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Pitfalls and value of organ specific approach in evaluating indeterminate lesions detected on CT in colorectal cancer by [F18] FDG PET/CT

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ABSTRACT

Objective: The objective of this study is to evaluate the value of FDG PET/CT for different involved organs showing Indeterminate/ equivocal / suspicious lesions detected on IV contrasted CT during surveillance follow up for colorectal cancer.

Materials and methods: A total of 67 patients with colorectal cancer how are on regular surveillance follow up by IV contrasted CT scans revealing indeterminate lesions were studied. Subsequent FDG PET/CT evaluation was performed as a problem solving modality. PET/CT results were statistically characterized when compared to biopsy results or to follow/up results. Also Statistical parameters were calculated for each organ involved. The evaluation of all CT indeterminate lesions by FDG PET/CT showed overall sensitivity of 93%, Specificity of 81%, Negative predictive value of 94%, Positive predictive value 80% and accuracy of 87%. However in an organ specific approach the highest accuracy was for lymph nodes with results showing a 100% accuracy and the lowest accuracy was for local disease at a value of 80%. Probable explanations for the falsely characterized lesions resulting in the pitfalls seen and in the imperfect accuracy were provided.

Conclusion: Study shows that FDG PET/CT is an excellent tool in characterizing CT indeterminate lesions during surveillance of colorectal cancer, However different organs showed variable accuracy results with the highest accuracy for our study was for lymph node status (100%) and the lowest accuracy being for local disease at the original site of primary tumor (80%).

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in the world. Although CRC mortality has been progressively declining since 1990 at a rate of approximately 2.5–3% per year [1], it still remains the third most common cause of cancer death in the United States in women, and the second leading cause of death in men. It is estimated that up to 40% of patients will present with recurrence after surgical resection of the primary tumor, often within 2 years [2]. The most common sites for recurrence are the liver and the local area of the initial surgery [3].

After initial treatment by surgery and chemo-radiotherapy continued surveillance is performed [2]. The most widely used morphologic imaging modality for surveillance is IV contrasted CT of the Neck/ Chest/ Abdomen/ Pelvis [4]. It is sometimes difficult to discriminate between recurrent disease from nonmalignant benign changes, such as post-surgical scars/fibrosis, inflammatory lesions and post chemo-radiotherapy changes including radiation necrosis and fibrosis by CT. Whole Body [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is an integrated imaging modality of anatomic and functional imaging that can show metabolic changes before morphological changes are evident [5], and can successfully provide a supplementary tool in differentiating benign findings from tumor recurrence.

Prior studies reported the overall diagnosis sensitivity of [18F] FDG PET-CT to be superior to CT for the detection of recurrent and metastatic CRC and sites of metastasis in patients with increased CEA level. The two techniques had similar specificity [6,7]. Currently NCCN guidelines recommend [18F] FDG PET/CT if there is rising CEA with negative

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physical exam, colonoscopy, and surveillance CT or if there is a resectable metachronous metastasis [4]. Several studies showed a role for [18F] FDG PET/CT in patients with normal CEA levels but suspected recurrence either clinically or radiologically [8,9].

There is limited literature on the value of [18F] FDG PET/CT in CT indeterminate lesions with characterization for each specific organ during initial staging. One study for instance evaluated the role of PET/CT in characterizing indeterminate lung lesion on staging CT in colorectal cancer [10]. NCCN guidelines recommend [18F] FDG PET/CT for indeterminate lesions detected on CT or MRI [4]. Several publications discussed value of [18F] FDG PET/CT in indeterminate lesions detected on CT/MRI as a whole [8,9,11,12]. However, we believe that more research is needed to evaluate the role of [18F] FDG PET/CT in characterizing indeterminate lesions for each specific organ in colorectal cancer patients suspicious for recurrence.

In this retrospective study, we aimed to evaluate the diagnostic performance of whole body [18] F FDG PET/CT scan in characterizing organ-based CT indeterminate lesions. Commonly affected organs are the Peritoneum, Liver, Lung, Lymph nodes, and locally at site of original primary tumor (site of anastomosis). Indeterminate lesions characterized by FDG PET/CT were finally diagnosed by either tissue biopsy or clinical/radiological follow-up. We also tried to provide an explanation for the falsely characterized lesions that represent the pitfalls of this study.

2. Materials and methods

2.1. Patient selection

This is a retrospective study conducted in a single tertiary institution. Institutional IRB approval from our institution with waiver of informed consent was obtained. This study was conducted on patients diagnosed with colorectal cancer between 2012 and 2019 who are on regular surveillance for follow up. Clinical evaluation, Lab tests, and IV contrasted CT Neck/Chest/Abdomen/ Pelvis were performed. The patients selected for study were patients that were found to have indeterminate findings on the surveillance follow up IV contrasted CT exams. Further evaluation by whole body [18F] FDG PET/CT to characterize these indeterminate/equivocal/ suspicious lesions was performed. Positive or negative findings on PET images were confirmed either by tissue biopsy or radiological follow up. Follow up exams included IV contrasted CT or whole body [18F] FDG PET/CT. Follow up time ranged from 2 to 90 months with a mean of 37 months. Patients included in this study had also CEA lab levels determined during the regular surveillance follow up evaluation visits at the time of clinical or radiological suspicion of tumor recurrence. CEA lab values ranged between 0.4 and 726 ng/mL with a mean of 32 ng/mL.

2.2. Patient characteristics

Table 1 summarizes the demographic characteristics of the total 67 patients included in this study. The mean age of the patients evaluated was 60 years. Thirty eight patients [57%] were <60 years old. Twenty nine patients [43%) were >60 years old. Thirty six patients (54%) were male and thirty one patients (46%) were female. The most common histopathologic diagnosis was moderately differentiated adenocarcinoma (76%) followed by mucinous predominant adenocarcinoma (14%). The most common disease stage was stage IV (37%) followed by stage II (31%).

2.3. [18F] FDG PET/CT protocol

Per Protocol at our institution patients were fasted for 6 h prior to [18] F FDG injection. Blood Glucose was checked to ensure level was below 200 mg/dl. Images were acquired on a GE PET/CT Scanner (Discovery 600; GE Medical Systems, Milwaukee, WI) from base of the skull to mid thighs. Non contrasted CT scan for purpose of attenuation correction and anatomic localization were acquired using a 16 slice multi-detector machine. The CT parameters were (transverse 2.5-mm section thickness, 120 kVp, and 80–180 mA according to local body thickness). Scanning started approximately 60 min after injection of [18] F FDG with mean dose of 260 Mbq (7 mCi) with 3 min per bed position in a 3-D mode. PET images were reconstructed with attenuation-weighted ordered-subset expectation maximization with and without attenuation correction.

Table 1
Patient characteristics.

Characteristic	No. of patients	Percentage
Age (total 66) <60 years/ >60 years	38/ 29	57%/ 43%
Sex (total 66) male /female	36 /31	54%/ 46%
Pathology (total 66) well differentiated adenocarcinoma /moderately differentiated adenocarcinoma/ poorly differentiated adenocarcinoma/ mucinous predominant adenocarcinoma /unknown	2/ 51/ 2/ 9 /3	3%/ 76%/ 3% / 14%/ 4%
Stage (total 66)		
I	4	6%
II	21	31%
III	12	18%
IV/	25	37%
Unknown	5	8%

2.4. Statistical analysis

Indeterminate lesions detected on CT that have underwent subsequent [18F] FDG PET/CT were characterized as True Positive/True Negative/ False Positive / False Negative. Reference was made to the biopsy results obtained from the indeterminate lesions or after asserting the lesions characterization by follow up scans including IV contrasted CT or [18F] FDG PET/CT. Afterwards the Sensitivity, specificity, Negative predictive value, Positive predictive value and Accuracy were calculated for all the indeterminate lesions detected on the IV contrasted CT scan as a whole. Consequently the same parameters were calculated for each specific organ where an indeterminate lesion was detected. Organs involved included the Peritoneum/ mesentery, Liver, Lymph nodes, locally at site primary disease (anastomosis), and in the lung.

3. Results

Lesions determined as indeterminate on IV contrasted CT for different organs were characterized on subsequent whole body [18F] FDG PET/CT in reference to biopsy results (18/67 patients) or results of follow up scans (49/67 patients). Criteria of indeterminate lesions in the liver was presence of hypodense lesions with absence of prior imaging to compare to. For peritoneal deposits criteria of indeterminate lesions was presence of one or more soft tissue nodularities in the peritoneum/ mesentery. Indeterminate criteria for lymph nodes was presence of an indeterminate sized lymph node on CT. However, local thickening on CT at site of primary tumor after treatment was considered indeterminate. In addition, presence of lung nodules with no prior CT imaging was considered indeterminate. Criteria for positivity on PET/CT was presence of uptake above that of the liver in the lesions of concern. Subsequently, True positive, True Negative, False positive, and False negative results was assigned for all the lesions as a whole. In addition lesions were characterized in subsets as True Positive/True Negative/ False Positive / and False Negative for each specific organ. Organs studied included the Peritoneum/Mesentery, Liver, Lymph nodes, Local site of primary tumor (anastomosis) and in the lung (as shown in Table 2). The results show that the most common site for CT indeterminate lesions was in the liver followed by the peritoneum/mesentery and then the lymph nodes and lung. However, the least common site for CT indeterminate

Table 2
This table shows the total number of lesions in addition to the number of lesions in each specific organ with characterization of the lesions in each specific organ as true positive/ true negative/ false positive/ and false negative.

	Deposit	Liver	LN	local	lung	Total
All	12	23	11	10	11	67
True positive	6	9	3	5	5	28
True negative	5	10	8	3	4	30
False positive	1	2	0	2	2	7
False negative	0	2	0	0	0	2

lesions was locally at the site of original primary tumor (anastomosis). The criteria of true positive or false negative as determined on follow up scans was an increase in size of subsequent lesions more than 25% in size and persistence of metabolic activity. The criteria for true negative or false positive was stability, reduction in size, or resolution of metabolic activity on subsequent images in the absence of intercurrent therapy. As a whole false results represent 13% of the results (9/67) with false positive results (7/9) outnumbering false negative results (2/9) and these false results represent the pitfalls of the study.

As for peritoneal/mesenteric deposits the total number of indeterminate lesions evaluated was 12. However, the sensitivity, specificity, Positive Predictive value, Negative Predictive Value, and Accuracy were 1, 0.83, 0.83, 1, and 0.92 respectively as shown in Table 3. A total of 23 liver indeterminate lesions were evaluated. Subsequently the Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy were 0.82, 0.83, 0.82, 0.83, and 0.83 respectively as shown in Table 4. A total of 11 lymph node lesions determined as indeterminate. Subsequently, the Sensitivity, Specificity, Positive Predictive, Negative Predictive Value, and Accuracy were 1 for all statistical parameters (perfect) as shown in Table 5. A total of 10 locally indeterminate lesions were evaluated. Subsequently, the Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy were 1, 0.6, 0.71, 1, and 0.8 respectively as shown in Table 6. A total of 11 lung indeterminate nodules all above 6 mm size were evaluated. Subsequently the Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy were 1, 0.67, 0.71, 1, and 0.82 respectively as shown in Table 7.

4. Discussion

Finding indeterminate lesions on computed tomography is a dilemma that is commonly faced during staging and surveillance in colorectal cancer. The incidence of indeterminate liver lesions on CT ranges from 12.7% to 25.5% with no definite consensus on how to approach such lesions [13]. For instance, indeterminate lung lesions on staging CT for colorectal cancer ranges between 4–42 % [10]. Also, indeterminate findings may be found at site of anastomosis during surveillance warranting differentiation between post treatment changes and local recurrence of malignancy. In addition loco-regional and distant Lymph nodes may show indeterminate criteria on CT for involvement by malignancy warranting further work up. Another site where indeterminate lesions can be seen is the peritoneum/mesentery. It is estimated that 22% of colorectal cancer presented with peritoneal/mesenteric tumor deposits as shown by Nagtegaal et al. [14]. However, there are rare causes of benign lesions mimicking peritoneal deposits such as splenosis [15]. Prior study by Mohamed et al. has found whole body [18F] FDG PET/CT is an excellent modality in differentiating benign from malignant lesions in the liver [13].Whole body [18F] FDG PET/CT has been shown to be highly accurate in characterizing indeterminate lung nodules as shown by Garcia-Velloso et al. [16]. On the other hand a study by Shyn et al. showed impressive results in the role of whole body [18F] FDG PET/CT in evaluating local recurrence at the site of anastomosis and differentiating it from post treatment changes with an overall accuracy of 97.5% [17]. To our knowledge there is no data on the role of [18F] FDG PET/CT in evaluating indeterminate peritoneal/ mesenteric deposits or for indeterminate lymphadenopathy in cases where colorectal cancer recurrence is suspected. In our study the false results we detected which represent the pitfalls of the study included 2 false negative cases in the liver that were ultimately explained by the patient's receiving recent chemotherapy before imaging which blocked FDG uptake by the metastatic liver deposits as shown by follow up exams, while there was two false positive cases in the liver as evidenced by follow up exams. The first case of false positive was attributed to be due to postoperative inflammatory changes at the site of prior metastectomy (Fig. 1). The second case of false positive liver lesion was confirmed by biopsy results to represent nodular regenerative hyperplastic nodules (Fig. 2). As for the lung there were 2 false positive cases explained by being inflammatory nodules on Follow up exams (Fig. 3). However there were no false negative lesions in the lungs. As for

Table 3
Peritoneal / Mesenteric deposits statistical analysis show the sensitivity/ Specificity/ Positive predictive value / Negative Predictive Value/ and Accuracy of the lesions.

Sensitivity	1
Specificity	0.83
Positive predictive value	0.83
Negative predictive value	1
Accuracy	0.92

Table 4
Liver Lesions statistical analysis show the sensitivity/ Specificity/ Positive predictive value / Negative Predictive Value/ and Accuracy of the lesions.

Sensitivity	0.82
Specificity	0.83
Positive predictive value	0.82
Negative predictive value	0.83
Accuracy	0.83

Table 5
Lymph Node Statistical analysis show the sensitivity/ Specificity/ Positive predictive value / Negative Predictive Value/ and Accuracy of the lesions.

Sensitivity	1
Specificity	1
Positive predictive value	1
Negative predictive value	1
Accuracy	1

Table 6
Local recurrence Statistical analysis show the sensitivity/ Specificity/ Positive predictive value / Negative Predictive Value/ and Accuracy of the lesions.

Sensitivity	1
Specificity	0.6
Positive predictive value	0.71
Negative predictive value	1
Accuracy	0.8

Table 7
Lung Lesions Statistical Analysis show the sensitivity/ Specificity/ Positive predictive value / Negative Predictive Value/ and Accuracy of the lesions.

Sensitivity	1
Specificity	0.67
Positive predictive value	0.71
Negative predictive value	1
Accuracy	0.82

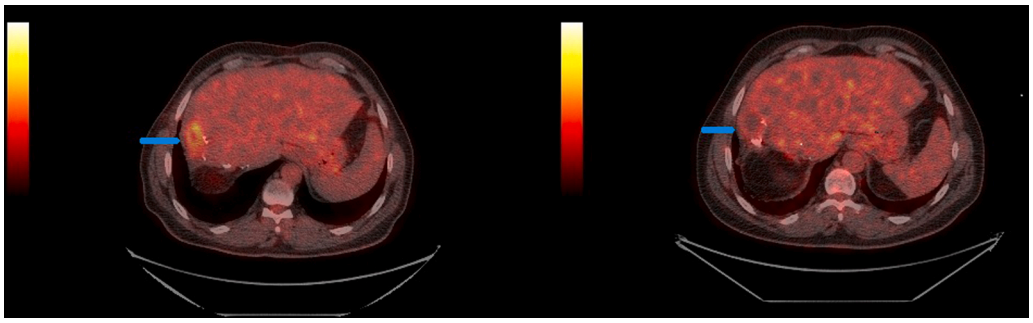

Fig. 1. 52 year old male patient with moderately differentiated adenocarcinoma of the colon with single liver metastasis status post colectomy and liver metastectomy and is on surveillance follow up for recurrence of disease with anatomic imaging showing indeterminate/equivocal/ suspicious findings at the site of the liver metastectomy. Image shows increased uptake in the liver on the post metastectomy scan at the site of prior metastectomy that was categorized as false positive due to postoperative inflammation given resolution on subsequent follow up FDG PET/CT.
A. represents image of postoperative FDG PET/CT image B. represents FDG PET/CT 2 years after follow up.

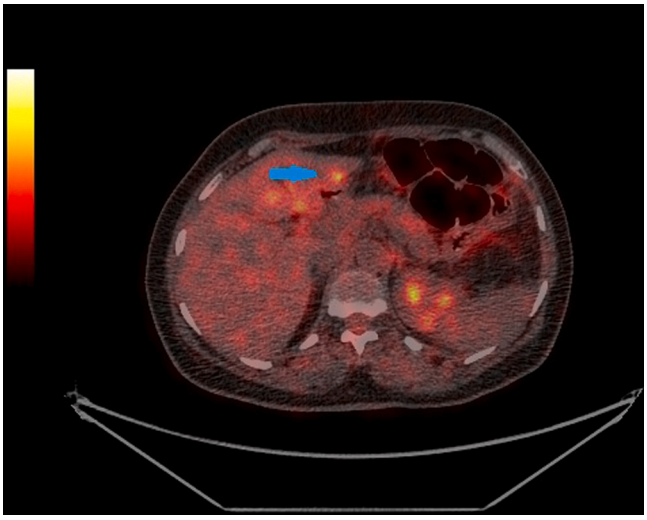

Fig. 2. 53 year old female patient with low grade to moderately differentiated adenocarcinoma of the colon found to have indeterminate/ equivocal/ suspicious lesion on anatomic follow up imaging and was evaluated by FDG PET/CT that showed high uptake in the liver lesions with subsequent surgery and biopsy of the lesions showing Nodular regenerative hyperplasia as a cause of the false positive uptake.

the local site of anastomosis there were 2 false positive results explained by post- treatment changes as evidenced by biopsy results (Fig. 4), and there were no false negative results. For peritoneal deposits our study showed that there was one false positive result that represented foreign body reaction due to glove talc reaction as evidenced by biopsy results (Fig. 5). However, there were no false negative results for the peitoneum.

The best performance for [18F] FDG PET/CT was for indeterminate lymph nodes with perfect accuracy and no false positive or false negative results. Overall the false results of this study (pitfalls) were 9/67 (13%) cases mostly representing false positive results (7/9 cases). However, only two of the nine false cases were determined to be false negative cases. Limitations of this study is that it is a retrospective, single institution study with limited number of patients. We recommend further studies regarding this topic involving larger number of patients with involvement of multiple institutions to validate the results of our study. Our study advocates using FDG PET/CT for characterizing indeterminate lesions detected on CT which would allow a more precise diagnosis in a shorter time frame.

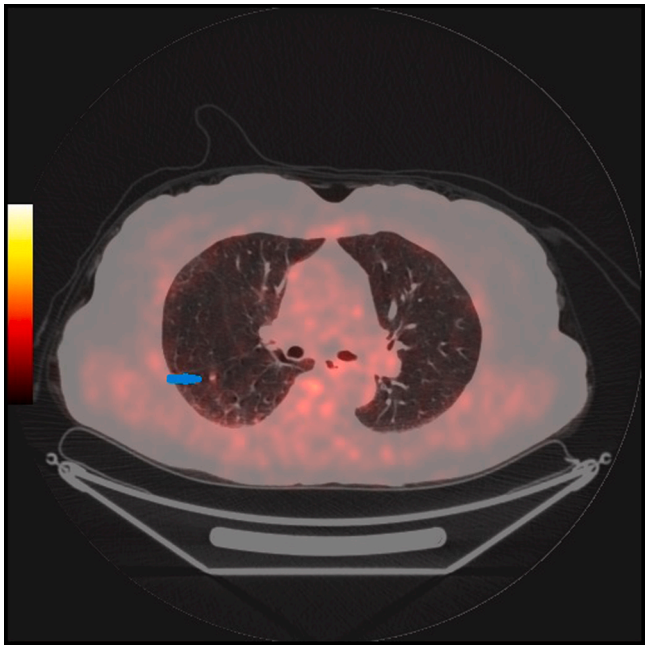

Fig. 3. 76 year old female with history of moderately differentiated adenocarcinoma of the colon and was found to have a new indeterminate/ equivocal/ suspicious lung nodule on follow-up anatomic imaging with the acquired FDG PET/CT showing increased uptake in the nodule that resolved on follow up scans and was considered a false positive lung nodule likely related to inflammatory/ infectious etiology.

5. Conclusion

[18F] FDG PET/CT is an excellent modality for characterizing CT indeterminate lesions in cases of suspicion of recurrence in colorectal cancer. Our study demonstrates very high overall accuracy. Perfect accuracy was demonstrated in the lymph nodes. Very high accuracy was demonstrated in peritoneal deposits. In addition, high accuracy in the liver, lung, and locally at site of original primary tumor (anastomosis) was demonstrated. Further studies are suggested to strengthen our findings. The pitfalls of this study (false results) were mostly false positive results largely out numbering false negative results with a ratio of 7:2.

Declaration of Competing Interests

Authors declare no conflict of interests.

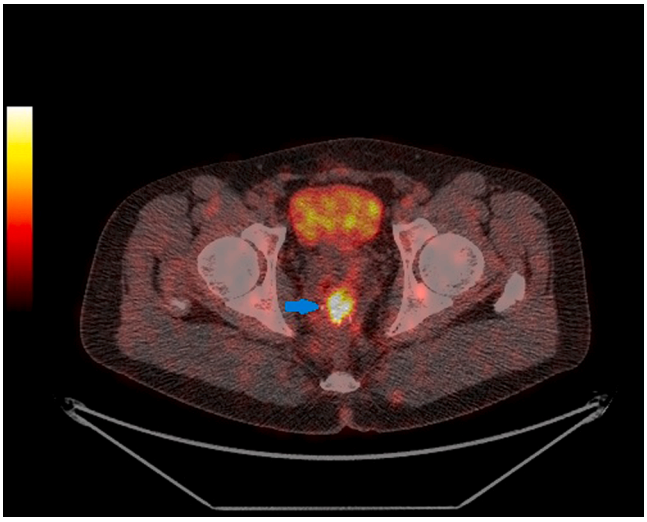

Fig. 4. 62 year old male patient with moderately differentiated adenocarcinoma of the colon with follow up anatomic imaging showing indeterminate/ equivocal/ suspicious changes at site of rectal anastomosis and subsequent FDG PET/CT showing increased uptake which was determined as false positive due to post treatment changes as shown by biopsy.

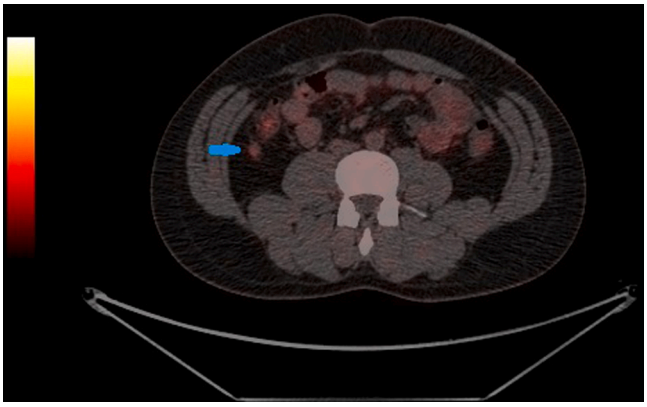

Fig. 5. 27 year old male patient with moderately differentiated adenocarcinoma with regular follow up anatomic imaging showing a indeterminate/ equivocal/ suspicious mesenteric nodule and showed increased uptake on FDG PET/CT and was determined as false positive given biopsy results showing foreign body reaction likely related to glove talc.

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