Chemotherapy response evaluation with FDG–PET in patients with colorectal cancer

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Background: The aim of this prospective study was to evaluate the value of F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) for early assessment of chemotherapy response in patients with advanced colorectal cancer.

Methods: Dynamic FDG–PET was carried out before and at 2 (n = 50) and 6 months (n = 19) after the start of treatment. Quantitative Patlak analysis [metabolic rate of glucose (MRGlu)] and a simplified method to measure glucose metabolism [standardized uptake value (SUV)] were evaluated. The predictive value of changes in glucose metabolism was assessed with Cox proportional regression analysis. Overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan–Meier estimates.

Results: There was an increase in the rates of death (P = 0.049 for ΔMRGlu PET1–2; P = 0.017 for ΔSUV PET1–2; P = 0.032 for ΔMRGlu PET1–3; P = 0.048 for ΔSUV PET1–3) and progression (P = 0.026 for ΔMRGlu PET1–2; P = 0.035 for ΔSUV PET1–2; P = 0.041 for ΔMRGlu PET1–3; P = 0.081 for ΔSUV PET1–3) associated with worse response as assessed by PET on Cox proportional regression analysis. The OS and PFS analysis showed a significant predictive value at broad ranges of ΔMRGlu and ΔSUV cut-off levels.

Conclusion: The degree of chemotherapy-induced changes in tumor glucose metabolism is highly predictive for patient outcome. The use of FDG–PET for therapy monitoring seems clinically feasible since simplified methods (SUV) are sufficiently reliable.

Key words: chemotherapy response monitoring, colorectal cancer, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET), Patlak analysis (MRGlu), standardized uptake value (SUV)

Introduction

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a molecular imaging technique that visualizes and quantifies metabolic processes in cancer cells. Currently, FDG–PET has an established role in staging colorectal cancer patients before surgical resection of metastases [1–4], in the localization of recurrence in patients with an unexplained rise of serum carcinoembryonic antigen (CEA) [5] and in the assessment of residual masses after treatment [6]. FDG–PET significantly improves patient management, reduces futile surgery, leads to substantial cost savings and probably also to a better patient outcome [7, 8].

There is an increasing interest in the role of FDG–PET beyond staging, for prediction of tumor response to therapy. Although the hallmark for evaluation of therapeutic effectiveness of cancer treatment, current morphological imaging techniques such as computed tomography (CT) have limitations in reliably distinguishing necrotic tumor or fibrotic scar from residual tumor tissue. FDG–PET could be helpful in solving this problem. The positron emitter FDG is transported into cells analogously to glucose and is converted to FDG-6-phosphate. This metabolite is trapped in the cell, as it will not be processed in the glycolytic pathway and hence will accumulate preferentially in cells with high glucose uptake, such as tumor cells [9]. FDG–PET can not only distinguish active disease from residual scar tissue [6] but also quantify FDG uptake to distinguish metabolically highly active from less active tumor tissues. Furthermore, metabolic alterations in tumor cells, indicative of tumor response to therapy, may occur before alterations in tumor size. The experience with FDG–PET in the assessment of therapy response in advanced colorectal cancer, however, is still limited. In the present prospective study, the value of FDG–PET for this indication is investigated, by measuring tumor glucose metabolism before and after 2 and 6 months of chemotherapeutic treatment.
patients and methods

patient eligibility criteria
From March 2002 to December 2005, all patients in the Radboud University Nijmegen Medical Centre with metastatic colorectal cancer, who were scheduled to undergo chemotherapy in a palliative setting, were asked to participate in the study. Patients with diabetes mellitus were excluded. In all patients, treatment decision making was done by a multidisciplinary team including medical oncologists, surgeons, radiation oncologists, pathologists, radiologists and nuclear medicine physicians. Clinicians were blinded to the results of the dynamic FDG–PET scans. The study was approved by the Institutional Review Board of the Radboud University Nijmegen Medical Centre and written informed consent was obtained from each patient.

FDG-PET
quantitative dynamic FDG–PET data acquisition and reconstruction. Dynamic FDG–PET was carried out at baseline and after 2 and 6 months of treatment. Patients fasted for at least 6 h before imaging. All scans were acquired on an ECAT-EXACT47 PET scanner (Siemens/CTI, Knoxville, TN). The field of view for dynamic acquisition was based on whole-body FDG–PET and CT scans were carried out for initial staging. A 20-min transmission scan was made, using the internal 68Ge/68Ga sources, to correct for photon attenuation. Subsequently, ~200 MBq FDG dissolved in 8 ml saline was injected i.v. over a 1-min period, using a constant infusion remote-controlled pump (Medrad, Indianola, PA). The dynamic data acquisition, carried out in septa-extended (two dimensional) mode, was started simultaneously with the injection of FDG and consisted of 16 time frames with variable frame length (10 × 30 s, 3 × 300 s, 3 × 600 s) for a total time of 50 min. A more detailed description of the data acquisition, reconstruction and analysis methods were published previously [10].

plasma time-activity curves. To measure the blood clearance of FDG, plasma time-activity curves were derived from arterial blood sampling when feasible. Arterial blood samples were taken manually to provide an arterial plasma input function as described previously [10]. The radioactivity in plasma was determined using the standard solution method as described by Greuter et al. [11].

When arterial cannulation was contraindicated or not feasible, an image-based input function was determined by measuring FDG counts in a volume of interest (VOI) over the abdominal or ascending aorta, which accurately determines FDG blood levels [10].

tumor time-activity curves. Tumor time-activity curves were obtained by placing VOIs semiautomatically over the tumor metastases using a threshold of 50% of the maximum pixel value within the lesion. For this purpose, the late frames (frame 14–16) were summed, yielding a static image of 30 min duration and a scan midtime of 35 min after injection. The tumor VOIs were then copied to the dynamic imaging sequence to obtain time-activity curves. A volume weighted mean value of tumor glucose use (metabolic rate of glucose, further mentioned MRGlu) of all lesions in each PET scan was derived to provide one value for each study. VOIs drawn on the first FDG–PET (before initiation of chemotherapy) were copied to the second and third FDG–PET (2 and 6 months after the start of treatment).

Patlak graphical analyses. For quantitative measurement of glucose metabolism, Patlak graphical analysis was used to calculate the MRGlu (expressed in μmol ml⁻¹ min⁻¹) in tumor tissue [12, 13]. A detailed description of the Patlak graphical analyses and its assumptions have been published elsewhere [10, 12]. In brief, the Patlak approach takes into account differences in the whole-body distribution of FDG at the time of scanning, which may affect the accumulation of FDG in the tumor tissue. Therefore, the MRGlu is in principle a more reliable measure of tumor glucose use than the standardized uptake value (SUV). The Patlak analysis was carried out over the period from 5 to 50 min after injection. Furthermore, the MRGlu in tumor was calculated by multiplication of the slope of the Patlak plot and the basic blood glucose level (expressed in μmol ml⁻¹) measured before FDG injection (hexokinase method, Arosit, Abbott Diagnostics, North Chicago, IL). The fractional change in MRGlu between the first, second and third FDG–PET was calculated.

standardized uptake value. FDG–PET scans were also evaluated semiquantitatively by SUV analysis. SUVs normalized to injected activity and patients’ body weight were calculated from the mean activity concentration in the tumor VOIs between 40 and 50 min after injection, which is the last time frame of the dynamic scan. A volume weighted mean value of each PET scan was derived from all lesions to give one average SUV (SUVavg, hereafter mentioned SUV) for each PET scan. The fractional change in SUV between the first, second and third FDG–PET was calculated.

clinical follow-up. Follow-up was carried out according to a stringent protocol for 3 years. Apart from clinical examinations, routine laboratory tests and CEA measurement, patients underwent a CT or magnetic resonance imaging scan of the abdomen every 3 months and a CT scan of the chest every 6 months, and in case of inconclusive findings, an ultrasound and/or an additional FDG–PET scan was carried out. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria without knowledge of the results of the PET studies. The date of progression was defined as the earliest date at which disease progression was confirmed. Patients who were progression free at the closeout date (1 March 2007) had their time to progression censored at that date. Survival was measured from the date of the baseline PET scan to the date of death. Patients who were still alive at the closeout date had their survival censored at that date.

statistical analysis. Survival and progression-free survival (PPS) served as the standard of reference. Cox proportional hazards regression analysis was used to assess the predictive value of response evaluation with FDG–PET as expressed in the fractional change in MRGlu and SUV between the FDG–PET at baseline and after 2 and 6 months of chemotherapy. Statistical significance was assessed using the Wald’s chi-square test. The overall survival (OS) and PFS with respect to AMRGlus and ΔSUV were calculated using Kaplan–Meier estimates. The fractional change in measurements between the first and second FDG–PET and the first and third FDG–PET were stratified by a range of cut-off values. However, to avoid the bias of data-driven significance for the cut-off level, also some predefined, prospective definitions of metabolic response were tested. For that purpose the population was categorized according to the definitions for metabolic response of The European Organization for Research and Treatment of Cancer (EORTC) into a group with complete or partial response (Δ < −25%), a group with stable disease (Δ −25% to +25%) and a group with progressive disease (Δ > +25%) [14]. Furthermore, the population was categorized according to the cut-off values also used for size measurement (RECIST), for which it applies that Δ < −30% is complete or partial response, Δ = −30% to +20% is stable disease and Δ > +20% is progressive disease [15]. Groups were compared using the log-rank test (for assessment of OS) and the Breslow test (for assessment of PFS). Since many events of progression occurred during early time points, the Breslow test was used to analyze PFS. Spearman’s rho correlations were used to determine the comparability between the different methods to measure glucose metabolism. Statistical tests were based on a two-sided significance level and the level of significance was set at 0.05.
results

patient characteristics
Sixty-one consecutive patients with advanced colorectal cancer were included in this prospective study. After the first FDG–PET, 11 patients were excluded due to technical issues (n = 1), refusal to undergo a second FDG–PET (n = 3), death before the second FDG–PET (n = 2) and early discontinuation of chemotherapy due to a significant decline in performance status (n = 5). Only in patients who were still on the same treatment schedule after 6 months, a third FDG–PET was carried out. Thus, complete data sets of two PET scans were available in 50 patients and of three PET scans in 19 patients. The mean interval between the first and the second FDG–PET was 61 ± 18 days and between the first and the third FDG–PET 171 ± 32 days. The assessable population consisted of 37 males and 13 females with a mean age of 61 years (range 45–79 years). Patient characteristics are summarized in Table 1.

quantitative changes in FDG uptake
Mean MRGlu at baseline was 0.121 ± 0.059 μmol ml⁻¹ min⁻¹ (range 0.014–0.267) during first evaluation 0.076 ± 0.063 μmol ml⁻¹ min⁻¹ (range 0.007–0.263) and during second evaluation 0.087 ± 0.074 μmol ml⁻¹ min⁻¹ (range 0.001–0.246). The median fractional change at first evaluation of MRGlu as compared with baseline was −52% ± 100% (range −90% to +388%) and at second evaluation −46% ± 57% (range −99% to +140%). Mean SUV at baseline was 5.16 ± 1.84 (range 1.68–9.81) during first evaluation 4.09 ± 2.11 (range 1.15–11.30) and during second evaluation 4.58 ± 2.13 (range 2.19–9.81). The median fractional change at first evaluation of SUV as compared with baseline was −28% ± 32% (range −64% to +61%) and at second evaluation −17% ± 54% (range −59% to +18%).

Figure 1 shows a typical example of a patient with liver metastases of colorectal carcinoma who responded to chemotherapy.

Figure 1. Last time frame of the dynamic data acquisition carried out in septa-extended mode and reconstructed using filtered backprojection. Transversal slice through the liver at baseline (A) and after 2 months of chemotherapy (B). This is a typical example of a patient with liver metastases that respond to chemotherapy. After 2 months of chemotherapy there is a 52% decrease in metabolic rate of glucose and a 41% decrease in standardized uptake value relative to baseline F-18-fluorodeoxyglucose–positron emission tomography.

Table 1. Patient characteristics

<table>
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<tr>
<th>Mean age</th>
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<td>Location of primary tumor</td>
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prediction of survival by FDG–PET

There was a significant increase in death rates associated with worsening response as assessed by PET on Cox proportional regression analysis ($P = 0.049$ for $\Delta$MRGlu and $P = 0.017$ for $\Delta$SUV after 2 months of chemotherapy and for $\Delta$MRGlu after 6 months of chemotherapy ($P = 0.041$ for $\Delta$MRGlu and $P = 0.081$ for $\Delta$SUV). The overall- as well as the progression-free Kaplan–Meier survival analysis showed significant discriminative $P$ values at broad ranges of $\Delta$MRGlu and $\Delta$SUV ($P = 0.035$) after 2 months of chemotherapy and for $\Delta$MRGlu after 6 months of chemotherapy ($P = 0.026$) and $\Delta$SUV ($P = 0.048$ for $\Delta$SUV after 6 months of chemotherapy). There was also an increase in the rates of progression associated with worsening response as assessed by PET on Cox proportional regression analysis that was statistically significant for both $\Delta$MRGlu and $\Delta$SUV cut-off levels. In Figure 2A ($\Delta$MRGlu, cut-off value of $-65\%$) and Figure 2B ($\Delta$SUV, cut-off value of $-20\%$), typical examples of Kaplan–Meier curves for OS are shown. Applying predefined, prospective definitions of metabolic response with cut-off levels according to Young et al. [14] (EORTC) and according to the cut-off levels also used for size measurement (RECIST), some significant differences in PFS ($P = 0.002$ for EORTC and $P = 0.001$ for RECIST) and OS ($P = 0.064$ for EORTC and $P = 0.023$ for RECIST) are seen for $\Delta$SUV between the first and second FDG–PET. For $\Delta$MRGlu, however, only the predefined cut-off levels according to EORTC showed statistically significant differences for prediction of PFS ($P = 0.036$).

discussion

This prospective study shows that fractional changes in tumor glucose metabolism were highly predictive for outcome, stratifying patients into groups with sharply distinguished OS and PFS probabilities. The strength of the study is that also some prospective definitions of metabolic response were evaluated. The results imply that measurement of treatment-induced changes in tumor glucose metabolism with PET is quite robust. This indicates that FDG–PET can be readily implemented when some basic requirements of quality assurance are met without the need for complex dynamic imaging protocols [16]. Also, a noncomplex approach will facilitate broad introduction in clinical practice and improve patient compliance, an important feature of successful clinical trials. Another advantage of the SUV is that it can be calculated from static whole-body FDG–PET studies, which depicts all metastases. In dynamic scans, only one axial field of view of typically 15–20 cm can be studied during the dynamic data acquisition. As metastatic lesions in different parts of the body may respond differently to chemotherapy, this represents a principal advantage of SUV over Patlak analysis.

Several studies indicated a possible role for FDG–PET in the prediction and evaluation of treatment response, such as monitoring of radiotherapy and multimodality treatment response in primary rectal cancer [17–23] and monitoring response after local ablative therapy of liver metastases [24–27]. The experience in the assessment of chemotherapy response in advanced colorectal cancer, however, is limited to four reports in mostly small series of patients with irresectable liver metastases [28–31]. Findlay et al. [28] studied 18 patients treated with 5-FU chemotherapy. A correlation was observed between the reduction of tumor metabolism 5 weeks after the initiation of chemotherapy and treatment outcome, which was not observed at 1–2 weeks on treatment. These results show the importance of a correct timing of FDG–PET after the onset of chemotherapy. Bender et al. [29] studied 10 patients with irresectable liver metastases before and 72 h after a single infusion of 5-FU and folinic acid. SUVs were correlated with therapy outcome, with a follow-up of at least 6 months. More recently, Dimitrakopoulou-Strauss et al. [30, 31] examined the ability of serial semiquantitative as well as quantitative dynamic FDG–PET examinations in 28 patients to predict

Figure 2. Kaplan–Meier estimates for overall survival (OS). Kaplan–Meier analysis of the relationship between OS and (A) $\Delta$metabolic rate of glucose (MRGlu) between the first and second F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) (dichotomized using a cut-off value of $-65\%$, $P = 0.009$) and (B) $\Delta$standardized uptake value (SUV) between the first and the second FDG–PET (dichotomized using a cut-off value of $-20\%$, $P = 0.021$).
response to second-line FOLFOX (5-FU/folinic acid/oxaliplatin) at baseline and after the first and second cycle. The authors postulated that quantitative, dynamic FDG–PET should be used preferentially for response monitoring. However, the results of the present study, that included almost twice as much patients, showed that semiquantitative analysis is sufficiently reliable.

In conclusion, FDG–PET imaging may be used to predict the clinical outcome of chemotherapy in patients with advanced colorectal cancer. The findings of the present study provide the basis for randomized clinical trials to evaluate if FDG–PET-based decisions to change treatment prevents toxicity and costs of ineffective therapy without negatively affecting OS.

references