Impact of $^{18}$F-FDG-positron emission tomography for decision making in colorectal cancer recurrences

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Abstract Diagnostic imaging for suspected tumour recurrence of primary colorectal cancer frequently lacks specificity and sensitivity. The impact of whole body $^{18}$F-FDG-positron-emission tomography (PET) on detection of local recurrences and hepatic or pulmonary metastases was evaluated in a prospective study. Results were compared with computed tomography (CT), ultrasonography, magnetic resonance imaging and conventional chest X-ray. The study included 71 patients (77 investigations) with suspected local recurrence, hepatic metastases or unexplained raised level of the tumour marker carcinoembryonic antigen (CEA). The results demonstrate that $^{18}$F-FDG-PET was clearly superior to CT with regard to detection of hepatic metastases. Sensitivity was 1.0 and specificity 0.98 compared with 0.87 and 0.91 for CT. In four cases, $^{18}$F-FDG-PET clarified otherwise unclear local recurrences. In five patients, $^{18}$F-FDG-PET showed pulmonary metastases that had previously been unknown. In a total of 16 patients (20.8%), $^{18}$F-FDG-PET provided additional information leading to a change of the treatment strategy. $^{18}$F-FDG-PET clearly has the ability to detect colorectal tumour recurrence and its metastases in a whole body format. Therefore, it may be applied in the follow-up of patients with primary colorectal cancer. Despite the costs, it is certainly recommended for patients with an otherwise unclear increase of CEA level or with unproven local recurrence.

Key words Colorectal cancer recurrence · PET · Liver metastases

Introduction

Overall survival for patients with colorectal cancer has been shown to be strongly correlated with tumour stage [1]. After diagnosis, 70–80% of patients undergo an apparently curative resection. However, only 45% of patients will be actually cured. Twenty to thirty percent of patients are found to have advanced, incurable disease. The remaining 25–45% present with recurrent disease, ranging from locoregional recurrence to widespread metastasis [2, 3]. In patients with apparently limited recurrent tumour, 5-year survival rates of 20–30% can be obtained after hepatic or pulmonary metastasectomy, or following curative resection of local recurrence [4, 5]. Therefore, the diagnostic approach to a recurrent tumour burden has to clarify a local or systemic character of the disease.

For routine follow-up of patients with colorectal cancer, an elevated carcinoembryonic antigen (CEA) level in the serum may indicate tumour recurrence. Ultrasonography (US) and chest X-rays are usually performed for screening for distant metastasis. If a lesion is suspected or the CEA level is raised, a computed tomography (CT) or magnetic resonance imaging (MRI) is used for further screening. However, differentiation between pelvic recurrence or postoperative fibrosis after rectal excision is frequently difficult [6]. The advent of positron emission tomography ($^{18}$F-FDG-PET) has made it possible to demonstrate sites of increased glycolysis due to
cancer [7, 8]. It has been shown that $^{18}$F-FDG-PET is a useful technique to observe changes of tumour metabolism after chemotherapy [9] or to distinguish chronic inflammation from cancer [10]. The glucose analogue FDG (2-(fluorine-18)-fluoro-2-2deoxy-D-glucose) is supposed to enter the cell in the same manner as glucose. However, in contrast to glucose, it is trapped within the cell after phosphorylation, as it is not further metabolised. Therefore, intracellular FDG concentration reflects intracellular glucose metabolism [11].

The purpose of this investigation was to evaluate the clinical impact of whole body $^{18}$F-FDG-PET for the detection and localisation of tumour recurrence and tumour spread in patients with colorectal cancer.

**Material and methods**

**Patients**

Seventy-one patients suspected of having a tumour recurrence or metastases (either due to a raised CEA level or to imaging methods) were included in this prospective study. Mean age of the 42 men and 29 women was 64 years (range 31–89 years). All patients had been operated between 8 months and 6 years before PET investigation. Forty-five patients had had rectal cancer; eight of those patients had a Dukes A, 10 a Dukes B and 23 a Dukes C stage (stage unknown in 4). An abdomino-perineal resection had been performed in 13 patients, an anterior resection in the other 32 patients. Twenty-six had had colonic carcinoma, one patient had a Dukes A, six patients a Dukes B and 17 a Dukes C stage (stage unknown in 2). In all patients with colonic carcinoma, a standard resection had been performed.

All patients received a whole body $^{18}$F-FDG-PET (77 investigations). Patients were enrolled consecutively between June 1995 and September 1998. Patients with an elevated fasting blood glucose level or diabetes were excluded. One patient received three investigations and three patients two. All patients were informed about the study and gave written consent.

**Radiopharmaceutical**

The isotope and the radiopharmaceutical were produced and synthesised as previously reported [12]. $^{18}$F-FDG (350±50 MBq) was injected into the cubital vein. Patients rested during a 90-min uptake period. This prolonged uptake period for FDG was chosen because results derived from kinetic tumour studies indicate that the glycolysis plateau is reached after 80 min at the earliest, which enables improved malignancy detection based on static PET imaging [10, 13].

**PET protocol**

PET investigation was performed at least more than 6 weeks after the last chemotherapy or more than 3 months after completion of radiotherapy. Patients fasted overnight, at least 12 h prior to the investigation. A bladder catheter was inserted routinely except in patients who denied catheterisation. Static whole-body PET imaging was performed on a Siemens/CTI ECAT-EXACT 921/31 tomograph. This device records 31 planes simultaneously, which encompass a 10.6-cm axial field of view. Patients were positioned with the aid of a laser beam and a vacuum support mattress. To correct for photon absorption, a transmission scan of 10 min per bed position was obtained prior to injection of the radiopharmaceutical. Beginning 90 min after injection of $^{18}$F-FDG, an emission scan of again 10 min per bed position was recorded. Coronal, sagittal and transaxial images were reconstructed using iterative image reconstruction [14]. Six to eight bed positions per patient were acquired.

**Image interpretation**

The PET images were interpreted by two experienced independent investigators, who were blinded to clinical data and results of other imaging procedures. The images were reviewed in hard copy as well as on a computer work station (SUNSparc 20) linked to a data archive and processing system commercially supplied by Siemens Medical Systems. The latter enabled the use of multiple operator-defined planes.

**Diagnostic criteria**

A lesion was classified as potentially malignant by (1) a focally increased radiotracer uptake which exceeded normal limits of regional FDG uptake in the respective area, or (2) a standardised uptake value (SUV) greater than 4. This cut-off criterion is based on a prolonged uptake period of the radiopharmaceutical prior to the delayed image acquisition which enables an improved lesion to background ratio [13].

**Further diagnostic procedures**

All procedures were performed routinely. For analysis, the reports of the imaging procedures were reviewed but not original films. Contrast CTs of the abdomen were ordered when CEA serum levels were raised and/or US revealed a focal lesion within the liver. Contrast CTs of the abdomen were ordered when CEA serum levels were raised and/or US revealed a focal lesion within the liver. In cases of tumour suspicion within the chest, a CT of the thorax was obtained [Somatom Plus 4 helical scanner (Siemens, Erlangen, Germany)]. Chest X-ray ($n$=69), abdomen-pelvis CT ($n$=68), chest CT ($n$=21) and the appropriate gadolinium augmented magnetic resonance imaging ($n$=22) were performed according to standard protocols. The criteria used for assessment of recurrent tumour, local invasion of fat or adjacent structures, lymph nodes, liver, adrenal glands, bone lesions and lung lesions have been described elsewhere [15]. US was performed with state-of-the-art real-time equipment with use of 5.0-MHz transducers. In all patients, a colonoscopy was performed using standard equipment to search for secondary adenomas or carcinomas. Image interpretation was not performed under study conditions.

Results of $^{18}$F-FDG-PET investigations were compared with results of CT, MRI, US and conventional chest X-ray. Sensitivity, specificity and predictive values were calculated for local recurrences, hepatic and pulmonary metastases. The $^{18}$F-FDG-PET findings were assessed as true positive either in patients with histological proof of malignancy ($n$=51) or in patients in whom all other investigations suggested malignancy. For PET findings, interobserver agreement was calculated with the use of the $k$ statistic ($k$=0.94). The $k$ statistic is a measure of agreement between two observers with respect to a categoric variable. A $k$ of 1 represents perfect agreement, while a $k$ of 0 indicates chance agreement.

**Results**

In 20 patients, malignancy was not detected by any method. Malignancy was confirmed by histology in 60