, such as PET scanners, plasma glucose level fasting duration, and region of interest parameters. However, MTV was a quantitative parameter that reflect the glucose uptake of the entire tumor. Thus, MTV was superior to SUVmax in predicting gene mutation status.[26,27] Several studies also demonstrated that MTV was an important factor in predicting the clinical outcomes in several kinds of tumors.[26,28–30]

Limitations

The limitation of this study was its retrospective character which existed inevitable bias. In addition, considering that WT KRAS left hemicolon cancer and WT KRAS right hemicolon cancer have different responses to cetuximab, there may be a discrepancy in biological behavior between colon cancers at different primary sites. Thus, it is necessary to analyze the association between PET/CT parameters and KRAS mutation status in left and right hemicolon cancer, respectively. PET/CT parameters were also found to be associated with neoadjuvant chemoradiotherapy response in patients with locally advanced rectal tumor.[31,32] Thus, monitoring the association between the quantitative changes of PET/CT parameters and KRAS mutation status is necessary. Regrettably, we did not analyze it due to limited sample size. Furthermore, comprehensive analysis of various metabolic parameter thresholds may be a good choice in further studies. Also, future studies should use standardized protocols for ^{18}F-FDG PET acquisition and correction of the partial volume effect or false-positive PET findings[33] to augment its predictive value.

Conclusion

PET/CT metabolic parameters can be used for KRAS mutation status prediction in CRC patients. In our study, we found that KRAS mutation status was associated with high MTV and high SUVmax using a threshold of 17.8 cm^3 and 8.7, respectively, and the predictive accuracy was 0.772 and 0.603, respectively.

Disclosure

The authors report no conflicts of interest in this work.

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