RESEARCH ARTICLE

Predictive value of ^{18}F-fluorodeoxyglucose accumulation in visceral fat activity to detect colorectal cancer metastases (prospective observational cohort study) [version 1; peer review: 2 approved]

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Abstract

Background: To evaluate functional visceral adipose tissue (VAT) activity assessed by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) as a predictive factor of metastases in colorectal cancer (CRC) patients.
Methods: We reviewed study protocols and PET/CT data of 534 CRC patients; 474 patients were subsequently excluded for various reasons. The remaining 60 patients with histologically confirmed adenocarcinoma were then prospectively assessed and were exposed to ^{18}F-FDG PET/CT after a surgical treatment and chemoradiotherapy. Age, histology, stage, and tumor grade data were recorded. Functional VAT activity was verified with maximum standardized uptake value (SUV_{max}) using ^{18}F-FDG PET/CT and tested as a predictive factor of later metastases in eight subdomains of abdominal regions (RE – epigastric region, RLH – left hypochondriac region, RRL – right lumbar region, RU – umbilical region, RLL – left lumbar region, RRI – right inguinal region, RP – hypogastric (pubic) region, RLI – left inguinal region) and pelvic cavity (P) in the adjusted regression models. In addition, we studied the best areas under the curve (AUC) for SUV_{max} with the corresponding sensitivity (Se) and specificity (Sp).
Results: In both adjusted for age regression models and receiver

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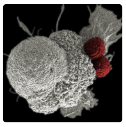
operating characteristic (ROC) curve analysis, ^{18}F-FDG accumulation in RLH (cut-off SUV_{max} 0.74; Se 75%; Sp 61%; AUC 0.668; p=0.049), RU (cut-off SUV_{max} 0.78; Se 69%; Sp 61%; AUC 0.679; p=0.035), RRL (cut-off SUV_{max} 1.05; Se 69%; Sp 77%; AUC 0.682; p=0.032) and RRI (cut-off SUV_{max} 0.85; Se 63%; Sp 61%; AUC 0.672; p=0.043) could predict later metastases in CRC patients, as opposed to age, sex, primary tumor location, tumor grade and histology.
Conclusions: Functional VAT activity was importantly related to later metastases in CRC patients and can be used as their predictive factor.

Keywords
18F-FDG, PET/CT, Colorectal cancer, Predictive value



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Introduction

Colorectal cancer (CRC) is one of the main causes of high worldwide oncological mortality, and its metastasis to the lymph nodes (LN) is an important prognostic factor.[1] Globally, CRC is the third most commonly diagnosed cancer, with an estimated 1.9 million (10%) new cases and 935,173 (9.4%) deaths.[2] Furthermore, CRC is the second leading cause of cancer mortalities in 2020, according to the WHO GLOBOCAN database.[3] In South-Central Asia, 102,987 (63%) new cases of CRC and 59,206 (36%) mortality incidences were registered in 2020.[2,4]

Positron-emission tomography/computed tomography (PET/CT) is a hybrid diagnostic method that shows the value of metabolic processes of the tissue at the molecular level in the tomographic mode. The advantage of PET/CT is to visualize viable tumor tissue and assess its biological activity by the degree of radiopharmaceutical agent accumulation in tissues and can be used to measure the hypermetabolic focus of visceral adipose tissue (VAT) activity. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is now extensively used to assess functional VAT activity during PET/CT; therefore, it can identify accumulation loci and further detect metastases.[5]

Although the predictive role of ^{18}F-FDG PET/CT in detecting metastases has been poorly studied, the studies on the reported prognostic value for various cancer locations have yielded inconsistent findings.[6–11] Thus, VAT has been shown to increase the CRC risk, but the relationship between VAT and the predictive outcome in CRC is ambivalent. VAT is closely associated with dysregulated visceral fat activity increasing adipokines related to systemic inflammation, and can play a role in oncogenesis and metastatic lesion.[1,12] The increased inflammatory condition of VAT activity might influence the status of LN in CRC patients.[13–17]

Byung Wook Choi *et al.* were among the few to retrospectively show the predictive value of metabolic parameters on ^{18}F-FDG PET/CT in classical rectal adenocarcinoma.[12] Another study by Sung Hoon Kim *et al.* retrospectively showed the prognostic factor of ^{18}F-FDG PET/CT for LN metastasis in rectal cancer,[18] whereas Kisoo Pahk *et al.* retrospectively showed the predictive value of functional VAT activity measured by preoperative ^{18}F-FDG PET/CT for regional LN or distant metastasis in CRC patients.[1]

Given that the findings of these studies have been inconsistent in showing the exact maximum standardized uptake value (SUV_{max}) readings indicative of a higher risk of metastases, more data is needed to verify whether PET/CT can assist in early metastases identification in CRC patients. Therefore, the objective of this study was to quantitatively define functional VAT activity via ^{18}F-FDG PET/CT in patients with CRC and its predictive potential for early LN metastases detection.

Methods

Ethical considerations

Approval was obtained from Local Bioethics Commission of the Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan (approval #17/2020 on 24 January 2020) and Local Ethical Commission of the Al-Farabi Kazakh National University (approval #102 IRB – A102 on 28 May 2020). All patients routinely provided written informed consent for all medical tests and examinations and written informed consent was obtained for participation in the current study. We minimized selection bias by enrolling all patients for whom data were available in the database and of sufficient quality. When calculating the sample size, we allowed the maximum standard deviation. The significance level (α) was 0.05, and the study power was 80%, with a confidence probability of 95% (t=1.96). This study follows the TREND guidelines.[19]

Study venue and patients

We enrolled 534 patients with CRC, among which 60 patients had no metastases, 175 patients had metastases, 98 patients had a postoperative relapse with high metabolic activity, and 201 patients had a primary cancer disease progression. Patients who had metastases, postoperative relapse with high metabolic activity and primary cancer disease progression were excluded from the study. In total, we have prospectively evaluated 60 patients with a histologically confirmed diagnosis of adenocarcinoma who underwent ^{18}F-FDG PET/CT in the Nuclear Medicine Unit of the Diagnostic Center of the Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan (Nur-Sultan) during the period time between November 2015 and June 2021.

The study included 60 patients (age 39–81; median 60 (interquartile range (IQR) 55–68) years; 46 women) after a surgical treatment and courses of Folfiri and Folfox chemoradiotherapy according to the regimen. During the initial screening for eligibility, patients with histologically unverified colon cancer or with metastases confirmed at the baseline examination were excluded from the study. We also excluded patients with concurrent cancers. Tumor, lymph nodes, and metastasis (TNM) staging system along with American Joint Committee on Cancer (AJCC) stages of recruited patients are shown in Table 1. As Table 1 presents, there were no patients with AJCC stage IV, whereas adenocarcinoma was identified in

Table 1. Overall baseline patient characteristics.

PTL	Sex (Female/ Male) (n)	Age (Me)	TNM stage			AJCC stage (n)	Histology (Adenocarcinoma) (n)
			T (n)	N (n)	M (n)		
Colon	17/3	60	T_1 – 1 T_2 – 2 T_3 – 4 T_4 – 13	N_0 – 9 N_1 – 8 N_x – 3	M_0 – 20	I – 2 II – 8 III – 10	I – 11 II – 1 III – 1 IV – 7
Sigmoid	16/3	59	T_1 – 0 T_2 – 2 T_3 – 10 T_4 – 7	N_0 – 3 N_1 – 8 N_x – 8	M_0 – 19	I – 0 II – 8 III – 11	I – 8 II – 0 III – 3 IV – 8
Rectum	13/8	61	T_1 – 0 T_2 – 5 T_3 – 14 T_4 – 2	N_0 – 9 N_1 – 5 N_x – 7	M_0 – 21	I – 0 II – 15 III – 6	I – 12 II – 0 III – 4 IV – 5

Note: PTL – Primary tumor location; TNM - Tumor, lymph nodes and metastasis staging system; AJCC – American Joint Committee on Cancer; Histology (Adenocarcinoma): I – Well-differentiated; II – Poorly differentiated; III – Low differentiated; IV – Moderate differentiated.

100% of patients. Of note, patients were classified into AJCC stages at their baseline examination, after which they were subjected to treatment and then underwent baseline PET/CT. By the time enrolled patients underwent baseline PET/CT, they had completed their treatment, had no signs of cancer or metastases, and this baseline PET/CT was considered as day 0 of the research.

Patients underwent ^{18}F-FDG PET/CT at the initial enrollment and then again at a follow-up medical examination scheduled six months or more (median 12, IQR 6–40) after the baseline examination. All images were reconstructed using dedicated workstations and software (image evaluation system Wizard). Patients' data were anonymized and de-identified before studies.

^{18}F-FDG PET/CT study protocol and image analysis

^{18}F-FDG was produced at the Republican Diagnostic Center (Nur-Sultan, Kazakhstan) and was used on the day of the study due to the ultra-short shelf life (109 minutes). The whole-body ^{18}F-FDG PET/CT images were completed using PET/CT scanner (Biograph TruePoint PET·CT, Siemens Medical Solutions USA Inc., USA) and carried out in conformity with the accepted clinical protocol of ^{18}F-FDG PET/CT examination.[20] Prior to PET/CT procedure and the corresponding ^{18}F-FDG injection, patients fasted for at least 6 hours, and the glucose serum level in all patients was <11 mmol/l. The average activity dose of the injected ^{18}F-FDG was 252.55 MBk, ranging from 132.5 to 465.3 MBk. The average effective radiation dose was 8.75 mSv, with a range from 6.8 to 17.1 mSv. CT scans were obtained following PET emission scanning. PET/CT study protocol included a topogram, a low dose CT to eliminate signal attenuation and anatomical correlation, and the collection of PET data. Duration of PET data collection depended on the patient's height and weight, but usually completed within 25–40 minutes. Once PET data were obtained, CT and PET images were reconstructed and stored in the transaxial, coronal, and sagittal slices.

Image analysis was performed using the extended Siemens workspace (Biograph TruePoint PET·CT operating manual) in a region of interest (ROI). We calculated the standardized uptake value accumulation (SUV) in VAT automatically with the software using the formula:

$$SUV = [ROI\ (MBq/g)]/[injected\ dose\ (MBq)]/[total\ body\ weight\ (g)]$$

VAT areas were identified by using predefined Hounsfield units (HU), ranging from [-70] to [-110] from background CT images. To measure the VAT activity, ROI (1.00 mm for each measured point) was divided into regions according to the topographic structure, including eight subdomains of abdominal regions (RE – epigastric region, RLH – left hypochondriac region, RRL – right lumbar region, RU – umbilical region, RLL – left lumbar region, RRI – right inguinal region, RP – hypogastric (pubic) region, RLI – left inguinal region) and pelvic cavity (P). They were located on three consecutive sections of the abdominal cavity to exclude the kidneys' extra physiological absorption of ^{18}F-FDG. We measured SUV_{max} in the axial plane for each area, and the average SUV_{max} of each area was calculated separately. All images were reconstructed in transaxial, sagittal and coronal multiplanar planes and read visually. With these functional parameters, the analysis was carried out by the status of metastatic LN lesions.

Data analysis and interpretation

The primary end-point of this analysis was SUV_{max} of selected nine locations at baseline and follow-up. Image analysis was performed by determining the maximum standardized uptake value (SUV_{max}) VAT accumulation in each abdominal and pelvic cavity point. Each measured point was 1.00 mm and varied depending on the volume of VAT of the measured area. VAT areas were identified from background CT images, and SUV_{max} was defined on PET images, including a hypermetabolic focus on ^{18}F-FDG PET/CT. We report SUV_{max} values for nine locations of the VAT, whereas the SUV_{max} at baseline and follow-up was a mean of several loci for each area with a 1-mm shift.

We first tested all variables for normality using the Kolmogorov-Smirnov test. Quantitative variables following the normal distribution pattern are presented as means (M) with the corresponding standard deviation (SD); alternatively, we reported medians with the corresponding IQR. SUV_{max} values for different locations and at different time periods (baseline or follow-up) were then compared with nonparametric tests, such as the Mann-Whitney U-test or Wilcoxon test. Because, in total, we selected nine locations to report SUV_{max} values, we tested SUV_{max} values for each location in the univariate analyses with regard to sex, primary tumor location, and other variables, using either Mann-Whitney U-test (for two groups) or Kruskall-Wallis test (for three or more groups). We also used a similar approach to compare groups depending on metastases status, including positive (pLM) patients in whom metastases were detected at a follow-up visit and negative (nLM) who showed no metastases. In such an analysis, we compared baseline SUV_{max} as a predictor. In addition, we tested age and sex as predictors of showing pLM at follow-up. Locations with significant differences between groups with regard to SUV_{max} and other tested predictors (age, sex) showing significant associations with LM status, were then tested in a logistic regression analysis, first crude, and then adjusted for other significant predictors, where we report the odds ratios (OR) of developing metastases at follow-up with the corresponding 95% confidence intervals (CI).

Finally, we applied receiver operating characteristic (ROC) curve analysis to assess the diagnostic performance of quantitative variables when predicting a categorical outcome. The optimal cut-off value of the quantitative variable was estimated using the Youden's J statistic. All statistical analyses were performed using StatTech v. 2.7.1 (StatTech LLC, Russia).

Results

There were more women in the studied group (n=46). The most prevalent primary tumor location (PTL) was the rectum (n=21), n=20 patients had the PTL in the colon, including n=6 as ascending, n=6 as descending and n=8 as transverse, whereas n=19 patients had tumor in the sigmoid, as presented in Table 2. With regard to tumor AJCC classification, most patients were classified as stage II (n=31) and III (n=27), with no patients having stage IV. At the baseline examination, the overall mean SUV_{max} was 0.80, with a significant difference in a nine-group comparison (p=0.016), whereas the highest accumulation level was found in RP (0.89) and the lowest in RLI (0.68). Sex affected the SUV_{max} in RLH (p=0.043) and RLL (p=0.048) locations, yielding higher readings in women compared to men. We also found differences in baseline SUV_{max} for colon, sigmoid and rectum in RRL (p=0.006), RU (p=0.016) and RLL (p=0.004), but not for a histological grade, TNM or AJCC stage (Table 2).[21]

At the follow-up examination of the 60 patients recruited initially, metastases developed in 16 (27%) patients, and these were classified as positive lymphatic metastasis (pLM), whereas the remaining 44 (73%) patients were classified as negative lymphatic metastasis (nLM). Such metastases location included LN of the neck, mediastinum, chest, peritoneum, retroperitoneum, and pelvis. We tested whether baseline SUV_{max} was different in those who developed metastases compared to those who did not. We found that such differences were statistically significant but not for all locations, only for RRL (1.29 vs. 0.82, p=0.032) and RU (1.00 vs. 0.74, p=0.041) (Table 3), indicative of some predictive potential of SUV_{max} in these two locations for metastasis at follow-up.

The median SUV_{max} of all locations increased from 0.8 at baseline to 0.94 at follow-up (p<0.001). We did not find a statistically significant SUV_{max} increase when considered separately in out of nine locations (Table 3), mostly because the sample size of each location was only 1/9 of the overall sample. We found the trend of SUV_{max} increase overall when stratified nLM to pLM, but it was insignificant. In addition, follow-up SUV_{max} for colon nLM equaled 0.93, with no difference compared to pLM (1.12; p=0.72). Similarly, we failed to confirm statistically significant differences of SUV_{max} when comparing nLM (0.93) with pLM (0.98) for sigmoid (p=0.62) and rectum (0.92 for nLM and 1.05 for pLM) (p=0.68).

In the univariate analysis, age and sex were not associated with metastases at follow-up (median age in nLM 59 vs. 63 years in pLM, p=0.12). We then tested whether baseline SUV_{max} of the selected two locations found to be significantly associated with metastases at follow-up, including RRL and RU, could predict metastases in the unadjusted and adjusted for age regression models. In the model adjusted for age, the OR for positive metastases at follow-up for RRL was non-significant and equaled 2.88 (95% CI 0.79; 10.70), and this model accounted for only 8% variability, whereas the OR

Table 2. Baseline patients' SUV_{max}.

Variable	n (%)	SUV_{max}								
		RE	RLH	RRL	RU	RLL	RRI	RP	RLI	P
Sex										
Female	46 (76.7)	0.83	0.81	0.88	0.85	0.90	0.79	0.91	0.74	0.89
Male	14 (23.3)	0.66	0.61	0.76	0.63	0.70	0.60	0.68	0.54	0.70
Primary tumor location										
Colon	20 (33.3)	0.93	0.79	1.08	1.07	0.93	0.92	0.96	0.74	0.89
Rectum	21 (35.0)	0.76	0.69	0.86	0.80	0.93	0.79	0.86	0.81	1.02
Sigmoid	19 (31.7)	0.67	0.61	0.74	0.62	0.78	0.58	0.75	0.59	0.67
T stage										
T_1	1 (1.7)	0.92	1.18	0.82	1.31	0.67	1.07	1.05	0.75	1.03
T_2	9 (15.0)	0.77	0.93	0.86	1.07	0.96	0.91	0.92	0.90	1.11
T_3	28 (46.7)	0.75	0.63	0.82	0.62	0.79	0.67	0.83	0.65	0.73
T_4	22 (36.7)	0.88	0.72	0.89	0.89	0.87	0.72	0.91	0.71	0.84
N stage										
N_0	21 (35.0)	0.84	0.76	0.82	0.92	0.87	0.77	0.92	0.75	0.89
N_1	21 (35.0)	0.75	0.66	0.89	0.76	0.79	0.78	0.87	0.59	0.89
N_x	18 (30.0)	0.76	0.77	0.86	0.80	0.95	0.63	0.84	0.77	0.76
M stage										
M_0	60 (100.0)	0.77	0.71	0.86	0.79	0.86	0.73	0.89	0.68	0.87
AJCC stage										
I	2 (3.3)	0.83	0.91	0.93	1.37	1.10	0.99	1.29	1.18	1.11
II	31 (51.7)	0.77	0.68	0.82	0.70	0.86	0.69	0.85	0.70	0.76
III	27 (45.0)	0.76	0.81	0.89	0.80	0.91	0.78	0.91	0.66	0.89
Histology (Adenocarcinoma)										
I	31 (51.7)	0.77	0.62	0.86	0.70	0.81	0.73	0.86	0.66	0.89
II	1 (1.7)	0.74	0.65	1.03	1.44	1.53	0.91	1.53	1.61	1.18
III	8 (13.3)	0.80	0.77	0.78	0.92	0.92	0.68	0.87	0.61	0.78
IV	20 (33.3)	0.80	0.83	0.84	0.96	0.83	0.72	1.00	0.76	0.80

Note: SUV_{max} - Maximum standardized uptake value; AJCC – American Joint Committee on Cancer; RE – Epigastric Region; RLH – Left Hypochondriac Region; RRL – Right Lumbar Region; RU – Umbilical Region; RLL – Left Lumbar Region; RRI – Right Inguinal Region; RP – Hypogastric (Pubic) Region; RLI – Left Inguinal Region; P – Pelvic Cavity.

Table 3. SUV_{max} change overall and two subgroups.

Location	Overall (n = 60)			nLM (n = 44)			pLM (n = 16)			p for B nLM vs pLM
	B	F	p	B	F	p	B	F	p	
RE	0.77	0.98	0.07	0.75	0.98	0.77	0.92	0.99	0.64	0.18
RLH	0.71	0.92	0.07	0.66	0.82	0.06	0.96	0.99	0.75	0.05
RRL	0.86	1.02	0.10	0.82	0.91	0.09	1.29	1.35	0.72	0.03
RU	0.80	0.96	0.07	0.74	0.87	0.08	1.00	1.01	0.49	0.04
RLL	0.87	1.01	0.08	0.86	0.98	0.12	0.95	1.13	0.42	0.47
RRI	0.74	0.77	0.32	0.73	0.75	0.39	0.90	0.95	0.66	0.16
RP	0.89	1.02	0.16	0.89	0.98	0.44	0.89	1.19	0.10	0.83
RLI	0.68	0.82	0.07	0.66	0.78	0.18	0.72	0.86	0.28	0.71
P	0.88	0.97	0.08	0.75	0.95	0.13	0.9	1.04	0.45	0.12
p-value	0.02	0.01		0.04	0.03		0.43	0.15		

Note: SUV_{max} - Maximum standardized uptake value; B – Baseline; F – Follow-up; pLM – positive Lymphatic Metastasis; nLM – negative Lymphatic Metastasis; RE – Epigastric Region; RLH – Left Hypochondriac Region; RRL – Right Lumbar Region; RU – Umbilical Region; RLL – Left Lumbar Region; RRI – Right Inguinal Region; RP – Hypogastric (Pubic) Region; RLI – Left Inguinal Region; P – Pelvic Cavity

for RU in a similar model adjusted for age was significant and equaled 5.42 (95% CI 1.20; 24.50), with an even greater R^2 (0.13).

Of the nine locations in which we tested SUV_{max} as a predictor of metastasis on the follow-up visit, the highest areas under the curve (AUC) were found for RLH, RRL, RU and RRI. For RLH, SUV_{max} of 0.74 yielded the greatest AUC (0.668; 95% CI 0.505 – 0.831) with quite high sensitivity (75%) and specificity (61%). Although this model was statistically significant (p=0.049) (Figure 1), we failed to identify SUV_{max} corresponding to high sensitivity (80% or above) with

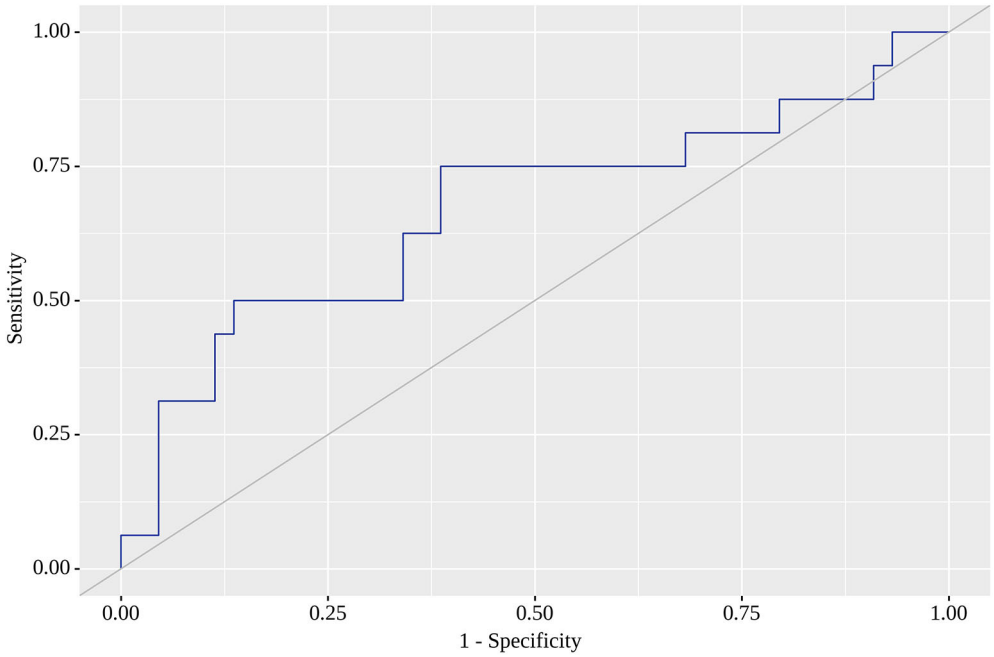

Figure 1. Receiver operating characteristic (ROC) curve showing areas under the curve (AUC) for positive outcome in left hypochondriac region (RLH).

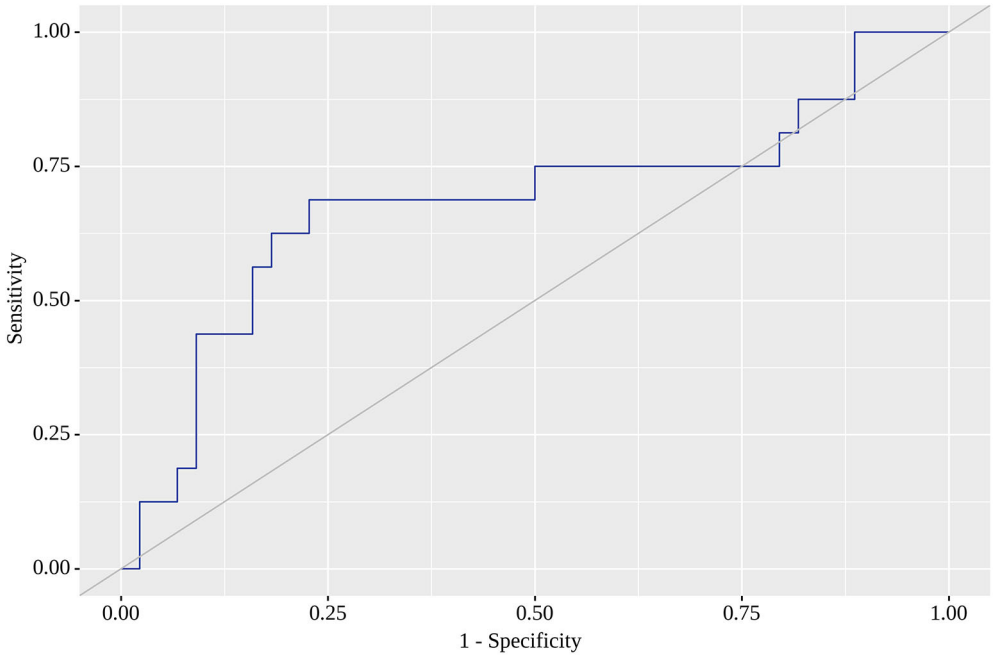

Figure 2. Receiver operating characteristic (ROC) curve characterizing positive outcome in right lumbar region (RRL).

acceptable specificity. When a high sensitivity of 80% was reached, we observed a dramatic fall in specificity. The corresponding SUV_{max} value with the highest AUC (0.682; 95% CI 0.520 – 0.843) for RRL was 1.05, for which sensitivity reached 69% and specificity was as high as 77%. This model was also statistically significant (p=0.032) (Figure 2). SUV_{max} value with the highest AUC (0.672; 95% CI 0.509 – 0.835) for RU was 0.85, for which sensitivity equaled 63% with almost similar specificity (61%). This model was also statistically significant (p=0.043), and Figure 3 illustrates AUC for this location. Finally, SUV_{max} with the highest AUC (0.679; 95% CI 0.517 – 0.841) for RRI was 0.78, for which sensitivity reached 69%, but specificity was only 61%, but statistically significant (p=0.035). Figure 4 reflects AUC for this analysis. Finally, PTL, tumor stage system, tumor grade and staging on LM did not affect SUV_{max}.

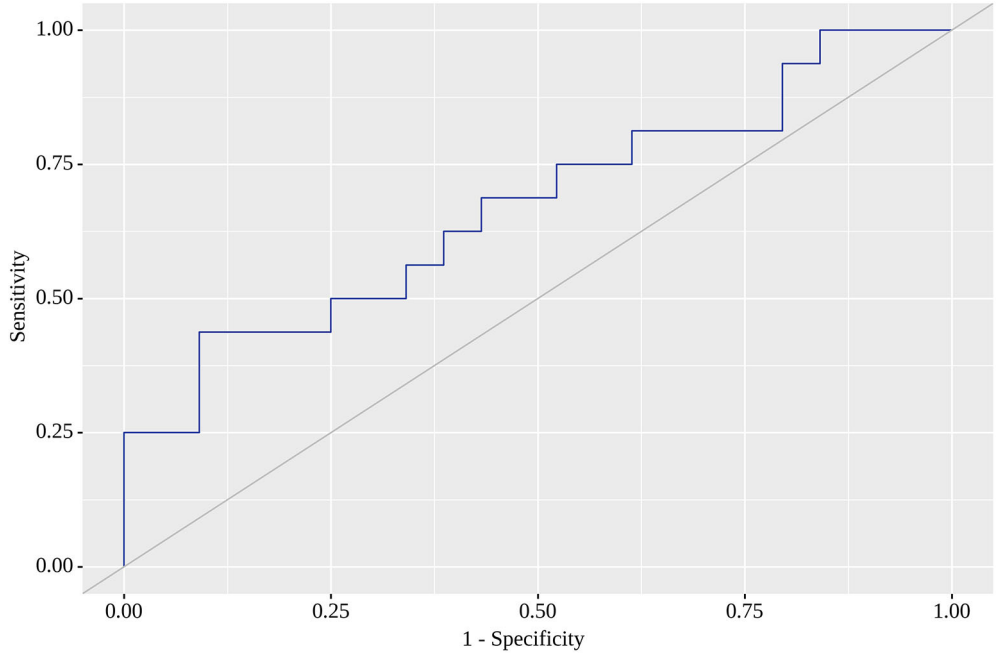

Figure 3. Receiver operating characteristic (ROC) curve showing positive outcome in umbilical region (RU).

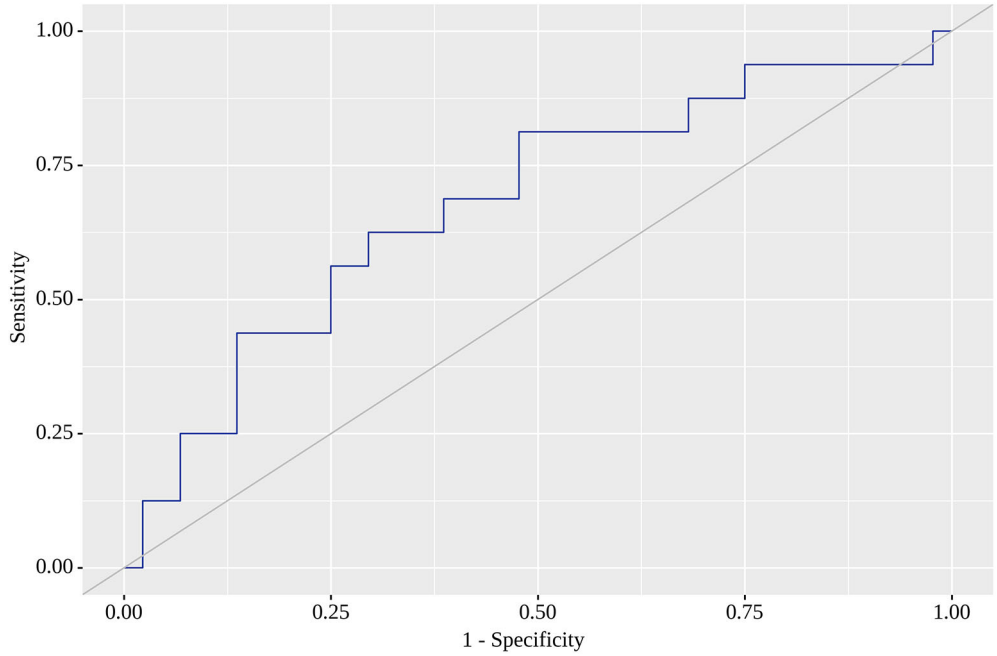

Figure 4. Receiver operating characteristic (ROC) curve characterizing positive outcome in right inguinal region (RRI).

Discussion

The current prospective observational cohort study is one of very few to identify the location of greater ^{18}F-FDG accumulation by functional VAT activity as early markers of later metastases indicative of the metastatic status of CRC patients. In a cohort of 60 patients in adjusted regression models and ROC analysis we showed that ^{18}F-FDG accumulation in RLH, RU and RRL and RRI were predictors of later metastases in CRC patients with moderate, but statistically significant sensitivity and specificity values. The threshold value of SUV_{max} 0.74 for RLH resulted in 75% sensitivity and 61% specificity, whereas the corresponding SUV_{max} for RRI was 0.78 with a sensitivity of 69% and a specificity of 61%. We also found that a threshold value of SUV_{max} 1.050 resulted in 69% sensitivity and 77% specificity for accumulation in RRL, whereas the SUV_{max} value of 0.85 warranted 63% sensitivity and 61% specificity for RU. In our analysis, ^{18}F-FDG accumulation in the remaining tested five locations was not associated with later metastases risk.

The predictive value of ^{18}F-FDG PET/CT for CRC has been reported in a number of preceding studies, reporting different SUV_{max} values. Byung Wook Choi *et al.* retrospectively emphasized the predictive value of metabolic parameters on ^{18}F-FDG PET/CT in classical rectal adenocarcinoma in 149 patients on two models (AUC 0.778 and 0.762, p=0.04; 0.814 and 0.779, p=0.83).[12] One more study by Sung Hoon Kim *et al.* retrospectively showed the prognostic value of ^{18}F-FDG PET/CT for LN metastasis in rectal cancer in 166 patients, nodal SUV_{max} 2.356, AUC 0.698 (p=0.04), 0.720 (0.033), 0.806 (p=0.04).[18] Finally, Kisoo Pahk *et al.* retrospectively showed the prognostic role of functional VAT activity evaluated by preoperative ^{18}F-FDG PET/CT for regional or distant LN metastasis in 131 CRC patients; however, the ratio of visceral to subcutaneous fat activity (VAT/SAT) was evaluated, while the ratio of SUV_{max} 1.88, AUC 0.862, sensitivity 84.6%, specificity 78.8%, p<0.001.[1] Emir Sokolović *et al.* showed the predictive metabolic value of SUV_{max} with metastatic CRC patients, and concluded that SUV_{max} could be used as a novel predictive factor of disease progression among metastatic CRC patients. Average ±SD progression-free survival with a SUV_{max} above 4.1 was 11.3±9.37 months, and a SUV_{max} below 4.1 was 19.6±12.05 months (p=0.001).[22] Esra Arslan *et al.* showed the predictive potential of ^{18}F-FDG PET/CT and KRAS mutation in CRC, where the mean SUV_{max} with primary tumor was estimated to be 21.1±9.1 (range= 6.0–47.5) and tumor mean SUV_{max} with a KRAS mutation (24.0±9.0) was found to be significantly higher than those without a KRAS mutation (17.7±8.2) (p=0.001).[23]

A number of prior reports ascertained the relationship between visceral adiposity and the prediction of CRC.[24] Nevertheless, the outcomes were versatile and did not reach consent. These analyses used CT to measure VAT volume as a surrogate marker of VAT activity. But, VAT volume is reportedly unrelated to the visceral fat inflammatory process,[25] whereas the identification of VAT volume by CT may not be satisfactory in affecting the current functional VAT activity.[5] Therefore, a functional imaging modality like ^{18}F-FDG PET/CT could be more suitable for evaluation of functional VAT activity than CT.

Previous research on functional VAT activity and ^{18}F-FDG PET/CT concentrated on systemic inflammatory diseases, such as atherosclerosis or chronic obstructive pulmonary disease.[5] Liang-qian Tong *et al.* illustrated the association between pulmonary ^{18}F-FDG metabolism and smoking history in 347 healthy adults with chronic obstructive pulmonary disease where differences in the pulmonary SUV_{max} according to smoking status were analyzed. The mean SUV_{max} of current smokers was higher than that of ex-smokers with a medium (1.03±0.14 vs 0.88±0.16) or larger tobacco burden (1.08±0.15 vs 0.89±0.11) (p=0.012, p<0.001, respectively). However, there were no differences between the mean SUV_{max} of ex-smokers (0.91±0.13) and current smokers (0.91±0.16) with a smaller tobacco burden (p=0.888). The mean SUV_{max} of ex-smokers and current smokers with less tobacco burden were both significantly higher than that of non-smokers (0.78±0.13) (p<0.001, p<0.001, respectively).[26]

This research used ^{18}F-FDG PET/CT to demonstrate the practical application of functional VAT activity for cancer disease, which can provide molecular data about inflammatory processes in CRC LM.

The current analysis has some limitations. Firstly, despite its prospective design, the study sample was limited, although patients were consecutively recruited for several years. Secondly, we could only enroll patients from a single nuclear medicine unit and only in the country's capital. However, PET/CT is not yet widely available elsewhere in the country; therefore, the current sample is comprised of patients who were forced to travel to the capital for the examination, thus, representing a population from almost the entire country. Thirdly, predictive value was evaluated for SUV_{max} only, and other crucial factors such as grade, and location of the primary tumor could not be analyzed. Further prospective research data with larger populations will be necessary to verify our outcomes.

Finally, functional VAT activity evaluated by ^{18}F-FDG PET/CT is substantially associated with LM. Furthermore, it is a useful factor for the prediction of LM. Implementing the results into practical medicine will help practitioners choose tactics and control CRC patients.

Consent

All patients provided written informed consent for the study and participation.

Data availability

Underlying data

Open Science Framework: 'Raw Underlying Data Colorectal Cancer for Predictive Value'. https://doi.org/10.17605/OSF.IO/NSZFK.[21]

This project contains the following underlying data:

- Raw Underlying Data CRC for PV.xlsx (Demographic and preparation accumulation data in the studied cohort)

Reporting guidelines

Open Science Framework: TREND checklist for 'Predictive value CRC' https://doi.org/10.17605/OSF.IO/PRM95.[19]

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Version 1

Reviewer Report 13 June 2023

https://doi.org/10.5256/f1000research.134853.r175503

✔ **Marianie Musarudin**
SCHOOL OF HEALTH SCIENCES, Universiti Sains Malaysia, Health Campus, Kelantan, Malaysia

This study highlights the potential for early LN metastases detection, by quantitatively measures the functional VAT activity using ^{18}F-FDG PET/CT. Eight subdomains of abdominal regions and pelvic cavity was included in the assessment. The study utilised ROC analysis as the statistical method.

Some clarifications needed:

1. "The average activity dose of the injected 18F-FDG was 252.55 **MBk**, ranging from 132.5 to 465.3 **MBk**." ----> Use SI unit, MBq.

2. The VAT areas were identified by using predefined HU, ranging from -70 to -110. Justify this selection with citation.

3. You have calculated the sample size. Is the sample size of 60 actually less than the estimated sample number? If yes, according to the sample size calculation, how much sample is actually needed? Some authors use a flow chart to show the study design and present the sample size and excluded sample number (with the causes).

4. Some studies considered total adipose tissue SUV (SUV_{TAT}) or relative SUV (SUV_{VAT} normalized to the SUV_{TAT}) for their analysis. Add a sentence explaining why SUV_{MAX} was used in this study.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nuclear Medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 08 December 2022

https://doi.org/10.5256/f1000research.134853.r156188

Jandos Amankulov
Department of Radiology and Nuclear Medicine, Kazakh Institute of Oncology and Radiology, Almaty, Kazakhstan

This article addresses the relationship between 18F-fluorodeoxyglucose uptake level in visceral adipose tissue (VAT) and the development of metastasis in colorectal cancer (CRC) patients. It addresses an important topic as early predictor markers of metastasis can improve the prognosis of the disease. Despite the rather small sample size noted by the authors, this study will be the beginning of further research on large samples.

However, there are a number of issues that need to be clarified/corrected:

1. Please use MBq as the unit of measurement instead of MBk.

2. Please use mmol/L as the unit of measurement instead of mmol/l, as a broader group more easily recognizes the capitalized version.

3. Many studies have extensively analyzed the effect of blood glucose levels and other confounding factors on 18F-FDG uptake in normal tissue and tumor. In your research, have you corrected the VAT SUVmax measurements based on the participant's blood glucose levels in normoglycemia?

4. The study results do not support the statement that implementation of VAT 18F-FDG uptake measurement will improve CRC patients' management. The clinical utility/usefulness of this biomarker was not assessed within this study. This hypothesis would need to be validated in other non-inferiority trials. So use "would/might help" instead of "*will help*" in the sentence "*Implementing the results into practical medicine will help practitioners choose tactics and control CRC patients*", or remove this sentence.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Radiology and Nuclear Medicine in Cancer Diagnosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.