Dual-time point images of the liver with $^{18}$F-FDG PET/CT in suspected recurrence from colorectal cancer

D. Fuster$^{a,b,*}$, S. Lafuentean, X. Setoain$^{a,b,c}$, I. Navales$^a$, A. Perissinottia, J. Pavia$^{a,b,c}$, P. Paredes$^a$, F. Lomeña$^a$, F. Pons$^{a,b}$

$^a$ Servicio de Medicina Nuclear, Hospital Clínic, Barcelona, Spain
$^b$ Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
$^c$ Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Barcelona, Spain

A B S T R A C T

Aim: To analyze the potential improvement of $^{18}$F-fluorodeoxyglucose (FDG) PET/CT using additional delayed images of the liver in operated colorectal cancer.

Material and methods: The study prospectively included 71 patients (22 women, 49 men) with mean age of 65 ± 11 years with clinical, biochemical or radiological suspicion of current disease. A whole body PET/CT scan was performed at 60 min (standard images) and after 2 h (delayed images) post-injection of 4.07 MBq/kg of $^{18}$F-FDG. Visual and quantitative SUV analysis of PET/CT findings were done. All findings were confirmed by histopathology and/or at least 6 months follow-up.

Results: Thirty-seven out of 71 patients were diagnosed of liver metastases (79 metastases). In 38/71 cases there was extra-hepatic disease in the form of local recurrence (10), abdominopelvic (3) or mediastinal (3) lymph nodes, bone (1) or lung metastases (16) and carcinomatosis (10). Sensitivity and specificity for the diagnosis of liver metastases was significantly higher (84% and 70%) than in standard images (57%). Sensitivity and specificity for PET/CT in the diagnosis of extra-hepatic disease were 84% and 70%, contributing to the detection of synchronous tumors in 5 patients.

Conclusions: PET/CT may be useful in the diagnosis of extra-hepatic disease in suspected recurrence of colorectal cancer. Delayed images on PET/CT may increase the sensitivity to identify liver metastases.

© 2011 Elsevier España, S.L. and SEMNIM. All rights reserved.

18F-FDG PET/TC con imagen hepática en dos tiempos en la sospecha de recidiva del cáncer colorrectal

Resumen

Objetivo: Analizar el potencial de la PET/TC usando imagen tardía del hígado en pacientes con sospecha de recidiva de cáncer colorrectal.

Materiales y métodos: Se han incluido prospectivamente 71 pacientes (22 mujeres, 49 hombres) con edad de 65 ± 11 años y sospecha clínica, analítica o radiológica de recurrencia. Se realizó PET/TC después de la inyección de 4,07 MBq/kg de $^{18}$F-FDG con imagen de cuerpo entero a los 60 min (imagen estándar) y hepática a las 2 h (imagen tardía). Se efectuó análisis visual y cuantitativo mediante SUV de los hallazgos de la PET/TC. Se obtuvo confirmación de las lesiones por estudio histopatológico y/o seguimiento mínimo de 6 meses.

Resultados: Se diagnosticaron metástasis hepáticas en 37/71 pacientes (79 metástasis). Un total de 38/71 pacientes mostraban enfermedad extra-hepática en forma de recidiva local (10), adenopatías abdominopélvicas (3) o mediastínicas (3), metástasis óseas (1) o pulmonares (16) y carcinomatosis (10). Se calculó la sensibilidad y especificidad para el diagnóstico de metástasis hepáticas en base a cada paciente para la imagen estándar (81 y 91%) y la imagen tardía (95 y 97%). El número de metástasis hepáticas diagnosticadas fue mayor con la imagen tardía (66/79) que con la imagen estándar (57/79). La sensibilidad y especificidad de la PET/TC en lesiones extra-hepáticas fue de 84 y 70%, contribuyendo al diagnóstico no sospechado de 5 tumores sincrónicos.

Conclusiones: La PET/TC es recomendable para descartar enfermedad extra-hepática en sospecha de recidiva de cáncer colorrectal. La realización de imagen tardía mejora la sensibilidad de la PET/TC en el diagnóstico de metástasis hepáticas.

© 2011 Elsevier España, S.L. y SEMNIM. Todos los derechos reservados.
Introduction

Colorectal cancer is the third most common type of cancer in both men and women and is the second cause of death associated with cancer in the United States of America. The clinical follow-up of these patients usually includes the determination of tumoral markers and the carcinoembryonic antigen (CEA), endoscopy and imaging techniques. Treatment with curative surgery is effective in up to 50% of the cases, although recurrence of colorectal cancer is high, being of up to 30–40% in stages II and III of the disease. An important part of the recurrences appears in only one organ allowing surgical treatment which is vital for the prognosis of the patient.\(^1\)

Colorectal cancer usually disseminates to the regional lymph nodes or the liver through the portal venous circulation. The liver is the most frequent visceral localization and constitutes the initial site of distant metastasis in one third of the patients with recurrence, finally affecting more than two thirds of the patients during the evolution of the disease.\(^2\) The treatment of liver metastasis of potentially resectable colorectal cancer is surgical if allowed by the conditions of the patient since it has demonstrated an increase in the survival of the patients.\(^3\) However, according to the number of nodes and the presence of risk factors (Fond criteria), the administration of chemotherapy or radiofrequency may be required to complement surgery in partially resectable lesions. Thus, correct staging of the presence of liver metastasis and the number of lesions is necessary to choose the optimum treatment for each patient.

At present, the staging and follow-up on the suspicion of recurrence of colorectal cancer are performed by computerized tomography (CT). It has been demonstrated that this technique may have difficulties in differentiating the presence of active disease from changes by fibrosis secondary to the surgery or other treatments or in detecting peritoneal invasion. In this regard several studies have demonstrated that positron emission tomography with \(^{18}\)F-fluorodesoxyglucose (FDG-PET) is more reliable in operated patients with suspicion of relapse.\(^4\)–\(^6\) With respect to liver involvement, CT has shown good results in local extension similar to those of FDG-PET,\(^7\) although adequate differential diagnosis with lesions of another etiology may be difficult with both techniques in small-sized lesions,\(^8\) with MR being the technique with the greatest capacity in its diagnosis.\(^9\)

Dual time-point images with PET/CT have been used in different clinical situations for the study of the behavior of malignant tumors in an attempt to improve the specificity of this technique. The studies performed have demonstrated that the behavior in the incorporation of \(^{18}\)F-FDG over time is different in benign or high grade or metastatic neoproliferative processes which may aid in establishing a correct differential diagnosis in the identification and nature of the lesions.\(^10\)–\(^16\) Some studies have suggested the utility of dual time-point PET/CT images in the diagnosis of liver metastasis, although heterogeneous groups have been studied and the parameters of adequate FDG uptake for analysis remain to be established.\(^17\)–\(^19\)

The aim of the present study was to determine the utility of an additional delayed image with PET/CT in the detection of liver metastasis in patients with suspicion of recurrence of colorectal cancer.

Material and methods

Patients

We prospectively included 71 patients (22 females, 49 males) with a mean age of 65 ± 11 years with previous intention-to-cure surgery for colorectal cancer and clinical, biochemical or radiological suspicion of disease recurrence. The time interval from the end of treatment to PET/CT was always greater than 2 months and did not include patients with a history of previous liver disease. The levels of lactate-dehydrogenase (LDH), alkaline phosphatase (AP) and CEA were determined, and the possible association with the presence of recurrence was evaluated. The clinical characteristics of the patients are shown in Table 1. All the findings were confirmed by histopathologic study of the lesions and/or a minimum follow-up of 6 months with diagnosis of progression by imaging techniques. The study was approved by the Ethical Committee of the hospital and informed consent was obtained from each patient.

Table 1

<table>
<thead>
<tr>
<th>Clinical characteristics of the patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>primary tumor</td>
</tr>
<tr>
<td>ascending colon</td>
</tr>
<tr>
<td>transverse colon</td>
</tr>
<tr>
<td>descending colon</td>
</tr>
<tr>
<td>rectosigmoid</td>
</tr>
<tr>
<td>Time from surgery (months)</td>
</tr>
<tr>
<td>LDH (250–450 U/L)</td>
</tr>
<tr>
<td>AP (90–290 U/L)</td>
</tr>
<tr>
<td>CEA (0.0–4.0 ng/mL)</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>adjuvant</td>
</tr>
<tr>
<td>neoadjuvant</td>
</tr>
<tr>
<td>radiotherapy</td>
</tr>
<tr>
<td>adjuvant</td>
</tr>
</tbody>
</table>

PET/CT acquisition

PET/CT was performed using a hybrid system (Biograph, Siemens, Erlangen, Germany) with a PET ECAT Exact HR+ BGO and a helical CT (Somatom, Emotion). The patient underwent a 4-h fast period with blood glucose levels less than 140 mg/dl prior to the intravenous administration of 0.11 mCi (4.07 MBq)/kg of \(^{18}\)F-FDG. Whole-body images were performed after 60 min (standard image) and 1–2 liver fields at 2 h post-FDG injection (delayed image). Patients were allowed to breathe normally during images acquisition and were placed in a supine position with their arms extended upwards. The mode of acquisition was 3D with a time of 5 min per bed. The PET images were reconstructed with attenuation correction based on the images obtained with the CT.

Quantification

Visual analysis of the PET/CT findings was performed by two observers who were unaware of the clinical information and the results obtained in the follow-up of the patients. A region of interest (ROI) was created around the liver lesions showing FDG uptake and areas of reference in the liver and the spleen, in both the standard PET image and the delayed PET image. The mean SUV (SUVmean) was calculated in the liver to observe possible washout of activity from this organ as well as in the spleen to obtain a stable area of reference. The maximum SUV (SUVmax) was calculated in the liver lesions detected on PET. These parameters are based on the main activity, the corrected dose injected by the decline and the weight of each patient: SUVmean = mean activity (ROI) (MBq/mL)/dose injected (MBq)/weight (kg); SUVmax = maximum activity (ROI) (MBq/mL)/dose injected (MBq)/weight (kg).
Statistical analysis

The results are expressed as mean ± standard deviation. The sensitivity and specificity were determined using conventional methods. The Kappa index was calculated to measure the concordance between the SUV values obtained. The variables were compared with Student’s t-test considering associations with p-values <0.05 as statistically significant. Normality could not be assumed on evaluation of CEA and thus, a logarithmic transformation was applied (log CEA).

Results

Confirmation of the presence of metastatic liver disease was obtained in 37/71 patients, detecting a single metastatic liver lesion in 15/37 cases and a total number of metastases of 79. The presence of liver metastasis was confirmed by histopathologic study in 29/37 cases and by lesion progression during follow-up in 8/37 cases.

Up to 38/71 patients showed disease dissemination at an extra-hepatic level as local relapse (19), abdominopelvic (3) or mediastinal adenopathies (3), bone (1) or pulmonary metastasis (16) and carcinoatosis (10). Involvement in both localizations (liver and extra-hepatic metastasis) was demonstrated in 21/71 patients (Table 1). Twelve of the 71 patients remained without lesions during the follow-up without the appearance of signs suggestive of disease recurrence. No significant association was found between the presence or absence of disease recurrence and the clinical indexes studied (AP, LDH and CEA). There were not significant differences based on the localization of the primary tumor and/or the performance of adjuvant or neoadjuvant treatment with chemotherapy and/or radiotherapy (RDT).

PET/CT in liver disease

The sensitivity and specificity for the diagnosis of liver metastasis were calculated based on the standard (81 and 91%) and delayed images (95 and 97%) of each patient. The total number of liver metastases diagnosed was greater with the delayed (66/79) than the standard images (57/79). The Kappa index indicates a good concordance in the diagnosis of liver metastasis between the dual time-point images (K=0.86), observing discrepancies in 5 patients with a single metastasis which only the delayed image was able to detect (Fig. 1). The concordance comparing the two images with the diagnostic follow-up of the liver metastasis was greater in the delayed (K=0.94) than in the standard images (K=0.8) (Table 2).

The SUVmax in the liver metastasis showed a significant increase between the standard and delayed images (standard SUVmax = 5.8 ± 2.5 and delayed SUVmax = 7.7 ± 3.8; p < 0.05). We did not observe any case in which the liver lesions showed a reduction in SUVmax in the delayed image. The SUVmean in the spleen did not show significant changes (SUVmean standard image = 1.78 ± 0.36; SUVmean delayed image = 1.79 ± 0.34) (p=ns), with a significant reduction in the healthy liver tissue (SUVmean standard image = 2.67 ± 0.58; SUVmean delayed image = 2.28 ± 0.43) (p<0.05) (Fig. 2).

PET/CT in extra-hepatic disease

PET/CT diagnosed 32/38 patients with extra-hepatic disease with a sensitivity and specificity of PET/CT of 84 and 70%, respectively (Fig. 3). FDG deposits were found and interpreted as recurrence in 10 patients who were found to be false positives due to: persistent inflammatory changes in the surgical bed of the primary tumor (3), reactive adenopathies (4), suspicion of carcinomatosis (2) and unspecific uptake in the parotid gland (1). PET/CT was not able to diagnose 6 cases with metastatic lesions, 4 of which had a high mucinous component. It should be mentioned that PET/CT contributed to the unsuspected diagnosis of synchronous tumors in the lung (2), transverse colon (1), cecum (1) and thyroid gland (1).

PET/CT with clinical indexes

The AP, LDH and CEA values were calculated taking into account the group of patients in which the PET/CT demonstrated liver disease, extra-hepatic disease and those who were free of disease. Significantly higher levels of AP were observed in the group of patients demonstrating active liver metastasis in both the baseline (p = 0.026) and the delayed PET/CT images (p = 0.029). A significant association was found between the CEA and the SUVmax of the liver metastasis (p < 0.05), observing that the SUVmax increased with the increase in CEA of the lesions of the standard (correlation coefficient of 0.54) and delayed images (correlation coefficient of 0.46) indicating a moderate linear correlation. No significant association was found between PET/CT findings and LDH levels.

Discussion

The use of PET/CT was found to be useful in patients with clinical suspicion of recurrence of colorectal cancer to detect the presence of locoregional recurrence or disease metastasis. However, the results of this technique in hepatic diagnosis and staging compared with anatomical imaging techniques such as CT and MRI are more controversial.

The additional acquisition of a delayed image has been successfully used in the differential diagnosis between neoplasms or metastasis and processes of benign etiology with the exception of some low grade tumors, infections and cases of treatment.

| Table 2 |
|-----------------|-----------------|-----------------|
|                | Standard image  | Delayed image   |
|                | M0              | M1              | Total            |
| Standard/delayed image | M0  | 36  | 5 (9)* | 41   |
|                   | M1  | 0   | 30 (57)* | 30   |
|                   | Total | 36  | 35 (66)* | 71   |
|                   | 56.70% | 49.30% | 100.00% |
| Standard image/definitive diagnosis | M0  | 34  | 7 (22)*  | 41   |
|                   | M1  | 0   | 30 (57)* | 30   |
|                   | Total  | 34  | 37 (79)* | 71   |
|                   | 47.89% | 52.11% | 100.00% |
| Delayed image/definitive diagnosis | M0  | 34  | 2 (13)*  | 36   |
|                   | M1  | 0   | 35 (66)* | 35   |
|                   | Total  | 34  | 37 (79)* | 71   |
|                   | 47.89% | 52.11% | 100.00% |

* Number of liver metastases.
No alterations were observed in the axial PET, CT and PET/CT slices in the liver in the standard images (a) while an active focal lesion can be seen in the delayed images, corresponding to a single liver metastasis (b).

(A) Correlation between the hepatic SUVmean obtained in the standard and delayed images. A reduction can be seen in the hepatic SUVmean in the delayed image. (B) Correlation between the SUVmean of the spleen obtained in the standard and delayed images. Stability is seen in the SUVmean of the spleen between the early and delayed images.

One documented theory reports that the acquisition of delayed images of high grade tumoral processes and metastasis may increase FDG uptake by up to 30%. In this study we observed a significant increase in FDG uptake in liver metastasis in the delayed images (standard SUVmax = 5.8 ± 2.5 and delayed SUVmax = 7.7 ± 3.8; p < 0.05) with a greater concordance between the presence of liver metastasis and the findings of the delayed (K = 0.94) than the standard images (K = 0.8). These results, together with the proven fact that a washout of metabolic activity was produced in the healthy liver in this series of patients (standard image SUVmean = 2.67 ± 0.58; delayed image SUVmean = 2.28 ± 0.43) (p < 0.05), contributed to achieving better evaluation of FDG uptake in the liver lesions. The stability of the uptake in the spleen found in this series of patients (standard image SUVmean = 1.78 ± 0.36; delayed image SUVmean = 1.79 ± 0.34) (p = ns) indicates that the variations in FDG uptake in the liver are probably organ-specific.

PET/CT demonstrated an evidently greater sensitivity and specificity for the diagnosis of liver metastasis in the delayed (95 and 97%) than in the standard images (81 and 91%). Taking the number of metastasis into account, a greater sensitivity was also observed in detecting lesions, with the delayed image being able to
visualize up to 9/79 liver metastasis which did not show evident uptake in the standard image. These findings are important in the management of these patients since the decision as to the performance of directed liver surgery, neoadjuvant therapy or palliative chemotherapy may depend on the grade of liver involvement. It is of note that 5 patients had a confirmed single metastasis which only the delayed PET/CT image was able to detect. In these patients this diagnosis was crucial to establish the diagnosis of liver recurrence and was decisive for both disease management and prognosis.

Lee et al. evaluated the utility of dual time-point PET/CT images in patients with operated colorectal cancer, although the study was retrospective and with inclusion criteria of heterogeneous patients. The authors recommended quantification of liver lesions in the delayed images using a tumor/background uptake index. In this study the potential contribution of this technique in the differential diagnosis of liver lesions visualized by CT with contrast and with histological diagnosis is analyzed, although the small number of benign lesions reported did not allow extrapolation of relevant conclusions. These authors coincide with our series of patients in that the delayed image findings did not cause a loss of specificity in the diagnosis of liver metastasis.

PET/CT is considered a good technique to rule out locoregional recurrence or extra-hepatic metastasis of colorectal cancer compared with reference technique in clinical practice which usually includes CT with thoracoabdominal contrast and, on some occasions, ultrasonography or MRI. The studies published indicate that PET/CT has greater sensitivity and specificity, being especially useful due to the difficulty of CT to evaluate the surgical bed and small adenopathies. The sensitivity and specificity of PET/CT to detect recurrence or extra-hepatic metastasis in this series of patients were 84 and 70%, respectively. However, suspicious lesions were detected in 10 patients who were finally shown to be false positives, thereby encouraging interpretation of findings with caution and avoidance of the indiscriminate use of PET/CT in patients with no clinical suspicion of recurrence. It should be taken into account that similar to what has been described in the literature, PET/CT in this series of cases also showed a low sensitivity for detecting disease recurrence in tumors with a high mucinous component, being falsely negative in up to 4 patients. PET/CT also contributed to the non-suspected diagnosis of synchronous tumors in 5/71 patients, thereby influencing the therapeutic management, probably being relevant in their prognosis.

The quantification of PET/CT by SUVmax has shown promising results in the evaluation of response to treatment and as a prognostic factor in colorectal cancer. In this series of patients significantly higher AP levels were found in the group demonstrating active liver metastasis on PET/CT, particularly in the delayed images (p = 0.029). We also found a significant association between CEA and the SUVmax of liver metastases (p < 0.05). These findings should be evaluated with caution due to the presence of contradictory results, although they do open a way of interest which should be analyzed by prospective studies to evaluate their potential use in clinical practice.

In conclusion, PET/CT is a useful technique for the diagnosis of locoregional recurrence and extra-hepatic metastasis in the therapeutic management of patients with suspicion of relapse of colorectal cancer. Dual time-point liver images improved the sensitivity of PET/CT to identify liver metastasis in this series of patients.

**Conflict of interest**

The authors declare no conflict of interest.

**Financial support**

This study received partial financial support from the RTICC (RD06/0020/0038) and AGAUR (2009 SGR 1049).

**References**


15. Döbert N, Hamscho N, Menzel C, Neuss L, Kovács AF, Grünwald F. Limitations of dual-time-point FDG PET in the differential diagnosis of liver lesions visualized by CT with contrast and with histological diagnosis is analyzed, although the small number of benign lesions reported did not allow extrapolation of relevant conclusions. These authors coincide with our series of patients in that the delayed image findings did not cause a loss of specificity in the diagnosis of liver metastasis.


