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Diagnostic Accuracy of ^{18}F-FDG PET/CT in Detection of Local Recurrence in Rectal Cancer and the Added Value of Dual Time Point Scanning

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ABSTRACT:

Objectives: To assess diagnostic accuracy of FDG PET/CT and the added value of dual time point PET/CT (DTP) in detection of local recurrence (LR) in patients with rectal cancer (RC). **Methods:** Patients (n = 50, 41 males and 9 female, mean age 52 ± 11 years). All patients underwent resection ± chemotherapy and/or radiotherapy. 37 patients were suspicious for LR on contrast enhanced CT (ce CT). All patients underwent whole body FDG PET/CT scan. In 18 patients 2 hours delayed pelvic PET/CT images were done. SUVmax cut off of 3.0 was set to differentiate benign from malignant lesions based on ROC analysis. Suspicious pelvic lesions were correlated with biopsies in 28 patients (56%) and with clinical and/or imaging follow-up (FDG PET/CT, CT or MRI) in 22 patients (44%). Sensitivity, specificity, positive and negative predictive values, and accuracy in detection of LR using ce CT data and following PET/CT were calculated. **Results:** Nine patients had LR (18%). SUV max was higher in all patients with LR. Sensitivity specificity, PPV, NPV, and accuracy for detecting recurrent lesions were significantly higher for PET/CT and PET/CT with tumor markers versus ce CT ($p<0.05$). Delayed pelvic PET/CT revealed increase in delayed SUV max (ΔSUV max >0) in 4/18 patients with confirmed LR (true positive) and revealed increase in delayed SUV max (ΔSUV max >0) 4/18 with no evidences of LR (false positive) while 10/18 showed decrease in SUV max (ΔSUV max $\leq$0) in delayed images with confirmed no LR (true negative). The combined early SUVmax and delayed increase in SUVmax revealed improvement in overall accuracy compared to either parameter alone. **Conclusions:** PET/CT has an excellent sensitivity and a higher overall accuracy for detection of local rectal cancer recurrence when compared to ce CT. Delayed PET/CT when performed is capable of improving the specificity, PPV and accuracy of the PET/CT study.

Key words: FDG PET/CT- rectal cancer- local recurrence.

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INTRODUCTION:

Colorectal cancer (CRC) is the third most common cancer and the fourth most frequent cause of cancer deaths worldwide. Surgical resection is the mainstay of treatment for rectal cancer for curative intent. There are a variety of surgical options and combinations with pre-operative therapies including preoperative radiotherapy or chemo-radiotherapy, all with various levels of morbidity and mortality risk [(1)]. Local recurrence is defined as evidence of recurrent disease within the pelvis after a surgical resection, including recurrence at the site of anastomosis and perineal wound. Few studies are in the literature on loco-regional recurrence (LR) after a potentially "curative" resection of a rectal cancer because many authors mix colonic and rectal cancer and primary rectal cancer with recurrent disease [(2)]. The overall recurrence rate of CRC was 27.9%, the anastomotic recurrence rate was 11.7%, and the distant metastasis rate was 14.4%.12. The average time for recurrence was 21.3 months [(3)]. Locoregional recurrence is more common in rectal carcinoma than colonic cancer, typically in the pre-sacral region. Surgery is the main treatment with curative potential for recurrent and metastatic disease. Early diagnosis of local recurrence and small metastases is crucial, since surgery has a higher chance of success with 5 year survival rate of up to 30% in asymptomatic patients with limited disease [(4-7)]. Confirmation of recurrence of CRC has been evaluated by physical examinations, colonoscopy and conventional diagnostic imaging (CDI) such as US, CT and MRI [(8)]. However; there are several common features which limit the value of these CDI methods such as postoperative inflammatory scarring may persist for months and post irradiation changes frequently seen in the presacral space and in the muscles and may lead to an erroneous diagnosis of LR. Functional imaging using 18F-FDG PET/CT is a well-established method for the evaluation of patients with suspected CR. There are many studies in the literature compared FDG PET/CT with in carcino-embryonic antigen (CEA) measurement and contrast-enhanced abdominal computed tomography (ceCT) in the detection of colorectal cancer (CRC) recurrence. Many of these studies showed higher sensitivity, specificity, and accuracy than ce CT and CEA [(9-13)].

Our study is a retrospective comparative study in which we compared the diagnostic accuracy of FDG PET/CT, ce CT and tumor markers (CEA and/or CA19-9) in detection of rectal cancer recurrence and to evaluate the added value of DTP in detection of local rectal cancer recurrence.

PATIENTS AND METHODS:

Informed consent was not required for this retrospective analysis.

Patient Population:

50 consecutive patients with rectal cancer, 41 males and 9 female, mean age 52 ± 11 years) were retrospectively reviewed. All patients treated by resection ± chemotherapy and/or radiotherapy. All patients underwent an abdominal ce CT and whole body FDG PET/CT scans. In 18

patients 2 hours delayed (DTP: dual time point) pelvic PET/CT images were done.

PET/CT scanning

Patients fasted at least 4 hours before the tracer injection and received an intravenous injection (some patients were injected manually and the other by automatic injector) of approximately 5.18 MBq/Kg (0.14 mCi/Kg) of 18F-FDG, with a maximum of 444 MBq (12 mCi). Blood glucose level was measured immediately prior to FDG injection and was < 165 mg in all studied cases. Patients were sitting calm in a quiet injection room without talking during the subsequent 40-60 min of the FDG uptake phase. Patients were allowed to breathe normally during image acquisition without specific instructions. All scans were acquired using a Gemini TF PET/CT scanner (Philips Medical Systems). Emission data were acquired for 18-22 bed positions (identical to the CT protocol). Emission scans were acquired at 1 minutes per bed position always in 3D which may increase up to 2 or 3 minutes per bed position in case of obese patients dependent on the body mass index (BMI). The FOV was from the base of the skull to mid thigh with the arms above the head unless the patient cannot tolerate positioning the arm above the head, arms down position was used and if there was a significant truncation artifact from the arms in the pelvic region a localized PET/CT scan was done with the arms over the chest. The CT scans were used for attenuation correction purposes and to help in anatomic localization of FDG. The 3-dimentional (3D) WB acquisition parameters consisted of a 128 x 128 matrix and an 18 cm FOV with a 50% overlap.

CT scanning:

The CT scan of the PET/CT scanner consisted of a 16 slice CT. Gantry allows for a patient port of 70 cm. CT Parameters: It is a single sweep: 120–140 KV and 50–100 mAs (based on body mass index), 0.5 second per CT rotation, Pitch – 1.675:1, Slice thickness is 5mm and 512 × 512 matrix. CT acquisition was performed before emission acquisition. CT data were used for image fusion and the generation of the CT transmission map. All patients received gastrographin oral contrast in baseline PET/CT studies according the division protocol at that time for patients with gastrointestinal (GIT) cancer. In some patients who had follow-up PET/CT they received 1000 mL of water orally 30 minutes before imaging as negative contrast agent due the division protocol modification for GIT cancer patients. No IV contrast was used. Breathing technique is hold breath after normal expiration. If patient can't do it, then shallow breathing is acceptable.

Image analysis:

PET/CT scan or scans of each patient in our study population was reviewed by two nuclear medicine physician. Any suspicious lesion for local recurrence in CT or in FDG PET/CT (either FDG avid or not) were evaluated and either correlated by biopsy or follow-up FDG PET/CT or other imaging modalities (CT and/or MRI) and recorded and tabulated. Two hours delayed pelvic PET/CT was done in 18 patients out of 50 and interval changes in SUVmax (maximum standardized uptake value) were recorded. In the current study pelvic lesions were considered as local recurrence only if located at site of surgical anastomosis, perirectal or pre-secral and such lesions were analyzed as follows: *True positive (TP)* if initial SUVmax ≥3.0, increased SUV in delayed image (ΔSUV max >0) or both combined and confirmed to be malignant; *False positive (FP)* if

initial SUV max ≥3.0, ΔSUV max >0 or both combined and no evidence of malignancy on biopsy or follow up; *True negative (TN)* if initial SUV max <3.0 and/or ΔSUV max ≤0 and no evidence of malignancy on biopsy or follow up; *False negative (FN)* if initial SUV max <3.0 and/or ΔSUV max ≤0 and confirmed to be malignant. All the available non radionuclide imaging modalities such as CT and MRI were reviewed by consultant radiologist.

Statistical analysis:

Statistical analysis was performed using SPSS software (SSPS 13.0) and MedCalc (10.2.0.0). Sensitivity, specificity, positive predictive value (PPV) negative predictive value (NPV), and accuracy were calculated for the diagnostic CT and for the PET/CT study. ROC analysis is used to define the best cut off value of SUVmax to differentiate benign from malignant lesions. McNemar test was used to test the difference between paired patient proportions using different methods of stratification, namely ce CT, PET/CT or combined PET/CT and tumor markers. Comparison of differences between area under the curve AUC of the different ROC curves for different ways of stratifying patients using ce CT, PET/CT or combined PET/CT and tumor markers had been performed. Non-paired student T-test was used to compare mean difference in SUV max or ΔSUV max between patients with confirmed positive and those with negative local recurrence (LR). For statistical significance a p value of <0.05 was required.

RESULTS: The characteristics and clinical data of the study population are shown in Tables (1). Out of the 50 patients included in this study, 25 (50%) showed elevated blood levels of tumor markers (CEA ≥3.4 ug/l and/or CA19-9 ≥35 U/ml). Nine of them were confirmed to have local recurrence, associated in 6 patients with distant metastases while 8 patients had isolated distant metastases. Metastatic sites included the liver in 8 patients, lungs in 12 patients, bone in 3 patients and abdominal lymph nodes in 1 patient. **(Table1)**. Of the remaining 25 patients without elevated tumor markers none had local recurrence while only 1 patient had isolated distant metastases to the lung **(Table2)**. The sensitivity, specificity, positive, negative predictive values and accuracy of tumor markers to detect local recurrence and/or metastases are 94% (17/18), 75% (24/32), 68% (17/25), 96% (24/25) and 82 (41/50) respectively **(Table 2)**. Based on ce CT 37 patients were suspicious for having local recurrence and was able to identify 8 out of 9 patients with confirmed local recurrence with only 1 false negative, 12 true negative but with high number of false positives of 29 patients.**(Table 2)**.

Table (1): Demographic and clinical data of the study population

Study group	Study group (n=50)
Mean age (years)	52.0 ± 11.0
Males	41 (82%)
Previous surgery	50 (100%)
Prior Chemotherapy	33 (66%)
Prior Chemotherapy & Radiotherapy	20 (40%)
Prior Radiotherapy	21 (42%)
Elevated tumor markers (CEA &/or CA19-9)	25 (50%)
Distant metastases	14 (28%)
Liver Lungs Liver and Lungs Lungs and Bone Liver, Lungs and bone Lung and Abdominal LNs	2 3 5 2 1 1
Follow up:	
Biopsy	28 (56%)
CT, PET/CT or MRI	22 (44%)
Follow up time if no biopsy (months)	8.8 ± 5.2 (2-21)

Table (2): Comparison between patients with elevated tumor markers and those with non-elevated tumor markers as regards local recurrence and distant metastases.

	N	LR	DM	LR & DM	No LR or DM
Elevated Tumor Markers	25	3 (12%)	8 (32%)	6 (24%)	8 (32%)
Non-Elevated Tumor Markers	25	0	1 (4%)	0	24 (96%)

N, number; LR, local recurrence; DM, distant metastases.

Sensitivity, specificity, positive and negative predictive values and accuracy of ceCT to detect local recurrence were 88.9%, 29.3%, 21.6%, 92.3% and 40% respectively. The mean SUVmax in lesions with confirmed local recurrence was significantly higher than in those with no confirmed recurrence (5.40±2.84 vs. 2.59±1.83; $p<0.001$). Using an SUVmax cut off value of ≥3 FDG PET/CT was able to detect all 9 patients with local recurrence in which 5 of them had the lesions located in the presacral region, 2 with the lesions in the surgical anastomotic site and 2 had lesions in perirectal regions. Twenty seven patients had no significant FDG uptake

(SUVmax <3) and were considered true negative while 14 patients had high FDG activity (SUVmax ≥3) and were considered false positive based on negative biopsy that revealed either inflammatory changes or granulation tissue in 8 patients while the other 6 patients showed no evidence of malignancy on imaging follow up. Sensitivity, specificity, PPV and NPV and accuracy of FDG PET/CT (SUVmax ≥3) to detect local recurrence were 100%, 65.9%, 39.1%, 100% and 72% respectively with highly significant improvement (p=0.00031) compared to ceCT. After exclusion of 3 patients with SUVmax ≥3, high tumor markers and known distant metastases, addition of elevated tumor markers to further stratify patients together with early SUV max ≥3 resulted in again identification of all 9 patients with local recurrence though with significant reduction in the number of false positives from 11/47 to only 4/47 and significantly boosting the specificity, positive predictive value and accuracy from 71.1%, 45.0% and 76.6% to 89.5%, 69.2% and 91.5% respectively (p=0.0156) (Table 3). Comparison of ROC curves for detection of local recurrence using ce CT, FDG PET/CT as well as combined FDG PET/CT with tumor markers is show in figure 1. The area under the curve (AUC) of the ROC curve for PET/CT was significantly larger than that for ce CT (p=0.049) while the difference was highly significant when using combined PET/CT and markers versus ce CT (p=0.003) **(Table 4).**

Table (3): Comparison between different stratification methods as regards sensitivity,

	N	Sens.	Spec.	PPV	NPV	Acc.	p-value
Ce CT	50	88.9%	29.3%	21.6%	92.3%	40.0%	0.00013
Initial SUVmax≥3	50	100%	65.9%	39.1%	100%	72.0%	
Ce CT*	47	92.3%	32.3%	32.3%	92.3%	51.1%	<0.0001
Initial SUVmax≥3 + TM*	47	100%	89.5%	69.3	100%	91.5%	
Initial SUVmax≥3*	47	100%	71.1%	45.0%	100%	76.6%	0.0156

specificity, PPV, NPV and accuracy for detection of local recurrence in the entire study population.
* Three patients with isolated distant metastases and high tumor markers were excluded.

Table (4): Pairwise comparisons between AUC of the different ROC curves for ce CT, PET/CT (SUVmax≥3) and combined PET/CT (SUVmax≥3) with tumor markers.

	AUC Difference	P-value
ceCT ~ PET/CT	0.253	P = 0.049
ceCT~ PET/CT & Markers	0.345	P = 0.003
PET/CT ~ PET/CT & Markers	0.0921	P = 0.302

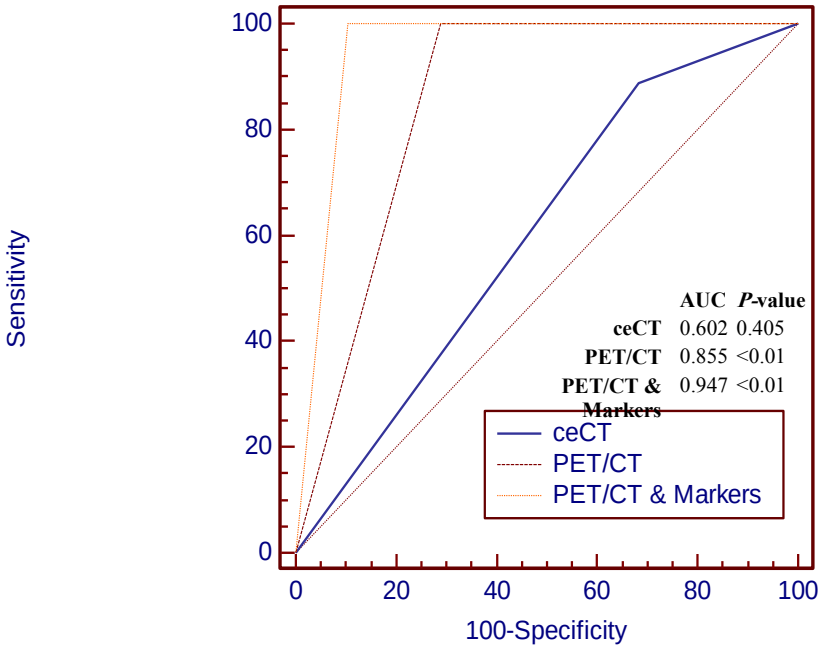

Figure (1): Pairwise comparison of ROC curves for ce CT, PET/CT (SUVmax≥3) and combined PET/CT (SUVmax≥3) with tumor markers (47 patients).

Among the subgroup of 18 patients who had delayed PET/CT images, 4 patients had confirmed local recurrence (early mean SUV max = 4.38±1.33 vs. delayed SUV max = 5.70±2.36; p=0.084) and were all identified by early images using SUV max of ≥3.

Another 4 patients had increase in delayed SUV max but no evidence of local recurrence and were considered false positive (early mean SUV max = 3.98±1.02 vs. delayed SUV max=5.35±1.42; p=0.025). The remaining 10 patients had no increase in delayed SUV max with no evidence of local recurrence and all were considered as true negative (early mean SUV max = 3.64±2.13 vs. delayed SUV max = 3.16±1.84; p=0.009). Three of these 10 patients were converted from being false positive due to SUVmax of ≥3 in early images to being true negative after no increase but actually significant decrease in delayed SUV max (early mean SUV max = 4.65±2.13 vs. delayed SUV max= 4.23±1.84; p=0.032). The change in SUV max (ΔSUV max) was significantly higher in the 4 patients with proved local rectal recurrence compared to the 14 patients with no proven recurrence (1.33 ± 1.04 vs. 0.53 ± 0.99; p<0.04). On the other hand, p value did not reach statistically significant level between both groups as regards the stand alone early SUV max (4.38 ± 1.33 vs. 3.73 ± 1.84; p=0.53) or the stand alone delayed SUV max (5.70 ± 2.36 vs. 3.79 ± 1.97; p=0.12) respectively.

Table (5): Comparison between different stratification methods as regards sensitivity, specificity, PPV, NPV and accuracy for detection of local recurrence in patients with delayed PET/CT imaging.

	N	Sens	Spec	PPV	NPV	Acc
Initial SUV max≥3	18	100%	42.9%	33.3%	100%	55.6%
ΔSUV max > 0	18	100%	71.4%	50.0%	100%	77.8%
Initial SUVmax≥3 + ΔSUV max> 0	18	100%	78.6%	57.1	100%	83.3%
	N*	Sens	Spec	PPV	NPV	Acc
Initial SUV max≥3	17	100%	46.2%	36.4%	100%	58.8%
ΔSUV max> 0	17	100%	76.9%	57.1%	100%	82.4%
Initial SUVmax≥3 + TM	17	100%	76.9%	57.1%	100%	82.4%
Initial SUVmax≥3 + ΔSUV max> 0	17	100%	84.6%	66.7	100%	88.2%
ΔSUV max> 0 + TM	17	100%	84.6%	66.7	100%	88.2%
Initial SUVmax≥3 + ΔSUV max > 0 + TM	17	100%	84.6%	66.7	100%	88.2%

*1 patient with isolated liver metastases and elevated tumor markers was excluded.

Sensitivity, specificity, positive and negative predictive values and accuracy of delayed PET/CT to detect local recurrence based on ΔSUV max > 0 were 100%, 71.4%, 50%, 100% and 77.8% respectively **(Table 5).**

Stratifying the patients using both the early SUV max ≥3.0 and increase in delayed SUV max revealed further improvement in specificity, PPV and accuracy to 78.6%, 57.1% and 91.5% respectively.

After exclusion of 1 patient with isolated hepatic metastases and elevated tumor markers, addition of tumor markers as a stratifying factor together with initial SUVmax ≥3.0 showed sensitivity, specificity, PPV, NPV and accuracy of 100%, 76.9%, 57.1%, 100% and 82.4% respectively. The same values were obtained by using the delayed increase in SUVmax alone. The sensitivity, PPV and accuracy were further improved to 84.6%, 66.7% and 88.2% by stratifying patients using combined early SUV ≥3.0 and delayed increase in SUV with no more improvement when adding tumor markers to the combined early and delayed imaging **(Table 5).**

Illustrated examples from our patient population PET/CT images to detect local rectal cancer recurrence are shown in figures **(2, 3 and 4).**

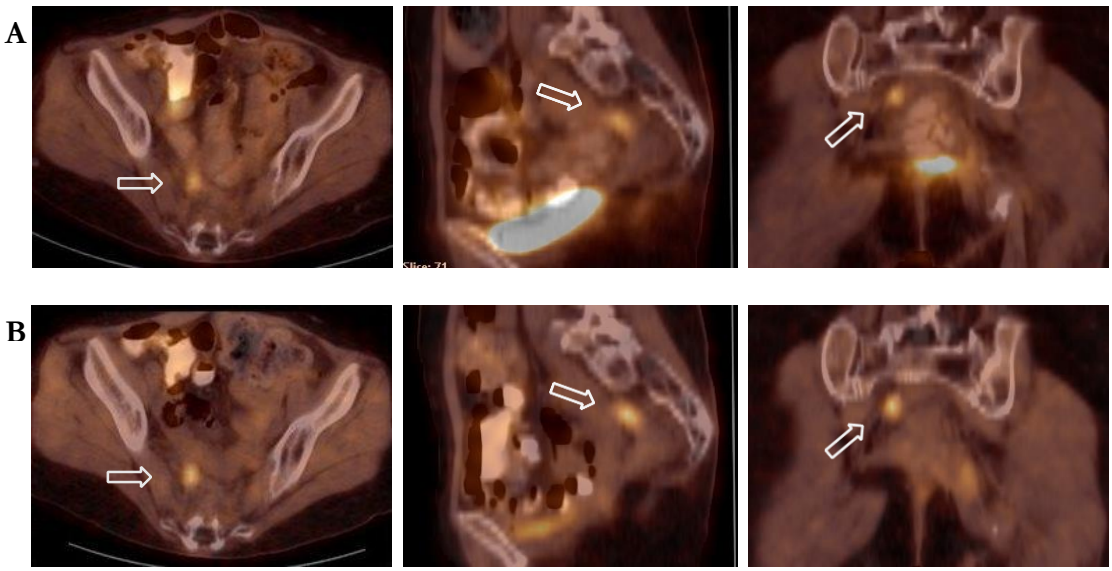

Figure (2): 52 year old female with rectal cancer, post surgery with elevated tumor marker and CT showed enhancing lesion in the pelvis, FDG PET/CT to R/O recurrent or residual: (A) Early FDG PET/CT showed focal FDG avid soft tissue density in the right presacral region with SUVmax of 3.9 that increased to 4.4 in the 2 hours delayed pelvic FDG PET/CT images (B). The lesion confirmed to be malignant on biopsy.

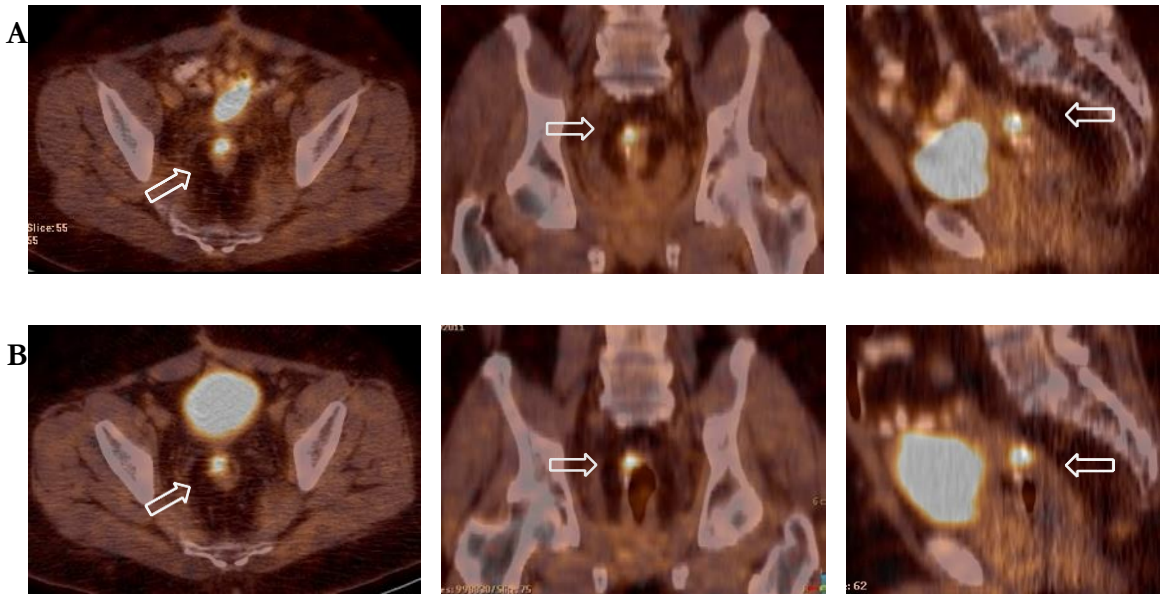

Figure (3): 51 year old male with rectal cancer, post surgery, chemotherapy and radiotherapy. (A) Early PET/CT showed FDG avid lesion in rectal anastomotic site with SUVmax of 7.6 decreased to 6.5 in the 2 hours delayed pelvic FDG PET/CT images (B). Biopsy revealed non-specific inflammatory changes.

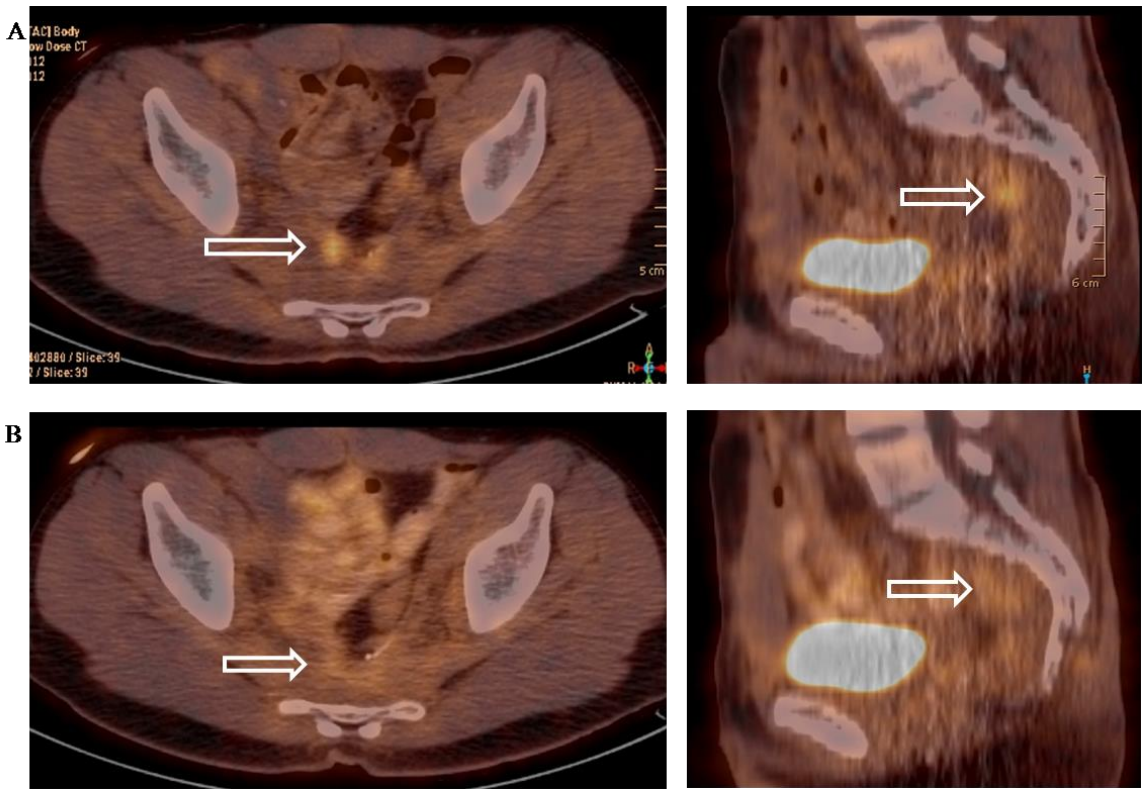

Figure (4): 56 yrs male patient with cancer rectum, post surgery and chemotherapy, CT showed perirectal soft tissue density, FDG PET/CT done to rule out recurrence. (A) Early FDG PET/CT showed heterogeneous FDG uptake in the perirectal soft tissue density with SUVmax of 4.0. (B) 2 hours delayed pelvic FDG PET/CT showed decreased in SUV max to be 2.3 in the perirectal soft tissue density. Biopsy showed inflammatory changes with no evidence of malignancy.

DISCUSSION:

Unlike colonic cancer that tend to spread to intramural, peri-visceral and mesenteric nodes, that are easily resected, rectal cancer cells tend to invade perirectal and inferior mesenteric nodes as well as adjacent structures making surgery more complicated [(14)].

While many previous studies had discussed the use of PET/CT in detection of colorectal cancer recurrence [(9-10, 15-22)], only few had emphasized its role in rectal cancer recurrence [(12-14, 21, 23)].

O'Connor mentioned that local recurrence is more common in patients with rectal rather than colon cancer ranging from 7% to 33% and 1–19%, respectively. About 20% of recurrences are local and 43% are concurrent local and distant [(24)]. In the current study, patients with local recurrence and/or distant metastases were 18/50 (36%) of the total population. Pure local recurrence was noted in 3 out of 18 patients (17%), while 6/18 patients (33%) had combined local and distant metastases and 9/18 (50%) patients had only distant metastases.

This was close to what mentioned by Brethauer et al. reporting that 54% of recurrences had distant metastases alone at the time of recurrence and 67% had distant

metastases as a component of local failure [25]. About 25% of patients with initially respectable colorectal cancer will have a recurrence within 2 years of resection [26]. As a tumor marker CEA had been the most widely studied and used for preoperative staging and follow up, in patients with colorectal cancer [15].

All patients with detected local or distant recurrence in our study had elevated CEA level except for one patient with isolated lung metastases. Moreover in 8/25 (32%) of patients who had elevated CEA, none had been confirmed to have local or distant recurrence using biopsy in 2 and on clinical and imaging follow up in the rest, despite that 5 patients of them showed enhanced FDG activity either in presacral space or around surgical bed, and such patients were treated as false positive.

According to Even et al. [23], CEA levels may detect recurrent colorectal cancer months before it can be detected on a CT scan, though its benefit to patient survival or quality of life had not been well established, likely because the lack of lesion localization. Studies established the utility of PET in identifying a source of elevated CEA in a very high fraction of patients who had negative findings on CT [23]. We believe that failure to confirm or even localize recurrent disease in some patients with elevated tumor markers could be related to inadequate follow up, histopathologic types of tumors that are less FDG avid or even inaccurate biopsy site in some patients. It had been also reported that the sensitivity of FDG-PET imaging for detection of mucinous carcinoma is significantly lower than in non-mucinous carcinoma (58% and 92%, respectively) [27], however in our study we did not perform an analysis for tumor histopathology in comparison to the FDG PET findings.

Our analysis revealed a significantly higher SUVmax in patients with confirmed local recurrence versus those with no confirmed local recurrence. The local recurrence sites were presacral in 5 patients, perirectal in 2 patients and in surgical anastomotic site in 2 patients. Such locations following surgical resection are frequently difficult to assess by CT or even MRI due to post operative fibrotic or inflammatory changes. Delbeke and coworkers found that the greatest utility of 18F-FDG-PET in evaluating colorectal carcinoma was in differentiating tumor recurrence from scar as at the site of surgical resection, which could be difficult to assess by conventional imaging modalities [15].

For detecting local rectal recurrence we found that the initial PET/CT imaging using SUVmax ≥3.0 is significantly better than ce CT with a sensitivity of 100% versus 92%, specificity of 71% versus 32% and accuracy of 77% versus 51% respectively. Several studies had reports that the FDG-PET accuracy in detecting CRC recurrence is higher than that of CT. A study by Chiwvit et al., showed that 18F-FDG-PET had an overall sensitivity of 94.4%, specificity of 66.7% and accuracy of 87.5% for recurrent colorectal cancer, with a lower values for ce CT, which had a sensitivity of 79% and a specificity of 73%.27 [9]. Ozkan et al., in a study of 69 patients reported a sensitivity and specificity of 97% and 61% respectively for 18F-FDG PET/CT compared to 51% and 61% for ce CT in the detection of disease recurrence [10]. In other study for 62 patients by Even-Sapir et al., PET/CT achieved an overall accuracy of 92% for detection of rectal recurrence [23]. Selzner et al., reported that local recurrence at the

primary colorectal resection site were detected by ce CT and PET/CT with a sensitivity of 53% and 93%, respectively (P= 0.03) and PET/CT was superior to ce CT for the detection of recurrent intrahepatic tumors most other studies as regards the relatively low specificity and PPV of FDG PET/CT for detection of local rectal recurrence except for a meta-analysis by Huebner and coworkers [21] in which 5 studies (366 patients) were considered for assessment of local/pelvic recurrence and reported both high sensitivity and specificity of 94.5% and 97.7% respectively.

We found that there is an additive value for both delayed PET/CT imaging (ΔSUV max>0) and elevated tumor markers when used to stratify patients combined with the initial SUVmax ≥3.0. The addition of tumor markers led to substantial improvement in specificity, PPV and accuracy from 71.1%, 45% and 76.6% to 81.5, 61.3 and 91.5%, respectively.

Several previous studies had studied the accuracy of PET/CT imaging in comparison to tumor markers to detect colorectal cancer recurrence, however to the best of our knowledge there is no available studies addressing their combined accuracy specifically for rectal cancer recurrence. Our results revealed a significant improvement in specificity, PPV and accuracy from 71.1%, 45.0% and 76.6% to 89.5, 69.3 and 91.5%, respectively (p=0.0156) when tumor markers were used as an additional stratifying factor in addition to the initial SUV max ≥3.0. Ozkan et al. [10], reported an improvement in specificity of 18F-FDG PET/CT from 60% to 75% when measured in patients with elevation in CEA level less than two-fold compared to those with CEA elevation less than three-fold, however there was no further improvement in specificity when measured in patients with higher CEA level. In a recent study by Panagiotidis et al. [11] F-FDG PET/CT had higher accuracy (100%) in detecting recurrent colorectal cancer only in the group of patients with elevated tumor markers? We found that by the addition of ΔSUV max >0 to the initial SUVmax ≥3.0 as a stratifying factor, there was improvement in specificity, PPV and accuracy from 46.2%, 36.4% and 55.6% to 84.6, 66.7 and 88.4%, respectively, with no improvement when tumor marker results were used as an additional stratifying factor. Multiple previous studies [29-32] have shown that DTP imaging of FDG PET are potentially helpful in differentiating malignant from benign lesions. In a study by Lan et al. [31] to assess the value of DTP imaging in 96 patients with variable types of cancers, the author reported that 54 of 59 (92%) patients with malignant lesions including 17 of 18 patients with digestive system carcinoma had early SUVmax values ≥2.5 and all lesions showed an increase in SUVmax in delayed images. They also showed an improvement in sensitivity and specificity when using delayed imaging compared to early imaging [30]. In another study to detect loco-regional breast cancer recurrence, the best diagnostic accuracy was achieved by the combined use of delayed SUVmax > 2.5 and %ΔSUV max > 0%, with an overall accuracy better than that of delayed SUV max > 2.5 alone or %ΔSUV max > 0% alone [31]. In a third study on 26 esophageal cancer patients specificity to detect metastatic lesions was improved when retention index (RI) ≧ 10% was used to supplement the early SUVmax of ≥ 2.5 [32]. On the other hand there are other studies that reported no improvement in diagnostic

accuracy by the use of delayed imaging [33-36]. In most of these studies the delayed SUVmax or RI were used separately versus the early SUVmax and not in conjunction with the early SUVmax. Furthermore some of these studies although showed no improvement in overall accuracy still demonstrated substantial improvement in specificity with the use of delayed SUVmax or RI as in the recent study by Choi et al. [36] that mentioned an improvement in specificity to detect extra hepatic cholangio-carcinoma lesions from 60% using the early SUVmax (cutoff 2.5) to 100% using the delayed SUVmax (cutoff 3.1) though with some corresponding deterioration in sensitivity from 97.6% to 88.2%.

Study Limitations:

A potential limitation point in our study are the relatively small sample size specially when it comes to the application of delayed imaging since it is only ordered by the nuclear medicine physician in selected patients when it is considered helpful in better clarifying equivocal findings or differentiating between pathologic and physiologic activity in the early images. The retrospective nature of the study is probably another potential limitation since the baseline clinical and laboratory data for some patients cannot be retrieved. A third potential limitation is the lack of histopathological gold standard in substantial portion of our patients (44%) and depending instead on follow up imaging with variable follow up imaging modalities and intervals, though the same methodology had been previously applied in multiple published studies and is probably accepted specially when the biopsy would not be clinically justified or would be questionable from the ethical or medicolegal aspects.

CONCLUSIONS:

The results of the current study suggest an excellent sensitivity and NPV of combined PET/low-dose non-enhanced CT in the detection of local recurrence in rectal cancer patients. On the other hand the FDG PET/CT specificity and PPV appear to be relatively less impressive, obviously due to the frequent false positive rate that is likely related to post-operative or inflammatory changes. The use of the combined PET/CT together with tumor markers to stratify patients, significantly improves the specificity and PPV of FDG PET/CT in detection of local recurrence. The addition of delayed imaging appears effective as well in improving the specificity and PPV regardless of tumor markers results. The correlations of PET/CT findings with tumor markers as CEA as well as the use of delayed imaging in some patients with equivocal findings in early images are both valid options whenever more confidence is needed in reporting PET/CT positive findings. We believe that the delayed PET/CT imaging to assess the change in SUV is helpful mainly in improving the specificity of the study and provides more data when compared to the interpretation of early or delayed images separately.

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