Assessment of postoperative local and distant recurrence in colorectal cancer patients: Comparison between PET/CT and CECT

Ahmed Mohamed Hussein*, Mohamed Amin Nassef1

Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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KEYWORDS
Cancer colon; 18F-FDG PET/CT; Recurrence

Abstract  Objective: To assess the diagnostic performance of 18F-FDG PET/CT scan in the detection of recurrent disease in CRC patients who have suspected local and/or distant recurrent disease compared to contrast enhanced CT scan (CECT).

Material and method: 96 CRC treated patients with suspected recurrence were examined by CECT and 18F-FDG PET/CT. Pathological results, clinical or imaging follow-up, or the responsiveness of the lesion to the treatment with chemotherapy or radiation therapy were reviewed for gold standard.

Results: Recurrent or metastatic disease was found in 74 (77.1%) of 96 patients. Calculated sensitivity, specificity, and accuracy of 18F-FDG PET/CT were 92%, 72.7%, and 88.5%. The specificity of 18F-FDG PET/CT was statistically significantly better than that of CECT as it can reduce the false positive results of CECT in 13 patients, however regarding the sensitivity.

18F-FDG PET/CT showed better value but without statistical significance.

Conclusion: 18F-FDG PET/CT is a better method to evaluate postoperative CRC patients with suspected tumor recurrence or distant metastasis than CT with significantly higher specificity.

1. Introduction

Colorectal carcinoma (CRC) is considered one of the most common types of cancer in men and women (1). About fifth of the cancer patients present with distant metastases if left untreated with a five-year survival rate of less than 10% (2).

During follow-up after primary surgery approximately 40% of patients develop local and distant recurrences (3).

Patient survival and quality of life might be improved by surgery, radiotherapy and chemotherapy; thus, early detection of recurrence is of great importance. Resection of the metast-
tases in selected patients has been reported to result in 5-year survival rates exceeding 30% (4).

Metastatic disease in colorectal cancer is most common in liver and lung, but can affect the whole body. Imaging of the whole-body is of great importance during staging to detect local or distal tumor spread and as a part of surveillance program after surgery or when a recurrence is suspected on clinical basis. Most accurate modality for whole-body staging is still unclear. Currently, computed tomography (CT) is used to detect recurrence, however having high false-negative rate for extrahepatic intra-abdominal lesions (e.g. para-aortic nodes) and a high false-positive rate for pulmonary lesions (5,6).

This disadvantage has led to the increased use of 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/CT as an imaging modality, in both preoperative assessment and during follow-up. 18F-FDG PET has presented high accuracy in the detection of recurrent and metastatic CRC (7), however, being cost-effective only in the staging of recurrent/metastatic colorectal cancers (8).

The purpose of the current study was to evaluate the diagnostic performance of 18F-FDG PET/CT scan in the detection of local or distal recurrence in suspected colorectal cancer patients compared to contrast enhanced CT scan (CECT).

2. Materials and methods

This prospective study was conducted during the period between February 2014 and September 2015 at a private Radiology centre in Cairo on 96 patients (62 males and 34 females), who were treated for colorectal cancer with suspected recurrence. Written and verbal consents were obtained from all patients as well as an agreement of the local ethics committee.

2.1. FDG-PET/CT examinations

The patients were examined from base of skull to midthigh using a Philips Gemini Time of-Flight PET/CT machine equipped with LYSO crystals (Philips, Holland). Manufacturer’s review station (Brilliance, Philips, Holland) was used to draw regions of interest (ROIs).

Table 1 Ninety-six patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61.4(42–76)</td>
</tr>
<tr>
<td>Female</td>
<td>58.6(33–81)</td>
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<tr>
<td>Primary lesions</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>55</td>
</tr>
<tr>
<td>Rectum</td>
<td>41</td>
</tr>
<tr>
<td>Indication for 18F-FDG PET/CT scan</td>
<td></td>
</tr>
<tr>
<td>Assessment of resectability</td>
<td>41</td>
</tr>
<tr>
<td>Abnormal conventional imaging</td>
<td>35</td>
</tr>
<tr>
<td>Elevated serum CEA &gt;7 ng/ml or rising</td>
<td>23</td>
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Fig. 1 Male patient with history of colon cancer and partial colectomy; Study performed on June 2014, CECT (A) showed no definite focal lesions, however the PET/CT (B) showed multiple metabolically active hepatic lesions. Follow-up study done on December 2014, CECT (C) showed small left lobe focal lesion, while the PET/CT (D) revealed predominantly disease progression with newly developed FDG avid lesions more pronouced on the left lobe.
Fig. 2  Male patient with history of cancer colon operated upon with postoperative radiotherapy and chemotherapy. (A) CECT showing sternal expansible osteolytic lesion with multiple fractures and multiple vertebral osteolytic lesions. (B) PET/CT detected metabolic activity at the sternum, C1–C3, D1–D7, D11-L5 most active at D3 and D4. (C) CECT revealed multiple enlarged para-aortic and mesenteric lymph nodes. (D) PET/CT showed metabolic activity in the detected lymph nodes with the mesenteric being the most active. (E) CECT showed multiple bilateral common iliac and external iliac LNs. The largest on the right external iliac group. (F) PET/CT detected marked metabolic activity in the iliac lymph nodes. (G) CECT showed sheet-like and nodular thickening of the pelvic peritoneal reflection. (H) PET/CT detected increased FDG uptake in the peritoneal reflections with the most active nodule seen in the midline “supra-pubic region”, from which biopsy was done and revealed its metastatic nature.
The applied tracer was 18F-FDG. It was injected intravenously (i.v.) with an aimed dose of 0.1–0.14 mCi/kg adjusted according to patient’s weight.

The patients fasted for at least 6 h before imaging and their blood glucose level was kept below 160 mg/dl at the time of tracer injection.

Uptake time from tracer injection to onset of emission scan was aimed at 60 ± 10% min.

A 64 integrated multi-slice CT machine was used to perform the standard diagnostic contrast-enhanced examinations covering the thorax, abdomen, and pelvis. Iodinated contrast agent (Omnipaque 350) was given orally: 20 mL in 500 mL bottled water (4% solution), 30 min before scan start, and i.v.: 100 mL with an injection flow of 5 mL/s immediately before scan start.

Imaging parameters: 120 kVp, 300 mAs, 512 × 512 matrix size, acquiring field of view (FOV) of 500 mm using dose automated modulation in the Z direction.

2.2. Diagnostic criteria

The diagnosis of recurrent disease was made by pathologically proven malignancy, the progression of clinical or imaging follow-up, or the responsiveness of the lesion to the treatment with chemotherapy or radiation therapy.

The diagnosis of non-recurrent disease was made by the pathologically proven benign lesion, no interval change of the lesion without treatment on follow-up imaging or no abnormal finding on follow-up imaging for more one year at least after 18F-FDG PET/CT scans.

2.3. Data interpretation

The fused PET/CT and Ce-CT images were separately interpreted by a team of one nuclear medicine physician and one radiologist with knowledge of aim of the study.

2.4. Statistical analysis

Sensitivity, specificity and accuracy of 18F-FDG PET/CT scan, compared to the gold standard (pathophysiology, clinical or imaging follow-up for at least one year) and contrast enhanced CT scan (CECT) were calculated and analyzed on patient bases and lesion bases.

Statistical significance between the two imaging modalities was calculated by McNemar, in which p-value of less than 0.05 was considered statistically significant.

3. Results

Patient characteristics and demographic data are shown in Table 1.

Recurrent disease was found in 74 patients (77.1%), of which 46 patients were pathologically proven and 28 patients demonstrated progression of disease or response to treatment on follow-up imaging (Figs. 1 and 2).

Ninety-four regions in 74 patients with recurrent disease are shown in Table 2.

We found that 18F-FDG PET/CT scan could reduce false positive result of CECT in thirteen patients (local, chest, liver and peritoneal lesions); therefore, the specificity of 18F-FDG PET/CT scan was better than CECT (p = 0.012). However, there was no significant difference between the sensitivity and the accuracy of these two modalities (p = 0.696 and 0.263) (Table 3).

18F-FDG PET/CT was falsely negative in 6 patients (Fig. 3).

Regarding the 23 patients with elevated CEA 18F-FDG PET/CT detected recurrence/metastases in 21 patients (91.3%) (Fig. 4), however one patient was missed by CECT.

There were 178 lesions detected by CECT or 18F-FDG PET/CT, 128 of which showed recurrence. 18F-FDG PET/CT scan can reduce false positive of CECT for 16 lesions (5 local recurrences, 4 intraabdominal lymph nodes, 3 peritoneal nodules, 2 pulmonary nodules and 2 liver lesions) (Table 4).

However, 18F-FDG PET/CT scan also gives false positive for nineteen lesions (5 local recurrences, 5 mediastinal lymph nodes, 5 peritoneal nodules, and 4 liver lesions).

18F-FDG PET/CT scan provided the better sensitivity, specificity, and accuracy than that of CECT but did not reach the statistical significance (Table 5).

4. Discussion

Computed tomography (CT), has an important role in the detection of early recurrence in patients with CRC, however depending on size criteria in the diagnosis of malignancy limits its reliability. Though the larger the mass the more likely to be malignant, yet some benign masses composed by fibrous tissue tend to reach large sizes.

Inability to differentiate viable from nonviable tumor lesion is another drawback. 18F-FDG PET/CT has an important role in the detection of local and distant recurrence and in the differentiation of malignant and non-malignant masses, by cellular glucose metabolism detection (9).
In the present study recurrent disease was found in 77.1% of the patients, while in the previous study by Chiewvit et al. (9) 75% of the patients had disease recurrence.

In our study we found that 18F-FDG PET/CT scan could reduce false positive results of CECT in thirteen patients; therefore, the specificity of 18F-FDG PET/CT scan was better than CECT \( (p = 0.012) \). However, there was no significant difference between the sensitivity and the accuracy of these two modalities \( (p = 0.696 \text{ and } 0.263) \).

Maas et al. (10) in their meta-analysis found that PET/CT has a high diagnostic performance with an area under curve (AUC) of 0.94. CT had a significantly lower diagnostic performance than PET/CT with an AUC of 0.83. PET/CT was the most accurate modality utilizing metabolic imaging.

Fig. 3  70 years old male patient with history of colorectal cancer, underwent surgical excision. Known to have polycythaemia rubra vera. Study done on January 2015; (A) CECT showed a tiny left upper lobe subpleural nodule. (B) PET/CT detected no metabolic activity in the nodule. (C) CECT showed small peritoneal nodule lateral to the enlarged spleen. (D) PET/CT no metabolic activity in the nodule. Follow-up study done on June 2015; (E) CECT showed increased size of the nodule. (F) PET/CT detected increased metabolic activity in the nodule which was not detected in the previous study. (G) CECT showed increased size of the peritoneal nodule. (H) PET/CT detected increased metabolic activity in the nodule. Thus the PET/CT missed the pulmonary and peritoneal nodules in the previous study.
Fig. 4  72 years old female patient with history of cancer colon, underwent partial colectomy and chemotherapeutic treatment, and the patient reported previous hysterectomy. (A) CECT showed bulky non-homogenous uterine cervix stump seen protruding into the fluid filled distended vagina. (B) PET/CT detected increased metabolic activity at the stump as well as the lower anal canal with no CT correlate. Biopsy was done and revealed local recurrence.

Table 4  CECT and 18F-FDG PET/CT result for recurrence by lesion-based analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Lesion based analysis ($n = 178$)</th>
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<tbody>
<tr>
<td></td>
<td>Positive by golden standard</td>
</tr>
<tr>
<td>18F FDG PET/CT</td>
<td>Positive 113</td>
</tr>
<tr>
<td></td>
<td>Negative 15</td>
</tr>
<tr>
<td>CECT</td>
<td>Positive 99</td>
</tr>
<tr>
<td></td>
<td>Negative 29</td>
</tr>
</tbody>
</table>

Fig. 5  A 54-year-old female patient with history of cancer rectum underwent surgical excision. (A) CECT showed mural thickening with few diverticular outpouching along the recto-colic anastomosis with associated pre-sacral and left para rectal soft tissue sheet and edema. (B) PET/CT detected increased FDG uptake is seen along recto-colic anastomosis, pre-sacral and left para rectal soft tissue. Biopsy was performed and revealed postoperative changes with no malignancy.
techniques that provide information on the nature of a lesion based on differences in glucose metabolism. The metabolic changes precede the morphological changes (examined by CT), giving the higher sensitivity for PET/CT for detection of small malignant lesions.

Meta-analysis data of 11 articles by Huebner et al. (11) found overall sensitivity of 97% and an overall specificity of 76% for 18F-FDG PET in the detecting recurrent CRC throughout the whole body altering the patient management in about 30% of cases.

In the study by Lee et al. (12) on postoperative patients with suspected recurrence, 107 suspicious recurrent lesions were detected in the 63 cases examined by 18F-FDG PET/CT. The result showed that the overall sensitivity, specificity and accuracy were 94.7%, 86.4%, and 92.4% for PET/CT, and 98.2%, 4.5 and 72.2% for conventional imaging.

CT had a lower diagnostic performance than PET/CT. The cause may be that the accuracy of CT for extraperitoneal metastasis detection is lower than that of PET/CT. CT is known to be more accurate in the detection of hepatic being less sensitive for extraperitoneal metastases, making it less ideal for whole-body staging. Studies have shown that with respect to the detection of extraperitoneal lesions CT performs worse with sensitivities ranging between 50%–70% and specificities ranging between 50%–80% compared to PET/CT having sensitivities ranging between 70%–100% and specificities ranging between 40%–100% (13).

In a study by Stückle et al. (14) with multislice CT acknowledged the low sensitivity (38–82%) for local recurrence detection.

In our current study 18F-FDG PET/CT detected recurrence/metastases in 21 patients (91.3%) of the 23 patients with elevated CEA while one patient was missed by CECT. The previous study by Metser et al. (15) included 158 patients who had a history of CRC, elevated or increasing CEA levels. The sensitivities of PET/CT and CT for patient base were 97.3% and 70.3% (p = 0.002) and that the specificities for patient base were 94.4% and 94.4% (p = 1.0). The tumor site-based analysis showed the sensitivities of PET/CT and MDCT were 98.1% and 66.7% (p < 0.0001) and the specificities were 75% and 62.5% (p = 0.56). The specificity in Metser U study by PET/CT and CT was higher than our study. The study by Mittal et al. (16) analyzed histopathologically proven patients with CRC.

After treatment in relation to CEA, PET/CT was 100% positive in cases that had CEA level of more than 50 ng/ml.

In the study by Chen et al. (17) in 56 recurrence and/or metastasis CRC patients, PET/CT had a sensitivity of 94.6%, and a specificity of 83.3% for recurrence/metastases, detecting one or more occult malignant lesions in eight cases where abdominal/pelvic CT showed negative findings. Furthermore, it detected more lesions than CT did about 30% of cases. Recurrence and/or metastasis were detected in about 90% of cases with elevated serum CEA levels by 18F-FDG PET/CT imaging.

In the study by Choi et al. (18) 269 CRC patients were operated for colorectal cancer, and PET/CT detected more lesions than conventional imaging in local recurrence and peritoneal carcinomatosis, however detecting the same number of lesions in abdominal lymph nodes and hepatic metastases.

5. Conclusion

PET-CT has significant role in the assessment of patients with CRC, detecting previously unrecognized sites of metastatic disease.

This study demonstrates that, when undertaken in selected colorectal cancer patients, 18F-FDG-PET/CT imaging provides useful information and has a considerable impact on disease management in a significant proportion of patients avoiding unnecessary surgeries, enabling the identification of recurrent disease as early as possible enabling curative surgery for the patient.

18F-FDG PET/CT is a better method to evaluate postoperative CRC patients with suspected tumor recurrence or distant metastasis than CT with significantly higher specificity.

Conflict of interest

The authors declare that there are no conflict of interest.

References

(8) Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, et al. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorec-

| Table 5 Diagnostic performance of CECT compared with 18F-FDG PET/CT by patient based analysis and lesion based analysis. |
|-----------------|-----------------|-----------------|
| Sensitivity     | Specificity     | Accuracy        |
| Study by patient based analysis |                 |                 |
| 18F FDG PET/CT  | 92%             | 72.7%           | 88.5%          |
| CECT            | 87.8%           | 13.6%           | 70.8%          |
| p-value         | 0.696           | 0.012           | 0.263          |
| Study by lesion based analysis |                 |                 |
| 18F FDG PET/CT  | 88.3%           | 67.4%           | 64.1%          |
| CECT            | 77.3%           | 30%             | 80.9%          |
| p-value         | 0.188           | 0.085           | 0.998          |

The authors declare that there are no conflict of interest.


