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Selective Use of ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography and Computed Tomography in the Management of Metastatic Disease from Colorectal Cancer

Results from a regional centre

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الاستعمال الانتقائي للتصوير المقطعي ذو الانبعاث البيزوتروني المستخدم لمادة فلورو ديوكسي جلكوز والتصوير المقطعي في معالجة المرض المنتشر من سرطان القولون والمستقيم

نتائج مركز إقليمي

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ABSTRACT: ***Objectives:*** Computed tomography (CT) scans are routinely used for primary staging and disease surveillance in patients with colorectal cancer. However, these scans have limited sensitivity in some organs and can only detect lesions with morphological changes, whereas ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) scans are able to detect areas of metabolic change before morphological changes appear. The aim of this study was to evaluate the impact of ^{18}F-FDG-PET/CT scans over conventional imaging during preoperative work-ups or follow-ups in a selected group of patients. ***Methods:*** This retrospective cohort study, which took place between July 2009 and May 2011, assessed 1,043 patient records from the South East Scotland Cancer Network colorectal cancer database. A total of 102 patients who underwent ^{18}F-FDG-PET/CT scans in addition to conventional imaging were included in the study. These patients had potentially resectable metastases, equivocal findings on CT scans and elevated carcinoembryonic antigen levels with negative conventional imaging. ***Results:*** Of the 102 patients included in the study, 22 underwent a preoperative ^{18}F-FDG-PET/CT scan and 80 underwent a follow-up 18F-FDG-PET/CT scan. In the preoperative scan group, the ^{18}F-FDG-PET/CT scan had a major impact on 16 patients (72.75%) and no impact on six patients (27.25%). In the follow-up scan group, the ^{18}F-FDG-PET/CT scan had a major impact on 51 (63.75%), a minor impact on four (5%), no impact on 22 (27.5%) and a negative impact on three (3.75%) patients. ***Conclusion:*** The results of this study demonstrated that ^{18}F-FDG-PET/CT scans have a considerable effect on disease management when undertaken among indicated colorectal cancer patients.

Keywords: 18F Fluorodeoxyglucose; Positron Emission Tomography; Colorectal Cancer; Metastases; Cancer Staging; Recurrence; Carcinoembryonic Antigen; United Kingdom.

الملخص: الهدف: تستخدم فحوصات التصوير المقطعي (CT) روتينيا في التحديد الأولي لمرض سرطان القولون والمستقيم، وفي مراقبة المرضى ومتابعتهم غير أن هذه الفحوصات محدودة الحساسية في بعض الأعضاء، ولا يمكنها الكشف عن الإصابات والأذى إلا في الأعضاء التي حدثت فيها بالفعل تغيرات مورفولوجية. وعلى العكس من ذلك، فإن فحوصات التصوير المقطعي ذو الانبعاث البيزوتروني المستخدم لمادة فلورو ديوكسي جلكوز (^{18}F-FDG-PET/CT) يمكنها الكشف عن مناطق الجسم التي حدثت فيها تغيرات أيضية قبل ظهور تغيرات مورفولوجية فيها. وغرض هذه الدراسة هو تقييم تأثير ومزايا فحوصات ^{18}F-FDG-PET/CT على الفحوصات التقليدية في مرحلة التشخيص قبل العملية، أو متابعة ذلك التأثير عند مجموعة مختارة من المرضى. **الطريقة:** تمت هذه الدراسة الاستعادية بين يوليو 2009 ومايو 2011م ملفات بمراجعة ملفات مجموعة بها 1,043 مريضا في قاعدة بيانات مرض سرطان القولون والمستقيم في شبكة السرطان في جنوب شرق اسكتلندا. وشملت الدراسة أيضا متابعة حالة 102 مريضا من هؤلاء الذين خضعوا لفحص بالتصوير بـ ^{18}F-FDG-PET/CT بالإضافة للفحوص التقليدية. وكان أولئك المرضى لديهم انتشار في السرطان قابل للإزالة الجراحية، وكانت نتائج فحصهم بـ CT ملتبسة، ولديهم أيضا تركيزات مرتفعة من مستضدات سرطانية مضغية عند فحصهم بالطرق التقليدية. **النتائج:** قبل العملية، تم عمل فحوصات بواسطة ^{18}F-FDG-PET/CT في 22 من المرضى في هذه الدراسة (وعددهم 102)، وتمت متابعة حالات 80 منهم بعد فحصهم بواسطة ^{18}F-FDG-PET/CT. ووجد أنه كان هنالك تأثير لذلك الفحص عند 16 مريضا (أي ما نسبته 72.75%)، بينما لم يكن للفحص أي تأثير عند ستة مرضى (أي بنسبة 27.25%). وفي المجموعة التي تمت متابعتها بعد العملية كان لفحص CT/

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18F-FDG-PET تأثير مهم في 51 مريضا (أي ما نسبته 63.75%)، وتأثير قليل عند أربعة مرضى (أي ما نسبته 5%)، وعند 22 مريضا (أي ما نسبته 27.5%) لم يكن هنالك أي تأثير. ووجد أن لذلك الفحص تأثيرا ضار في ثلاثة مرضى (3.75%). **الخلاصة:** أوضحت الدراسة أن فحوصات 18F-FDG-PET/CT لها أثر كبير في معالجة مرض سرطان القولون والمستقيم عندما تجرى في أعداد كبيرة من المرضى المحددين.

مفتاح الكلمات: التصوير المقطعي؛ التصوير المقطعي ذو الانبعاث البيزوتروني المستخدم لمادة فلورو ديوكسي جلكوز؛ سرطان القولون والمستقيم؛ انتشار السرطان؛ تحديد درجة السرطان؛ عودة السرطان؛ مستضدات سرطانية مضغية؛ المملكة المتحدة.

Advances in Knowledge

- *This study demonstrates that 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/computed tomography (CT) is a useful diagnostic tool and can have a valuable impact on the disease management of indicated colorectal cancer patients.*
- *Only a select group of patients with colorectal cancer, i.e. those with potentially curable disease and resectable metastases, benefit from FDG-PET/CT in addition to CT during preoperative work-ups and disease follow-ups.*
- *18F-FDG-PET/CT is beneficial during follow-up treatment for cancer patients, particularly in the identification of occult recurrence among those with elevated carcinogenicembryonic antigen levels.*

Application to Patient Care

- *18F-FDG-PET/CT is useful in identifying metastatic or recurrent disease at an early stage in patients with colorectal cancer. Early identification may improve patient survival.*
- *Results from 18F-FDG-PET/CT scans can inform disease management in patients with potentially resectable disease or in those with equivocal findings from conventional imaging.*

Colorectal cancer is one of the most common malignancies in the UK and is a major health problem worldwide.[1] Accurate disease staging is fundamental to making appropriate management decisions. Approximately 20% of cancer patients present with distant metastases; if untreated, these patients face a five-year survival rate of 7%.[1] Furthermore, local and distant recurrences develop in 30–50% of patients during follow-up after primary surgery.[2] The early detection of recurrence is vital because surgery, radiotherapy and chemotherapy (either separately or as part of a multidisciplinary approach) may improve patient survival and quality of life. Although only 20–30% of patients with recurrent metastatic disease are suitable candidates for curative resection, the five-year survival rate in this group is 30–40%.[3]

Metastatic disease in colorectal cancer is most commonly detected in the liver or lungs but can affect any part of the body. Conventional imaging has limitations of sensitivity and specificity depending on the disease and the organ affected. For example, computed tomography (CT) is usually performed for primary staging and surveillance but has a high false-positive rate for pulmonary and extrahepatic intra-abdominal lesions.[4,5] These shortcomings have led to the increased use of 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/CT as an additional imaging modality, both in preoperative settings and during follow-up. However, a recent review showed this modality to be cost-effective only in determining the staging of recurrent colorectal and metastatic cancers.[6]

In the Colorectal Unit of the Western General Hospital in Edinburgh, Scotland, 18F-FDG-PET/CT scans are performed selectively in patients who appear to have potentially curable metastatic disease on initial imaging or in those suspected of having occult recurrence. The aim of this study was to evaluate the clinical impact on patient management of performing 18F-FDG-PET/CT during preoperative work-up or follow-up in a select group of patients.

Methods

This retrospective cohort study took place between July 2009 and May 2011. Patient data were retrieved from the electronic South East Scotland Cancer Network (SCAN) colorectal cancer database during the study period. Records from the SCAN colorectal cancer database were included in the study if the patients had undergone 18F-FDG-PET/CT in addition to conventional imaging. Indications for the use of 18F-FDG-PET/CT were as follows: potentially resectable metastases identified by a CT scan at primary staging or during post-resection surveillance; equivocal CT findings at primary tumour staging or during post-resection surveillance, and rising carcinogenicembryonic antigen (CEA) levels identified by negative conventional imaging during follow-up surveillance.

The following data were recorded from the electronic patient record database: primary operative procedure; pathological findings; neoadjuvant treatment; indications of the use of 18F-FDG-PET/CT; intervals between surgeries and 18F-FDG-PET/CT

Table 1: Comparison of conventional imaging and ^{18}F-FDG-PET/CT findings among preoperative colorectal cancer patients (N = 22)

CT finding	^{18}F-FDG-PET/CT finding			Total
	Resectable	Unresectable	Negative	
Resectable	6	3	2	**11**
Equivocal	6	5	0	**11**

CT = computed tomography; ^{18}F-FDG-PET/CT = ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography.

scans (where applicable); results of conventional imaging and ^{18}F-FDG-PET/CT scans; clinical actions taken after ^{18}F-FDG-PET/CT and/or CT scan results, and follow-up information.

Following data collection, the additional value of ^{18}F-FDG-PET/CT over conventional imaging was assessed with regards to patient management. The clinical impact of ^{18}F-FDG-PET/CT was divided into the following four categories. ^{18}F-FDG-PET/CT imaging was determined to have had a major impact if there was evidence of inoperable disease that was either indeterminate or occult on prior conventional imaging or if there were additional ^{18}F-FDG-PET/CT findings which had altered disease management. Additionally, ^{18}F-FDG-PET/CT was considered to have had a minor impact if CT findings were indeterminate and ^{18}F-FDG-PET/CT did not identify any disease. Imaging was classified as having had no impact when ^{18}F-FDG-PET/CT showed no additional findings and no alterations were made to planned treatments as a result. Finally, ^{18}F-FDG-PET/CT scans were deemed to have had a potential negative impact in cases of false-positive findings which had potentially led to further investigations or inappropriate disease management.

Ethical approval for this study was granted by the Audit Department of Western General Hospital, in Edinburgh, Scotland.

Results

A total of 1,043 patients were identified in the SCAN colorectal cancer database during the study period. Of these, 102 patients had undergone ^{18}F-FDG-PET/CT as well as conventional imaging either as part of primary staging or for disease surveillance. There were 40 female and 62 male patients. The median age of the patients was 63 years (range: 29–88 years).

A total of 22 patients received ^{18}F-FDG-PET/CT for preoperative staging while 80 patients received ^{18}F-FDG-PET/CT during follow-up. Overall, ^{18}F-FDG-PET/CT findings were concordant with conventional imaging results in only 28 patients (27.4%).

In the preoperative group, potentially resectable metastases were detected in 11 patients by ^{18}F-FDG-PET/CT whereas the other 11 patients had equivocal CT findings. Among those with detected resectable diseases, CT findings denoting resectable diseases were confirmed by ^{18}F-FDG-PET/CT in six cases (54.5%). However, three patients whose CT results had detected potentially resectable metastases were instead deemed inoperable by ^{18}F-FDG-PET/CT. Furthermore, two patients were downstaged after their ^{18}F-FDG-PET/CT findings were negative. Of the 11 patients with equivocal CT findings, ^{18}F-FDG-PET/CT identified six patients with resectable metastases and five patients with unresectable metastases. A comparison of CT and ^{18}F-FDG-PET/CT findings is provided in Table 1.

Table 2: Summary of the treatment and pathological findings of colorectal cancer patients during follow-up (N = 80)

Treatment	n
Operative procedure	**80**
Right hemicolectomy	25
Anterior resection	17
Anterior resection with TME	33
Abdominoperineal resection of rectum	3
Total colectomy	2
Neoadjuvant treatment	**27**
Short course radiotherapy	23
Preoperative chemoradiotherapy	4
TNM stage	
T stage	80
T1	6
T2	8
T3	43
T4	23
N stage	**80**
N0	37
N1	29
N2	14

TME = total mesorectal resetion; TNM = tumours/nodes/metastases staging system.

In the follow-up group, indications for ^{18}F-FDG-PET/CT included rising CEA levels identified by negative CT results (n = 10), resectable metastases or local recurrence on conventional imaging (n = 31) and equivocal CT findings (n = 39). The operative and pathological details of the patients in the follow-up group can be seen in Table 2. The mean interval between surgery and ^{18}F-FDG-PET/CT scanning was 587 days (range: 15–2,555 days). Of the 10 patients

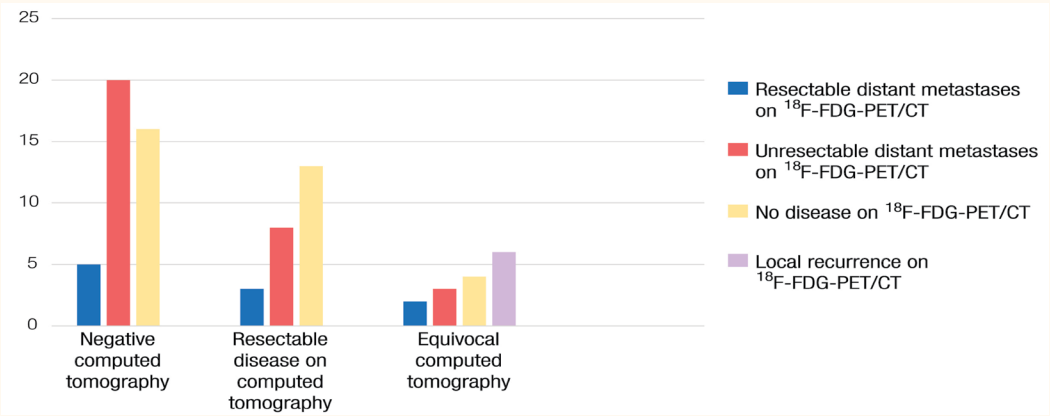

Figure 1: Comparison of computed tomography and ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography findings among colorectal cancer patients during follow-up (N = 80).

with rising CEA levels, two patients had negative ^{18}F-FDG-PET/CT scan results, five patients were found to have resectable disease and three patients had unresectable distant metastases. Of the 31 patients with resectable disease findings on CT scans, ^{18}F-FDG-PET/CT confirmed these findings in 20 patients, demonstrated unresectable metastases in eight patients and excluded local or distant recurrence in three patients. Among the 39 patients with equivocal CT findings, ^{18}F-FDG-PET/CT scans demonstrated negative results in four patients, resectable local recurrence or distant metastases in 22 patients and unresectable disease in 13 patients [Figure 1].

Combined ^{18}F-FDG-PET/CT imaging had a major clinical impact for 16 patients (72.7%) in the preoperative group, including eight patients whose treatment was altered from curative to palliative due to the presence of inoperable disease, six with resectable metastases identified after an indeterminate CT scan and two who avoided unnecessary surgery due to negative ^{18}F-FDG-PET/CT findings. Furthermore, ^{18}F-FDG-PET/CT findings had a major impact and altered disease management for 51 patients (63.7%) in the follow-up group. Of these, 24 patients were offered palliative treatment due to findings which indicated inoperable recurrent disease that had not been diagnosed from CT scans; this included 13 patients with indeterminate CT findings, eight whose CT findings had indicated resectable metastases and three with negative CT results. Resectable recurrent disease was found in 24 patients (five and 19 patients with negative and indeterminate CT findings, respectively). All of the patients who underwent curative resection were later confirmed to have recurrent colorectal cancer on histological examination. Surgery was avoided in three patients whose CT results had detected resectable disease but subsequent ^{18}F-FDG-PET/CT imaging had revealed a negative result. These patients remained under close follow-up with no clinical or radiological evidence of disease recurrence.

A minor impact on the clinical disease management of four patients (5%) in the follow-up group was noted due to ^{18}F-FDG-PET/CT imaging. These patients had had equivocal CT scan results but were downstaged as a result of their ^{18}F-FDG-PET/CT results. Three of these patients had lesions detected in their lungs and one patient had a liver lesion which was ^{18}F-FDG-PET/CT-negative and which remained unchanged on serial imaging.

Disease management remained unaltered for six patients (27.2%) in the preoperative group and 22 patients (27.5%) in the follow-up group. In these cases, ^{18}F-FDG-PET/CT imaging had no impact as the combined imaging confirmed the original CT findings. In the follow-up group, a total of 20 patients were found to have recurrent disease while two patients with elevated CEA levels had a negative result from both CT and ^{18}F-FDG-PET/CT scans. Two patients with liver metastases confirmed by CT and ^{18}F-FDG-PET/ CT findings refused surgery and one patient underwent a hepatic segmentectomy for a malignant lesion which had a complete response to chemotherapy.

The clinical impact of ^{18}F-FDG-PET/CT imaging was negative in three patients (3.7%) who had equivocal CT findings and positive ^{18}F-FDG-PET/CT results revealing uptake at the anastomotic site. All three patients underwent direct visualisation of the anastomosis; two via colonoscopies with biopsy and one via an examination under anaesthesia with biopsy. No histological or clinical evidence of disease recurrence was found for any of the patients. In addition, one patient underwent excision of an umbilical lesion identified on both CT and ^{18}F-FDG-PET/CT scans. This lesion was later revealed to be histologically benign.

In terms of patient outcomes, 56 patients (54.9%) were offered curative surgery and 50 underwent metastasectomies as a result of their ^{18}F-FDG-PET/CT findings. Metastatic lesion resection was performed in 46 patients, including the liver only (n = 32), the lungs (n = 7), the abdominal wall (n = 3) and the peritoneum (n = 3). Additionally, one patient underwent a synchronous renal tumour and liver resection. Four patients did not undergo surgery; this was either due to the progression of the lesion to an unresectable form (n = 1), the complete resolution of a lung lesion following chemotherapy (n = 1), comorbidities (n = 1) or the patient's choice (n = 1). Palliative treatment was offered to 32 patients (31.3%). Nine patients (8.8%) were downstaged, three (2.9%) were over-investigated (PET/CT showed suspected local recurrence but there was no evidence of this on endoscopic examination) and two (1.9%) did not require further investigations or treatment.

Discussion

The present study investigated the role of ^{18}F-FDG-PET/CT imaging in the clinical management of 102 patients with metastatic or recurrent colorectal cancer being considered for curative resection. The data in the current study showed that ^{18}F-FDG-PET/CT scans are a useful diagnostic tool in managing patients with colorectal cancer since treatment based on conventional CT imaging was modified in almost two-thirds of the cohort.

In this study, ^{18}F-FDG-PET/CT findings were consistent with conventional imaging findings in only 27.4% of the patients, which is much lower than other studies reported in the literature.[7,8] A possible explanation is that ^{18}F-FDG-PET/CT scans were carried out selectively among the studied cohort, in patients whose management could have been altered by the additional imaging. Combined ^{18}F-FDG-PET/CT imaging proved particularly useful in differentiating lesions which were considered indeterminate on CT scans, allowing more accurate characterisation in almost half of the patients in this cohort.

The liver is the most common site for colorectal metastases and the reported sensitivity of ^{18}F-FDG-PET/CT scans in detecting hepatic metastases varies. Selzner *et al*. found that while ^{18}F-FDG-PET/CT was comparable to conventional CT in detecting liver lesions, it was superior in detecting extrahepatic lesions.[9] In their study, ^{18}F-FDG-PET/CT imaging was performed on all patients being considered for liver metastasis resection and had a major impact on 21%. A study by Ruers *et al*. showed that the rate of futile laparotomies among their cohort was reduced from 45% to 28% through the utilisation of ^{18}F-FDG-PET/CT scans.[10] Weiring *et al*. also demonstrated the utility of ^{18}F-FDG-PET/CT scans, as this modality was found to reduce futile laparotomies by 38%.[11] There have been no large series or comparative studies so far between ^{18}F-FDG-PET/CT scans and conventional CT scans concerning the detection of pulmonary metastases. The accurate determination of pulmonary metastases which are indeterminate via CT imaging is particularly important if curative resection is being considered elsewhere in the body. In the present study, six patients with liver metastases were also found to have lung metastases on ^{18}F-FDG-PET/CT scans.

Serum CEA levels are commonly monitored during follow-up in colorectal cancer patients, in addition to physical examinations and conventional imaging. While some researchers consider CEA levels to be the most effective indicator in detecting recurrent disease,[12] others have found marginal benefits and concluded that the majority of potentially curable recurrent tumours are detected by surveillance imaging techniques when CEA levels are normal.[13,14] Patients with elevated tumour markers and negative results on conventional imaging pose a clinical challenge. Several studies have demonstrated the value of ^{18}F-FDG-PET/CT imaging in patients with rising serum CEA levels and no identifiable lesions on conventional imaging.[15–17] In the present study, eight out of 10 patients with elevated CEA levels were found to have metastatic disease even when conventional imaging did not show disease recurrence. The other two patients with normal ^{18}F-FDG-PET/CT results showed no clinical or radiological signs of subsequent disease recurrence. Other studies have also reported that a negative ^{18}F-FDG-PET/CT scan result is accurate in excluding recurrence.[18,19] In the case of local recurrence at the site of primary colorectal cancer, CT findings are often difficult to interpret due to benign post-surgical or radiotherapeutical changes. Selzner *et al*. reported a 93% accuracy rate in detecting local recurrence with the use of ^{18}F-FDG-PET/CT imaging.[9] However, three out of eight patients with equivocal CT results in the current study had false-positive ^{18}F-FDG-PET/CT readings, suggesting anastomotic recurrence. These cases required direct visual examination to exclude disease recurrence.

Although the current study's results showed that the use of ^{18}F-FDG-PET/CT imaging had a primarily positive impact on disease management, several disadvantages of this modality have been reported. Research has indicated that ^{18}F-FDG-PET/CT imaging has reduced sensitivity in detecting subcentimetre lesions, which means that small metastatic deposits can therefore be missed on the scans.[20] In addition, ^{18}F-FDG-PET/CT imaging can reportedly yield false-positive readings among patients with benign

inflammatory conditions and false-negative readings for patients with high blood glucose levels or those who have had recent chemotherapy treatments.[9,21] A major limitation of this study was the lack of histopathological confirmation of ^{18}F-FDG-PET/CT-positive lesions in 36 out of 88 patients (41%). This lack of histopathological confirmation occurred primarily because the distant metastases in question were inoperable. The results of this study should therefore be interpreted in light of this.

Conclusion

This study demonstrates that, when undertaken in selected colorectal cancer patients for clear indications, ^{18}F-FDG-PET/CT imaging provides valuable information and has a considerable impact on disease management in a significant proportion of patients. This impact was primarily seen via improvements in staging accuracy and the avoidance of unnecessary surgeries. Additionally, ^{18}F-FDG-PET/CT imaging enabled the identification of recurrent disease at an early stage at which point curative surgery can be offered to the patient.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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