Early detection of recurrence by \textsuperscript{18}FDG-PET in the follow-up of patients with colorectal cancer

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We assessed the potential benefits of including systematic \textsuperscript{18}fluorodeoxyglucose positron emission tomography (FDG-PET) for detecting tumour recurrence in a prospective randomised trial. Patients (N = 130) who had undergone curative therapy were randomised to undergo either conventional (Con) or FDG-PET procedures during follow-up. The two groups were matched at baseline. Recurrence was confirmed histologically; ‘Intention-to-treat’ analysis revealed a recurrence in 46 patients (25 in the FDG-PET group, and 21 in the Con group; \(P = 0.50\)), whereas per protocol analysis revealed a recurrence in 44 out of 125 patients (23 and 21, respectively; \(P = 0.60\)). In another three cases, PET revealed unexpected tumours (one gastric GIST, two primary pulmonary cancers). Three false-positive cases of FDG-PET led to no beneficial procedures (two laparoscopies and one liver MRI that were normal). We failed to identify peritoneal carcinomatosis in two of the patients undergoing FDG-PET. The overall time in detecting a recurrence from the baseline was not significantly different in the two groups. However, recurrences were detected after a shorter time (12.1 vs 15.4 months; \(P = 0.01\)) in the PET group, in which recurrences were also more frequently (10 vs two patients) cured by surgery (R0). Regular FDG-PET monitoring in the follow-up of colorectal cancer patients may permit the earlier detection of recurrence, and influence therapy strategies.

Keywords: FDG PET; CT scan; colon cancer; follow up

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in Western countries. Most newly-diagnosed cases already have a tumour invading across the bowel wall with lymph node invasion (stage III disease) and/or synchronous metastases (stage IV). Treatment is based on curative surgical resection (R0). However, approximately half of the patients who undergo curative R0 surgery go on to develop recurrent disease, and the median survival time after the operation is no more than 2 years (Griffin et al., 1987; Rodriguez-Moranta et al., 2006). Adjuvant chemotherapy improves prognosis in these patients, but more than one-third of them still experience recurrence within the 2 years following curative therapy (Moertel et al., 1995; Mitry et al., 2005; Van Cutsem and Costa, 2005). The preferred treatment for patients with recurrent disease is resection of the metastases in the liver or lung, and this can result in a 5-year survival rate of 35–40% (Scheele et al., 1990; Fong et al., 1997). This is why these patients should be followed-up using either clinical or biological exams, as well as imaging procedures (Desch et al., 2005; Rodriguez-Moranta et al., 2006; Sjovall et al., 2007).

Positron emission tomography (PET) using \textsuperscript{18}fluorodeoxyglucose (FDG) has emerged as a promising diagnostic imaging method in reassessing recurrent colorectal cancer, and can potentially improve the selection of patients for surgery, and hence may have a beneficial impact on the outcome of treatment. \textsuperscript{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) detects changes in glucose uptake and metabolism, and also provides information about the location of a cancer within tissues. It is now considered to be a sensitive and accurate technique, and several studies have suggested that it should be carried out before resection of liver metastases from CRC (Stokkel et al., 2001; van der Hiel et al., 2001; Fernandez et al., 2004; Truant et al., 2005; Wiering et al., 2005; Khan et al., 2006).

However, these studies focused mainly on the diagnoses obtained with FDG-PET, and most of them included only a retrospective analysis taking clinical management decisions into account. As far as we know, only one open pilot study has carried out a prospective analysis of the impact of FDG-PET in patients already undergoing conventional management, and who were potentially eligible for resection of colorectal liver metastases (Ruiers et al., 2002). Although CT scanning is the most common imaging procedure used to follow-up patients, FDG-PET is now sometimes used in patients with colon or rectal cancer. We do not know whether FDG-PET provides a more accurate assessment of the cancer stage than CT-scanning. This study was intended to assess the contribution of systematic FDG-PET to the detection and treatment of CRC recurrence following curative surgery in patients with a high risk of recurrence.
PATIENTS

Between January 2001 and June 2004, 130 patients from seven teaching hospitals underwent curative R0 surgery for colon or rectal cancer. They were routinely assessed prospectively at regular 3-monthly intervals up to 24 months after curative surgery, or until death.

METHODS

At the second visit after curative surgery (6-month follow up visit), compliance with adjuvant chemotherapy, and the absence of disease progression and/or missed synchronous metastases were checked. Patients were randomly divided into two groups: one group received a conventional work-up (Con) and the other underwent PET. The baseline date was that of the initial surgery. The study follow-up started from the ninth month after baseline, and continued until the twenty-fourth month or the patient’s death. All patients gave informed consent for the study, which comprised six visits (see schedule in Figure 1), a physical examination, biomarker assays (serum CEA or CA19-9, or both), an ultrasound scan (US) every 3 months (except after 9 and 15 months of follow-up), a chest X-ray every 6 months, and abdominal CT scans after 9 and 15 months of follow-up. Patients in the PET group also underwent 18FDG-PET after 9 and 15 months. Various study end points were recorded for the patients: the overall rate of recurrence in each group after 15-months follow-up, the time until a recurrence was detected by at least one of the imaging procedures described above, the time to second-line surgical removal followed by chemotherapy and/or drug treatment, including either chemotherapy and/or palliative care if required for multiple recurrent tumours. All imaging findings were correlated with the subsequent final histological diagnosis, based on findings at surgery and/or from biopsies. A new CT-coupled PET machine (PET-CT) became available from July 2004. This machine provided more effective PET/CT imaging than the first generation PET scanner; we therefore stopped recruiting patients to the study after including the one hundred and thirtieth patient. This was based on ethical concerns (the chances of patient survival with PET alone vs PET-CT) and methodological considerations (consistent imaging quality in all patients).

Statistical analysis

The primary end point was to detect recurrence after 9 and 15 months of follow-up in each group, on the basis of the intent-to-treat principle, that is, data from all randomised patients were analysed according to the strategy group to which they had been assigned when randomised. We assumed that the overall recurrence rate over the 2-year follow-up period would be similar in the two groups, but that recurrences might be detected earlier in the PET group. Assuming an overall estimated 30% recurrence rate, 30 patients with a recurrence need to be included in each group. By assuming a 30 percent difference in curative treatment for recurrence between the two arms (an estimated absolute gain of 10% in Con arm, and 40% in PET arm; z = 5% unilateral test and β = 20%), this requires 180 patients (90 in each arm) over a 2-year period.

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follow-up period. We compared the number of patients diagnosed as having a recurrence, the time to onset of recurrence after curative surgery, and the time until second-line therapy was started after the confirmed diagnosis of recurrence. Continuous variables were expressed as mean ± s.d., and were compared using Student’s t-test. Differences in qualitative variables were evaluated using χ² test, or the Fisher’s exact test when necessary. We used the Kaplan–Meier survival analysis and the log-rank test to describe and compare the time until recurrence or second-line therapy in the two groups of patients (PET and Con). All patients with malignant tumours detected during the follow-up were pooled, and analysed as a single recurrence group. Patients who died and in whom no recurrence had been detected were considered to have been in remission with progression-free survival until the time of their death. In other cases, the progression-free survival period lasted until the date of recurrence or the date of the patient’s death. The overall rates for sensitivity, specificity, positive predictive value and negative predictive values for the CT and PET strategies were calculated on the basis of the recurrences documented during the 2-year follow-up period.

RESULTS

One hundred thirty patients (65 in each group) were evaluated in an ITT analysis; five were excluded from the PP analysis because of missing data. The two arms were matched with regard to the characteristics of both the patients and tumours (Table 1). Overall, the number of patients with a detected recurrence was 44 (23 in the PET group and 21 the Con group; P = 0.60). Recurrence was confirmed either by biopsies or surgery in 27 (21.6% in the PP analysis) of these 44 patients: 15 out of the 60 (25%) patients in the PET-group, and 12 out of the 65 (18.5%) patients in the Con group (P = 0.19). Kaplan–Meier curves for the time from baseline until the detection of a recurrence of the disease during follow-up were obtained, and ITT analysis performed (Figure 2). There was no significant difference between the PET and Con groups with regard to actuarial curves of recurrence (log-rank, P = 0.55); however, for all the patients with a recurrence, the time from baseline until detection of the recurrence was significantly shorter (P = 0.01) in the PET group (12.1 ± 3.6 months) than in the Con group (15.4 ± 4.9 months). However, if we consider only asymptomatic patients without elevated serum tumour markers, then a recurrence was detected in 34 patients (20 PET group patients and 14 in the Con group) by imaging procedures (CT, PET, Chest X-Ray, US). In this case, the time from baseline until the detection of a recurrence was shorter (although not significantly so) in the PET group than in the Con group (log-rank test, P = 0.25) (Figure 3).

Impact on therapy management

As specified in the study design, a curative surgical tumour resection procedure was performed in 17 out of 44 patients (PP analysis): two in the Con arm and 15 in the PET arm (Table 2). In 11 patients, additional imaging procedures were needed before a final decision to treat could be reached: four in the PET group and seven in the Con group. An 18FDG-PET scan was performed in two patients in the Con arm, because despite elevated tumour marker levels, no evidence of recurrence was found using Chest X-ray, CT

Table 1 Patient characteristics

| Variables/patient group | FDG PET | Con | P |
|-------------------------|---------|-----|---|
| Patients, n             | 65      | 65  | — |
| Age, mean (year) (s.d.) | 58.1 (11.2) | 62.0 (12.1) | 0.63 |
| Location of tumours     |         |     |   |
| % Colon                 | 56.2    | 59.4 | 0.86 |
| % Rectum                | 43.8    | 40.6 |     |
| Differentiation of the tumour (%) | | | |
| Good                    | 67.2    | 57.8 |       |
| Intermediate            | 1.6     | 4.7  |       |
| Poor                    | 31.2    | 37.5 | 0.41 |
| Stage IV (%)            | 12.1    | 13.8 | 0.16 |
| Neo-adjuvant treatment (%) |     | | |
| Yes                     | 11.1    | 13.8 |     |
| No                      | 88.9    | 86.2 | 0.79 |
| Adjuvant treatment (%)  |         |     |   |
| Yes                     | 90.5    | 89.2 |       |
| No                      | 9.5     | 10.8 | 0.99 |
| Time (day) since surgery, mean (s.d.) | 231 (60.36) | 223.7 (60.36) | 0.69 |

Con = conventional, FDG-PET = 18fluorodeoxyglucose positron emission tomography.
*1 missing value. **4 missing values.
Recurrence of colon and rectal cancer may occur in asymptomatic patients, and this means that physical examinations, biological marker assays and imaging procedures must also be performed (Figueredo et al, 2003; Meyerhardt and Mayer, 2003). However, improvements in the survival of patients who have had curative therapy for colon or rectal cancer have been attributable to intense follow-up programmes including imaging procedures (Northover et al, 1994; Figueredo et al, 2003). Among these techniques, CT scans seem to be more sensitive than US for detecting liver metastases (Pietra et al, 1994; Schoemaker et al, 2000). PET scan and US. Curative R0 surgery (Table 3) could be performed in 12 cases, more frequently (P<0.01) in patients in the PET group (10 out of 23; 43.5%) than in those in the Con group (two out of 21; 9.5%). It is interesting that the FDG-PET examination was the only imaging procedure to provide a positive finding in six (out of 10) patients in the PET arm, whereas these recurrences were also detected by conventional imaging procedures in the other four patients. In five out of 17 patients who underwent surgery for detecting recurrence were 91, 93, 88.6 and 95% respectively in the PET group, leading to non beneficial procedures (surgery and/or additional imaging). Conversely, FDG-PET failed to detect peritoneal carcinomatosis that was subsequently confirmed by laparoscopy in two patients in the PET group; in one case the patient had rising serum tumour marker levels, and in the other, high protein levels and abnormal peritoneal fluid cytology. The rate of false-negative results was 8% (two of 25) in the PET group. However, in the Con group, recurrences were correctly identified in two patients using 18FDG-PET, and in the PET group recurrences were detected in four patients using 18FDG-PET as the only imaging procedure. Thus, the overall rates of sensitivity, specificity, positive predictive value, negative predictive values for detecting recurrence were 91, 93, 88.6 and 95% respectively in the conventional arm, and 96, 92.1, 89.2 and 97.2%, respectively in the PET arm.

### DISCUSSION

This is the first prospective controlled randomised study using FDG-PET to monitor patients with stage III or IV colon or rectal cancer. We show that FDG-PET is a valuable adjunct to conventional follow-up in patients with a higher risk of recurrence, including those who may be candidates for resection of colorectal, liver or lung metastases. One-third of our patients experienced a recurrence during a 2-year follow-up period, and the rate of curative surgery for liver and/or pulmonary metastases resection was higher in the PET group patients than in the Con group patients, probably due to earlier detection. Recurrence of colon and rectal cancer may occur in asymptomatic patients, and this means that physical examinations, biological marker assays and imaging procedures must also be performed (Figueredo et al, 2003; Meyerhardt and Mayer, 2003). However, improvements in the survival of patients who have had curative therapy for colon or rectum cancer have been attributable to intense follow-up programmes including imaging procedures (Northover et al, 1994; Figueredo et al, 2003). Among these techniques, CT scans seem to be more sensitive than US for detecting liver metastases (Pietra et al, 1998; Schoemaker et al, 1998; Secco et al, 2002), and this procedure is now recommended.
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