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ORIGINAL ARTICLE **CME**

Accuracy of ^{18}F-fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography for Detection of Recurrent or Metastatic Colorectal Carcinoma in Patients with Rising Carcinoembryonic Antigen Levels

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ABSTRACT

Objective: *A rise in carcinoembryonic antigen level is commonly encountered during follow-up of patients with colorectal carcinoma. This study aimed to evaluate the diagnostic performance of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) studies for detection of recurrent or metastatic colorectal carcinoma in patients with rising carcinoembryonic antigen levels.*

Methods: *Patients with colorectal carcinoma in clinical remission with rising carcinoembryonic antigen levels who underwent PET/CT in Prince of Wales Hospital, Hong Kong from 2008 to 2011 were included. Patient demographics, carcinoembryonic antigen levels, and clinical follow-up data were recorded. Outcomes were determined by histopathological findings or at least 12-month follow-up.*

Results: *Forty-two PET/CT studies of 37 patients (16 men and 21 women; mean [standard deviation] age, 65.8 [11.6] years) were included. Carcinoembryonic antigen levels ranged from 1.8 to 45 µg/l (9 patients had normal carcinoembryonic antigen levels of <5 µg/l, but serial carcinoembryonic antigen measurements showed a rising trend). Among the 42 events, 23 (55%) had a positive final diagnosis. The sensitivity, specificity, and positive and negative predictive values of PET/CT for recurrence or metastases were 91.3%, 89.5%, 91.3%, and 89.5%.*

Conclusion: *^{18}F-FDG PET/CT is a useful imaging modality to evaluate recurrence or metastases in patients with colorectal carcinoma in clinical remission but showing rising carcinoembryonic antigen levels.*

Key Words: *Carcinoembryonic antigen; Colorectal neoplasms; Positron-emission tomography; Tomography, X-ray computed; Whole body imaging*

中文摘要

使用^{18}F-脱氧葡萄糖正電子發射斷層掃描／電腦斷層掃描為癌胚抗原水平上升的結直腸癌患者檢測腫瘤復發或轉移的準確度

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目的：癌胚抗原（CEA）水平上升常出現於結直腸癌患者隨訪期間。本研究針對CEA水平上升的結直腸癌患者，評估使用^{18}F-脱氧葡萄糖正電子發射斷層掃描／電腦斷層掃描（^{18}F - FDG PET / CT）診

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斷腫瘤復發或轉移的表現。

方法：2008至2011年期間於香港威爾斯親王醫院接受^{18}F - FDG PET / CT掃描，臨床症狀緩解而CEA水平上升的結直腸癌患者被列入研究範圍。本研究記錄病人的人口學資料、CEA水平和臨床隨訪資料。由組織病理學發現或至少12個月的隨訪來決定結果。

結果：37名患者的42次PET / CT掃描納入研究，包括16名男性和21名女性，平均年齡65.8歲（標準差11.6歲）。患者的CEA水平介乎1.8至45 μg/l（其中9例為5 μg/l以下，屬正常水平，但連續檢測呈上升趨勢）。42例中，23例（55%）最終診斷為陽性。PET / CT對復發或轉移結直腸癌的敏感性、特異性、陽性和陰性預測值分別為91.3%、89.5%、91.3%和89.5%。

結論：對於臨床緩解但CEA水平上升的結直腸癌患者，^{18}F - FDG PET / CT是評估腫瘤復發或轉移的有效成像工具。

INTRODUCTION

Carcinoembryonic antigen (CEA) is a tumour marker routinely used in the surveillance of patients with colorectal carcinoma. The American Society of Clinical Oncology, in their 2006 update, recommended the use of CEA levels for monitoring colorectal cancer patients postoperatively as well as for metastatic disease.[1] CEA has been shown to correlate with tumour load.[2] A persistently raised CEA level therefore would increase suspicion for recurrent or metastatic disease and would warrant disease re-staging.[1] Various imaging modalities and clinical examinations, such as colonoscopy and contrast-enhanced computed tomography (CT), are available for evaluation of this commonly seen clinical situation. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT has been increasingly employed as a staging tool in initial management of malignancies, and also in disease re-staging and monitoring of treatment response.

There have been few studies investigating the use of PET/CT in evaluating recurrent colorectal cancer in postoperative patients,[3-8] but they have shown high sensitivity and specificity of PET/CT in detecting recurrence and/or metastases. The studies included patients with elevated CEA levels who had been treated for primary colorectal carcinoma or who were clinically suspected to have recurrence or metastasis. However, the post-treatment disease status of the patients was not specified in these studies. The current study aimed to evaluate a specific group of colorectal cancer patients who were in clinical remission, but had rising CEA levels.

METHODS

Patients

The PET/CT database at the Prince of Wales Hospital was retrospectively searched for studies performed from January 2008 to October 2011. Inclusion criteria were: treated primary colorectal carcinoma, clinical remission, and rising CEA level during clinical surveillance. Patients in clinical remission had received primary treatment with curative intent, had no evidence of residual disease clinically or radiologically on completion of treatment, and normal CEA level (reference range, <5.0 μg/l). Patients were excluded when the duration of follow-up was less than 12 months.

During the study period, ^{18}F-FDG PET/CT studies were retrospectively analysed. Patients' demographics, CEA levels, and clinical follow-up data were recorded. The final outcome was determined by histopathological studies, or at least 12 months of clinical follow-up when histological studies were not performed. The decision as to whether more invasive investigations were carried out to obtain histological proof depended on multiple factors, including the general health of the patients, their acceptance of invasive tests, disease status, and life expectancy. When histological studies were not performed, patients were closely followed up by various means of monitoring — including further radiological follow-up scans, clinical examination, and blood tests — to determine the disease status.

^{18}F-fluorodeoxyglucose Whole-body Positron Emission Tomography/Computed Tomography

Patient preparation included fasting for 6 hours, and blood glucose level test prior to radiotracer injection. A blood glucose level of <11 mmol/l was accepted. Patients were then given ^{18}F-FDG 10 mCi (370 MBq) via intravenous injection, and rested in an isolated room for 45 to 60 minutes before the scan. Scanning was performed with the Gemini GXL PET/CT scanner

(Philips Medical Systems International BV, Best, The Netherlands), with a covering vertex to below knee level. The brain was also included in scanning because brain metastasis, if present, would significantly alter the subsequent clinical management. First, plain low-dose CT was done with the incorporated 16-slice multidetector CT (MDCT) scanner (Philips Medical Systems International BV) using parameters of 140 kV, 30 mA, and slice thickness of 2 mm, followed by PET acquisition. The scan area was covered by approximately 13 bed positions (depending on the patients' build), each consisting a length of 180 mm, and was counted in 90-second segments. The image data were processed using a dedicated workstation (Philips Medical Systems International BV). The PET data were reconstructed into 4-mm slice thicknesses in a 256 x 256 matrix, and displayed with multiplanar reconstruction.

Image Interpretation

The PET/CT studies were reported by six dedicated radiologists (with 2 to 5 years of experience in PET/CT reporting) who were aware of the rising CEA levels and had full access to the patients' clinical information. The PET images with and without attenuation correction, low-dose CT images, and PET/CT fusion images were utilised for interpretation. Anatomical correlation was made with the image obtained from low-dose CT. Visual assessment and semi-quantitative assessment were made by measuring the maximum standardised uptake value (SUV_{max}) and were used for image interpretation. All the sites with abnormal ^{18}F-FDG uptake were recorded and graded as pathological, equivocal, or benign. In general, lesions with SUV_{max} of ≥2.5 were regarded as pathological. A delayed scan was performed when there were equivocal findings such as increased ^{18}F-FDG uptake without focal mass or a suspicious lesion with low SUV_{max}. A rise in SUV_{max} would be taken as suggestive of a pathological lesion, while a plateau or decrease in SUV_{max} would suggest a benign lesion. A delayed high-count scan of the liver was performed to detect hepatic metastases when the initial whole-body scan was equivocal. The PET/CT study was regarded as positive when the findings provided an explanation for the rising CEA level, including evidence of recurrence, metastases, or identification of a second primary malignancy. Otherwise, the study would be regarded as negative.

Data Analysis

Each PET/CT study was evaluated independently as a single event for its accuracy to account for the rise in CEA level. The PET/CT findings were compared with the gold standards of histopathology or at least 12 months of clinical follow-up. True positive (TP) study was confirmed by histopathological findings, or clinical / imaging follow-up showing disease progression when histological study was not available. True negative (TN) study was confirmed by negative histological findings, or absence of progression on follow-up. False positive (FP) study was defined as a positive PET/CT study, but negative histopathological findings or resolution on subsequent imaging / clinical follow-up without treatment. False negative (FN) was defined as a negative PET/CT scan that was subsequently confirmed as recurrence/metastases on follow-up.

Carcinoembryonic Antigen Level

The serial CEA levels were recorded. An increasing CEA level when compared with the post-treatment baseline was required as an inclusion criterion. When the CEA level showed a fluctuating trend, two consecutive readings higher than the baseline level were considered as a rising trend. The CEA level taken immediately before the PET/CT scan was used for analysis. The increase in CEA level was calculated as the difference between the CEA levels at the time of the PET/CT scan and the lowest post-treatment level within 1 year before the scan.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (Mac version 20.0; SPSS Inc, Chicago [IL], US). Sensitivity, specificity, and positive and negative predictive values were calculated based on the TP, TN, FP, and FN results. Mann-Whitney *U* test was used to compare the differences in CEA levels and rise in CEA levels between the groups with positive and negative final outcomes. Spearman's rank correlation coefficient was used to test for correlation between levels of CEA and SUV_{max} of lesions. Statistical significance was established when $p < 0.05$.

RESULTS

Patients' Demographics

Forty-two ^{18}F-FDG PET/CT scans of 37 patients (16 men, 21 women; mean ± standard deviation [SD] age, 65.8 ± 11.6 years) were included. PET/CT scan was the first imaging evaluation in this group of patients. Five patients had more than one scan performed for persistently rising CEA levels during the study period.

The time interval between the repeated scans was 2.5 to 13.0 months. Of the 37 patients, 36 (97%) had undergone resection of the primary tumour and one (3%) patient with stage IV disease at diagnosis was treated with radical chemotherapy. The initial staging of the patients was as follows: stage I (n = 1; 3%), stage II (n = 8; 22%), stage III (n = 24; 65%), and stage IV (n = 3; 8%). The staging for one (3%) patient who had colon cancer treated 20 years prior to the PET/CT scan was missing. All patients were in clinical remission and under surveillance with regular monitoring of CEA levels. The mean (± SD) duration of clinical remission was 32.0 ± 51.1 months.

Event-based Analysis

Among the 42 PET/CT scans, 23 (55%) had a positive final diagnosis by the gold standard, while no causes were identified for the rising CEA levels for the rest. In 16 (38%) events, the final diagnoses were determined by histopathological studies, and at least 12 months of clinical / radiological follow-up was used as the gold standard for the rest (62%) of the events. Table 1 shows the PET/CT findings correlating with final diagnoses of the events. Based on the 42 studies, sensitivity of 91.3%, specificity of 89.5%, positive predictive value of 91.3%, and negative predictive value of 89.5% were obtained.

Table 1. ^{18}F-fluorodeoxyglucose PET/CT scan correlation with final outcomes.

	PET/CT positive	PET/CT negative	Total
Final outcome positive	21	2	23
Final outcome negative	2	17	19
Total	23	19	42

Abbreviation: PET/CT = positron emission tomography/computed tomography.

The time interval between the latest CEA level and PEC/CT scan ranged from 0 to 48 days (mean, 17.4 days). The CEA levels at the time of PET/CT scan ranged from 1.8 to 45.0 μg/l (mean, 10.8 ± 9.8 μg/l) and the increase in CEA levels ranged from 0.8 to 41.9 μg/l (mean, 7.1 ± 9.1 μg/l). When compared with the negative outcome group, the positive outcome group had significantly higher CEA levels at the time of PET/CT scan (14.0 ± 12.0 μg/l vs. 6.8 ± 3.5 μg/l; p = 0.012) and higher increases in CEA levels (10.2 ± 11.3 μg/l vs. 3.3 ± 2.3 μg/l; p = 0.009). There was no significant difference in the duration of clinical remission between the positive- and negative-outcome groups (23.5 vs. 36.1 months; p = 0.760). No significant correlation was demonstrated between CEA levels and highest SUV_{max} (ϱ = 0.079, p = 0.719). In nine events, the CEA levels were within normal range (<5 μg/L) before the PET scan, but the CEA levels were rising and four had positive final outcomes. All the positive and negative events were correctly identified by PET/CT scans.

Of the 42 PET/CT scans, the scan was delayed for eight because the initial whole-body scan showed equivocal findings. Six of the delayed scans suggested the presence of metastatic or recurrent disease, although one was later confirmed to be falsely positive (patient 3 in Table 2). The other two delayed scans refuted the initial suspicion of pathological lesions. Two delayed high-count scans of the liver detected FDG-avid liver metastases, which were not apparent on the initial scan. In one of the patients, the delayed high-count scan of the liver detected one extra liver metastasis when compared with the contrast-enhanced CT additionally requested by the referring clinician (Figure).

Five patients had repeat PET/CT scans because of continued rising CEA levels. In four patients, the scans

Table 2. Summary of the patients with false-negative and false-positive ^{18}F-FDG PET/CT scans.

Patient No.	Age (years)	Sex	Primary malignancy	Rise in CEA level (μg/l)	PET/CT findings	Final outcome	FP/FN
1	82	F	Colon	2.4 → 11.0	No ^{18}F-FDG–avid lesion identified	Continued rise in CEA level to 67 μg/l*; died a few months after the scan	FN
2	46	F	Colon	10.0 → 21.0	No ^{18}F-FDG–avid lesion identified	Continued rise in CEA level, PET/CT 4 months later showed nodal relapse	FN
3	63	F	Colon	2.8 → 6.4	^{18}F-FDG uptake at anastomotic site	Biopsy at anastomotic site negative	FP
4	61	F	Colon	3.3 → 5.0	^{18}F-FDG uptake at anastomotic site	Biopsy at anastomotic site negative	FP

Abbreviations: ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; CEA = carcinoembryonic antigen; FN = false negative; FP = false positive; PET/CT = positron emission tomography/computed tomography.
* The initial rise in CEA was from 2.4 to 11 μg/l, but the scan was negative. On subsequent follow-up, the CEA further increased to 67 μg/l.

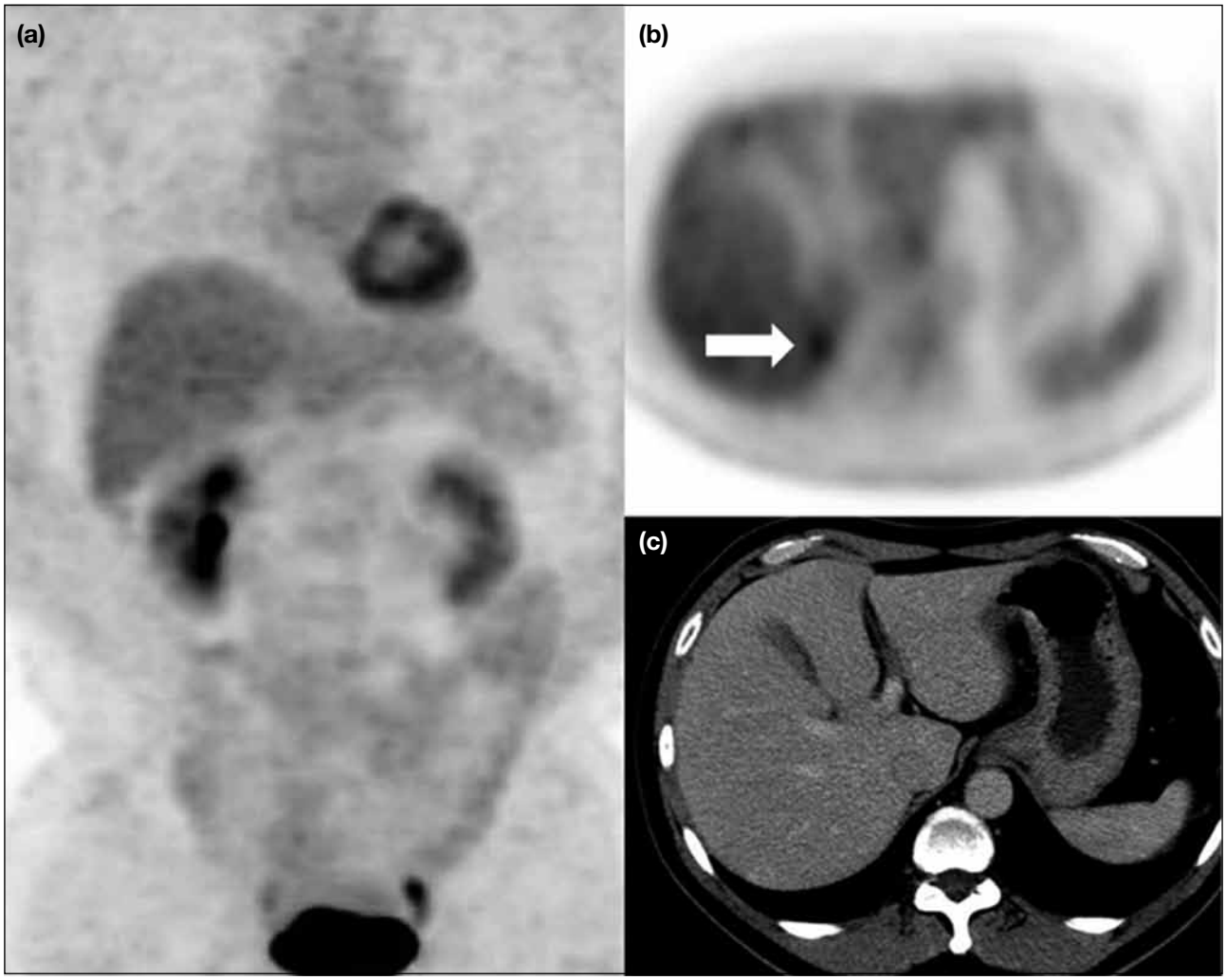

Figure. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scans of a 64-year-old man with colon cancer and rising carcinoembryonic antigen levels from 3.9 to 6.0 μg/l. (a) A maximum intensity projection image of the whole body does not show suspicious uptake in the liver region; (b) delayed high-count scan of the liver shows a few foci of ^{18}F–FDG-avid lesions suggestive of liver metastases. The lesion shown by the white arrow is not detected on (c) contrast-enhanced computed tomography.

remained negative, and were proven to be TN scans on follow-up. In one patient, the second scan, which was performed 5 months after the initial scan, depicted a new peritoneal nodule, which was subsequently proven to be a metastatic nodule on histopathological examination.

One female patient with a known malignant colonic polyp presented with CEA levels rising from 1.4 to 5.2 μg/l. PET/CT scan revealed an unsuspected second primary malignancy of the lung with nodal and bone metastases. She received chemotherapy and radiotherapy, and finally died after a few months of therapy.

There were two FP and two FN scans in this study. The details are listed in Table 2. In one patient (Patient 1) with a FN scan, there were no subsequent histological or imaging studies to confirm the recurrence as the patient was frail and unable to undergo further investigation. However, the continual rise in CEA levels (to 67 μg/l) and the patient's clinical deterioration were strongly suggestive of recurrence.

DISCUSSION

Results in the current study demonstrated a high sensitivity and specificity of PET/CT scan in detecting recurrence and / or metastatic disease in patients with colorectal carcinoma, who were in clinical remission,

and with rising CEA levels on follow-up. The high accuracy of PET/CT scan in this study was comparable with other studies evaluating postoperative patients.[3-8] In a meta-analysis by Maas et al,[9] it was shown that PET/CT scan was an accurate modality for whole-body imaging to detect recurrent colorectal cancer. In this study, nine patients had rising CEA levels, which were still within the normal limit (<5 μg/l). Even though the CEA levels were not high, four (44.4%) patients were found to have recurrent or metastatic disease. Although we were not able to suggest a cut-off value for CEA at which PET/CT should be performed, our results suggest that even with relatively low but rising CEA levels, patients could have recurrent or metastatic disease that could be detected by PET/CT.

Eight of the PET/CT scans were delayed, which were helpful for confirming or refuting the initial equivocal lesions, although one result was falsely positive, which was related to anastomotic site uptake. The increase in ^{18}F-FDG uptake of the anastomotic site is often a diagnostic dilemma as local inflammation or post-treatment changes could demonstrate SUV_{max} overlapping with that of local recurrence.[10] This finding should therefore be interpreted with caution. Correlation with colonoscopy and biopsy findings would be necessary to establish the correct diagnosis.

In this series, two delayed high-count scans of the liver were performed for detection of hepatic metastases. An extrahepatic metastatic lesion was detected by PET/CT scan, which was not seen on the contrast-enhanced CT scan (Figure). It has been shown that use of a delayed PET/CT scan could improve detection of liver lesions.[11] A delayed high-count scan of the liver is a potentially helpful and sensitive tool to detect early metastatic liver lesions, which do not yet show on contrast-enhanced CT. Detection of more than one metastatic liver lesion has an impact on patient management, since solitary liver metastasis can be treated by surgical resection, while alternative treatment would be used when multiple lesions are present.

Metser et al[12] showed that PET/CT had higher sensitivity for detecting recurrence and metastases than 64-slice MDCT, while the specificity was similar. The impact of PET/CT on patient management was assessed by Kalff et al[13] and Mittal et al[3] in which 56% and 55% of the management plans were changed according to the PET and PET/CT results, respectively, regardless of the CT results. Together with our results, this suggests that PET/CT is a useful investigation for evaluating colorectal cancer in patients with rising CEA levels as it is an accurate imaging modality and aids in clinical decision-making.

The major limitation of this study was its retrospective design and patient selection bias. Histopathological confirmation was only available for 38% of the events, and 12-month clinical follow-up was used as the outcome measurement for the rest. The relatively low percentage of histological results was likely to be related to the poor general health of patients with recurrence or metastases. A 12-month follow-up period was chosen for the study as it was considered sufficiently long to determine the accuracy of the PET/CT scan findings. With longer follow-up, the chance of newly developed recurrence or metastases would increase, rendering it difficult to match them to an initially negative scan. This study was not blinded as the interpreting radiologists were aware of the patients' rising CEA levels as this was stated on the PET/CT requests. There was also mild variation in scanning techniques and decisions on use of delayed scans based on the experience of the reporting radiologists. The number of PET/CT scans was also limited. Further studies with a larger number of patients, standardised scanning protocol, and double-blind review would be needed for more thorough evaluation of the impact and role of PET/CT scan in this selected group of patients.

This study demonstrated that PET/CT is a useful imaging modality in evaluating patients with colorectal carcinoma in clinical remission with rising CEA levels. PET/CT had high sensitivity and specificity for this indication, even in patients with CEA levels within the normal limits. Furthermore, the whole-body imaging protocol can be more cost-effective and time saving in clinical management than regional imaging.

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