Combined positron emission tomography / computed tomography using uptake of Fluorine 18 fluorodeoxyglucose by Lymph Nodes as prognostic factor in Colorectal Cancer

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ABSTRACT

Background: Management of colorectal cancer is rather difficult due to recurrences and metastasis. Therefore, there is a need for reliable prognostic indicators like non-invasive imaging methods.

Aim: To examine the prognostic importance of Fluorine 18 fluorodeoxyglucose uptake by lymph nodes preoperative using combined positron emission tomography / computed tomography (PET/CT) in colorectal cancer.

Methods: This prospective study included 150 adult patients with colorectal cancer. All patients were exposed to whole-body 18F-PET/CT preoperative at King Hussein Hospital/Royal Medical Services, JORDAN, from June 2015-May 2019. Tumor diameter and grade with lymph node metastasis were assessed. All patients were re-examined every 6 months if any abnormal findings were found; using 18F PET/CT.

Results: lymph nodes Standard uptake value (SUV_{LN}) of 1.3 was the cut-off point used to predict recurrence. SUV_{LN} was found to be significantly associated with tumor diameter, lymph node metastasis, and recurrence. Univariate and multivariate analyses, both demonstrated a statistically significant correlation between recurrence, SUV_{LN} and tumor grade. These were also found to be independent risk factors for recurrence. Conclusion: Preoperative SUV_{LN} was significantly correlated with recurrence and it is a significant prognostic characteristic in patients with colorectal cancer.

Keywords: prognosis; colorectal cancer; lymph nodes; Fluorine 18 fluorodeoxyglucose/ positron emission tomography / computed tomography; lymph nodes standard uptake value; recurrence.

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Introduction

Colorectal cancer is a common malignant tumor and a major health issue worldwide [(1)]. In addition, the total number of cases globally was 1.80 million, while the number of deaths due to colorectal cancer was 862,000. The main treatments for colorectal cancer are surgery and chemotherapy. Treatment management is plagued with problems like recurrence and metastasis [(2)].

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The TNM classification of the tumor predicts prognosis and determines the treatment course for colorectal cancer [3]. The rate of lymphatic metastasis is higher in colorectal cancer, which affects prognosis extensively [4]. Conventional imaging techniques can identify the lymph node metastasis and are helpful in gaining morphological information [5]. However these techniques fail to provide information about biological/functional behavior.

Currently, the most widely accepted method used to evaluate treatment response in cancer patients is change in tumor size (RECIST Criteria). According to the criteria, a decrease of at least 30% in tumor size is considered as a positive response. But measuring the morphological changes in the tumor size might not reflect the actual response in terms of patient outcomes. This may be due to the residual non-tumoral mass or the fact that imaging techniques cannot capture the therapeutic effect. Besides, newer treatments have a different mechanism of action on tumors and do not immediately show changes in tumor masses. This poses a challenge to the imaging modalities to measure the treatment response. As the anticancer therapy is getting more and more individualized, identifying and measuring an accurate response to the therapy at the earliest moment has become crucial to optimizing the treatment.

Fluorine 18 (^{18}F) fluorodeoxyglucose (FDG)–combined positron emission tomography (PET) and computed tomography (CT) is an evolving imaging technique. This technique identifies cancer cells from their increased glucose uptake and metabolism [6]. Tumor cells uptake the ^{18}F FDG during the imaging to form FDG-6-Phosphate which remains unbroken by the glycolytic pathway leading to accumulation and serves as imaging biomarker. The accumulated FDG-6-Phosphate is visualized and measured quantitatively on the PET/CT imaging scans. Thus, the ^{18}F FDG uptake is directly correlated with the viable tumor cells. Some studies demonstrated that they had lower specificity and sensitivity to identify the metastasis in early-stage colorectal cancer, compared to traditional imaging techniques like CT [7].

^{18}F-FDG PET/CT is improving the routine management plan for colorectal cancer patients by adding more visualization to the previously unknown metastases [8]. This imaging technique is employed in the post-surgical patient follow-up, to detect any residual tumor or recurrence and also, to follow-up patients undergoing systemic therapy to predict therapy response. Moreover some researchers demonstrated that FDG PET/CT is effective in identifying recurrence in patients without any clinical suspicion such as elevated CEA levels [9]. Also, some researchers have demonstrated that it is superior to conventional methods [10, 11, and 12]. Early prediction of responses can facilitate individualized and optimized treatment courses for better patient management. Furthermore, this can improve the selection of patients for more aggressive therapy.

^{18}F-FDG uptake by the tumor cell can be affected by a number of factors. Some studies in patients with lung, breast, head, neck, and esophageal cancers have established that high ^{18}FDG uptake in tumors is associated with lower survival rates [13]. In addition, some studies have demonstrated pretreatment ^{18}FDG uptake by tumor cells in patients with liver metastases is an independent prognostic factor, irrespective of the treatment used [14].

Currently, standardized uptake value (SUV) of ^{18}FDG is used as a quantitative method in PET. SUV is a quantitative analysis of ^{18}FDG uptake by the cells. It is a simple and highly reproducible method employed in PET scan. It helps practitioners evaluate patient responses to therapies when success/failure of the therapy is unclear and also to determine further treatment. The prediction capabilities have initiated many clinical studies to evaluate this imaging technique but the study results vary a lot due to differences like small sample size, patient characteristics, and strategies employed to analyze the collected data.

The effectiveness of ^{18F}F FDG SUV as a diagnostic tool in staging cancer and evaluating responses to the treatment has been assessed in various studies. Therefore, we conducted a prospective study to assess ^{18}F-FDG SUV as prognostic characteristics in patients with colorectal cancer.

This study assessed the correlation between ^{18}F-FDG uptake by lymph nodes with clinical and pathological features and whether SUV_{LN} may anticipate recurrence in colorectal cancer.

Methods

This prospective investigation enrolled 150 adult patients with adenocarcinoma colorectal cancer who planned for surgery. ^{18}F-FDG PET/CT was performed in all of the patients at the Nuclear Medicine Department, King Hussein Hospital, JORDAN, between the periods June 2015-May 2019. Informed written consent was obtained from all the included patients. The local ethical and Research Board Review Committee of the Royal Medical Services approved the study included patients had a radical resection of colorectal cancer with lymphadenectomy. Tumor diameter and grade and lymph node metastasis were assessed.

A preoperative whole-body ^{18}F-FDG PET/CT scan was preformed, with an intravenous ^{18}F-FDG, administered after fasting for 6 h and resting for 1 h. The CT was done without contrast.

Maximum standardized uptake values (SUV) for lymph nodes were recorded, and the lymph node having the highest ^{18}F uptake was selected for the analysis (peritumoral or paraaortic). All selected lymph nodes for semiquantitative analysis were more than 1.0 cm in size to avoid partial volume effect on SUV measurement.

The number of lymph nodes and metastases were recorded. Postoperatively, all patients had clinical follow-up including imaging studies every 6 months. ^{18}F-FDG PET/CT was done if the follow-up demonstrated any abnormal finding. Recurrence and metastasis were diagnosed.

Statistics

The correlation between the tumor features and recurrence were analyzed by the χ^2 test using Pearson correlation coefficient. The Kaplan–Meier method was used to determine the correlation between SUV_{LN} and recurrence. $p<0.05$ was considered to be statistically significant. The cut-off for anticipating recurrence and the optimal threshold of standard uptake value of lymph nodes were determined using univariate and multivariate analyses, respectively.

Results

A total of 150 patients (90 male and 60 female) participated in the study. The age ranged from 39 -73 years. The mean follow-up was 26 months (range 6–47 months). The mean uptake period was 45 min. In the study population, 105 patients (70 %) were well or moderately differentiated and 45 patients (30 %) were poorly differentiated. The median tumor diameter was 5.46 cm. There were 42 patients (28 %) with lymph node metastasis. Thirty patients (20%) had a recurrence (Table I).

Table I: Patients demographics and tumor characteristics related to recurrence.

		Total	Recurrence		P
Number		150	NO [120(80 %)]	YES [30 (20 %)]	
Age(yrs),mean		62	62	61	
Gender (no)	M	90	72	18	
	F	60	48	12	
Tumor diameter(median)(cm)		5.46	5.54	6.01	
Lymph node metastasis(no)	No	108	88	20	
	yes	42	32	10	
Tumor grade (No)	Well/moderate	105	89	16	<0.05
	poor	45	31	14	
SUV_{max}		3.21	2.92	4.28	<0.05

The most common location of recurrence was distant metastasis (14, 46.7%). Distant metastasis most frequently occurred in the liver (n=6) followed by lung (n=4), lymph node (n=2) and bone (n=2)]. Other recurrences were locoregional (9, 30 %) and peritoneal (7, 23.3 %) (Table II).

Table II: SUV_{LN} and location of recurrence.

Recurrence location	No (%)	SUV_{LN} (mean)
Distant metastasis	14(46.7%)	4.12
Peritoneal	7(23.3%)	3.07
Locoregional	9(30%)	4.29

No significant differences were found between colorectal cancer patients with or without recurrence irrespective of age, gender, tumor diameter or lymph node metastasis. There was a significant difference regarding SUV_{LN} and tumor grade between the groups (Table I). No significant differences were observed in SUV_{LN} of patients with distant metastasis or with peritoneal or locoregional recurrence ($p>0.05$; Table II).

SUV_{LN} of 1.3 was considered as the critical value to anticipate recurrence. Multivariate and univariate analysis both showed that SUV_{LN} and tumor grade are independent risk factors for recurrence (both $p<0.05$; Table III).

Table III: Regression analysis.

	Recurrence	**Univariate P**	**Multivariate P**
Age	More or less than 55		
Gender	M or F		
Lymph node metastasis	Yes or no		
Tumor grade	Poor or well/moderate	<0.05	<0.005

SUV_{LN}	More or less than 1.3	<0.05	<0.005

A statistically significant difference was observed in patients with SUV_{LN} > 1.3 and SUV_{LN} < 1.3 (p<0.005). Also, significant associations between SUV_{LN} and lymph node metastasis (p<0.05), tumor diameter (P<0.05), and recurrence (p<0.005) were observed (Table IV).

Table IV. SUV_{LN} profile.

			SUV_{LN}		**P**
			More than 1.3	***Less than 1.3***	
Age, yrs. (median)			63	60	
Gender(no)	**M**	90	47	43	
	F	60	34	26	
Lymph node metastasis(no)	**No**	108	62	46	<0.05
	yes	42	17	25	
Tumor grade(no)	**well/moderate**	105	58	47	
	Poor	45	17	28	

Recurrence (no)	**No**	120	71	49	<0.005
	yes	30	8	22	

Discussion

In this study, we tried to determine if lymph node metabolic activity before surgery possessed prognostic importance in colorectal cancer. Using ^{18}F-FDG PET/CT for assessing the preoperative metabolic activity of the lymph node is an evolving prognostic technique for anticipating recurrence in colorectal cancer. We studied the prognostic importance of SUV_{LN} before surgery for recurrence risk in patients with colorectal cancer who underwent a radical resection of the tumor.

A study found that ^{18}F-FDG uptake of tumors is a significant prognostic factor for anticipating recurrence in colorectal cancer patients scheduled for radical operative resection [16]. ^{18}F-FDG PET was beneficial in attaining prognostic information preoperatively. In addition, another study demonstrated that the recurrence and SUV_{LN} correlation in colorectal cancer patients pathologically indicated a node-positive disease [17]. In this study, we found that preoperative ^{18}F-FDG SUV_{LN} may anticipate the recurrence without knowing if the lymph node is positive.

Similarly, our investigation demonstrated that preoperative SUV_{LN} is positively correlated with tumor size, lymph node metastasis, and recurrence. It is an important functional marker to determine the tumor's aggressiveness and biological activity. The metabolic activity before surgery of lymph node in colorectal cancer recorded by ^{18}F-FDG PET/CT is a promising functional biomarker for anticipating recurrence before performing surgery. This might help in determining the treatment.

In early-stage malignancy, the density, diameter, and shape of the lymph nodes may not change significantly, rendering CT or MRI imprecise to determine metastatic lymph nodes. False-negative results are due to the limited spatial resolution of ^{18}F-FDG PET/CT. Therefore, preoperative SUV_{LN} in early-stage colorectal cancer is an important biomarker for anticipating recurrence. When the SUV_{LN} in colorectal cancer increased, the recurrence risk increased remarkably [18]. SUV_{LN} is an important prognostic marker before radical surgery. Early findings of recurrence could affect therapy and prognosis [19, 20].

A study has reported that the 5-year survival rate in patients with colorectal cancer with a negative ^{18}F-FDG PET/CT scan was significantly higher compared to patients with a positive ^{18}F-FDG PET/CT scan [21]. Also, another study demonstrated that the follow-up of patients with this imaging technique can predict overall survival [9].

The main limitation of our study was the small study group. Also, we have not included the factor of clinical suspicion in our study. A comparison with the number of cases with clinical suspicion based on established biomarkers of the recurrence and the recurrences predicted by the ^{18}F-FDG PET/CT may have given a better understanding of recurrence predictability of the ^{18}F-FDG PET/CT SUV. A study

demonstrated that FDG PET/CT was effective in identifying recurrence in patients without any clinical suspicion and invalidated recurrence in patients with clinical suspicion[9]. Our findings are consistent with these results demonstrating that the imaging method is effective in predicting recurrence preoperative.

Also, in our study only patients undergoing surgical resection were included; patients undergoing other treatments such as chemotherapy or radiotherapy were not included. A comparison of prognostic value of SUV with respect to the different treatment modalities might add value to the significance of prognostic value of SUV.

Another factor that should be considered while considering ^{18}F-FDG uptake by the lymph nodes as stand-alone factor is that it is affected by a number of factors that include biological (patient weight, blood glucose level, insulin, FDG uptake time, lesion size), and technical factors (variability in various scanner, calibration of scanners, differences in reconstruction methods, motion). Since this study was a single-center study, the technical factors – variability in the scanners used, its calibration and reconstruction method had no effect on the study results as a single machine was used throughout the study.

Also, the threshold SUV considered in this study was 1.3. The threshold SUV is not standardized, and hence a different threshold value might have a substantial effect on the results.

Many studies have demonstrated that SUV and tumor size correlation in NSCLC patients undergoing complete resection can identify the subgroup of those patients having a higher risk of death due to recurrence after surgery; hence, both used together serve as independent prognostic characteristics [22, 23, 24]. Similarly, the present study showed that the importance of metabolic activity of the metastases is also an important factor, indicating that intense glucose metabolism in metastases of colorectal cancer is a negative marker of prognosis. SUV is used to predict the TNM staging, appropriate patient selection for the treatment, and assess treatment response; our findings broaden the clinical utility of SUV, suggesting that preoperative SUV in patients with colorectal cancer can be used as a prognostic indicator of improved post-operative survival post-surgery.

Some researchers have reported that a weak correlation between the high value of SUVmax value in cancer patients did not necessarily indicate the presence of malignancy (25). False-negative PET findings are common, partly because the primary tumor has a high FDG uptake that blurs adjacent structures, and also because of the low PET sensitivity to microscopically involved lymph nodes. Hence, FDG PET has a high specificity (>90 %) but low sensitivity (<30 %) for regional metastases of the lymph nodes associated with colorectal cancer (26, 27). Researchers have, therefor, recommended using SUVmax along with analysis of the ROC curve analysis to get optimum results (28). Figures (1) and (2) are PET/CT images from two patients with metastatic colorectal cancer as an example of high SUV_{LN} with poor outcome (figure 1) and low SUV_{LN} with better outcome(figure 2).

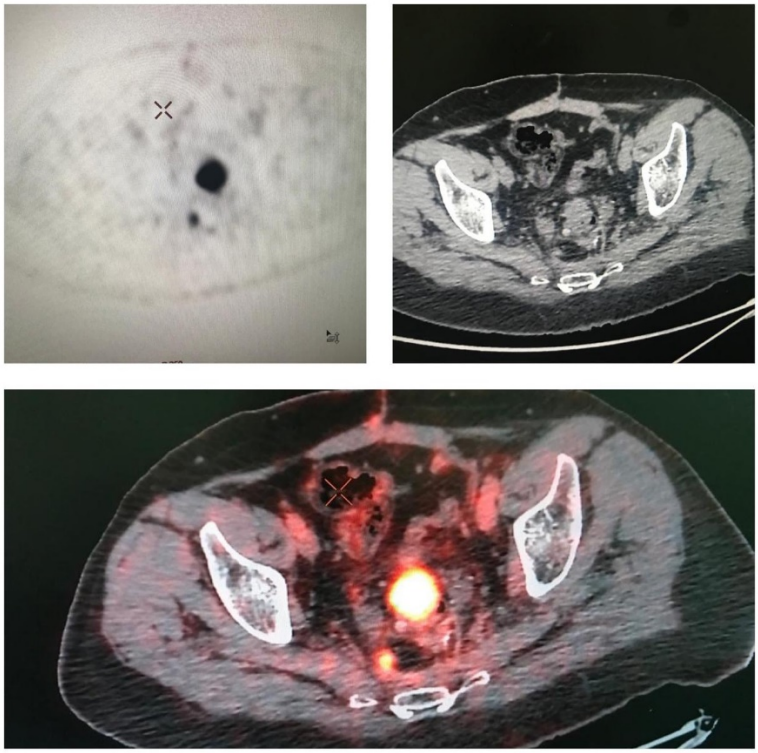

Figure (1).

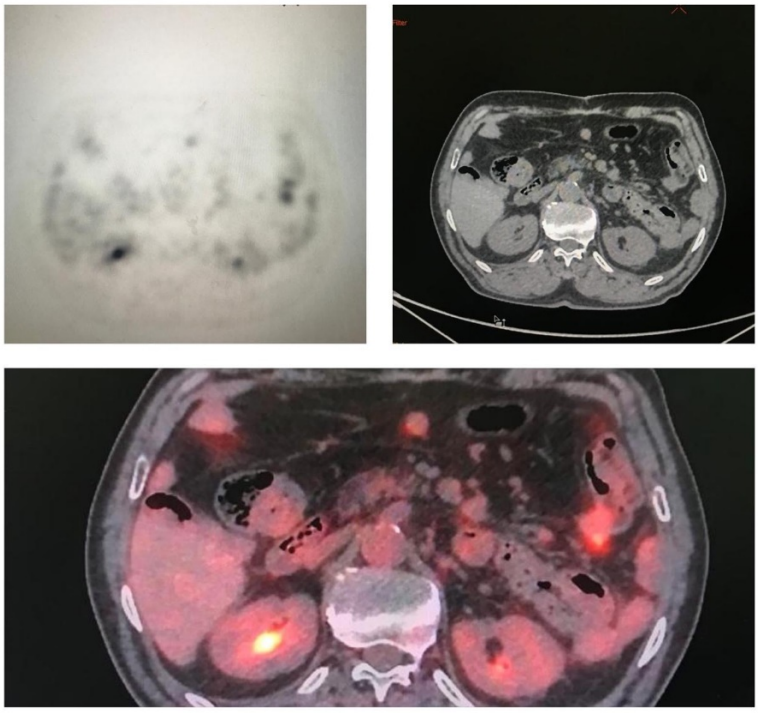

Figure (2).

Conclusion

In conclusion, preoperative SUV_{LN} significantly correlates with recurrence in colorectal cancer. Evaluation of SUV_{LN} before surgery is an important prognostic marker to recognize patients with an increased risk of colorectal cancer recurrence.

We believe that, SUV assessed using 18F-FDG PET/CT can be considered as a prognostic factor in patients with colorectal cancer to predict recurrence and optimize the course of treatment, accordingly. Our study results are expanding the clinical utility of SUV as a prognostic factor to predict recurrence in preoperative patients with colorectal cancer. We recommend larger study to include variability of treatment options, and effects of biological and technical factors on SUV. However; more studies evaluating this imaging modality as a prognostic characteristic are required.

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