PET Studies of Fluorodeoxyglucose Metabolism in Patients with Recurrent Colorectal Tumors Receiving Radiotherapy

Uwe Haberkorn, Ludwig G. Strauss, Antonia Dimitrakopoulou, Rita Engenhart, Franz Oberdorfer, Hermann Ostertag, Jürgen Romahn, and Gerhard van Kaick

Deutsches Krebsforschungszentrum, Heidelberg, Germany and Universitäts-Strahlenklinik, Heidelberg, Germany

Forty-four patients with recurrent colorectal carcinoma were examined prior to a combination of conventional photon radiotherapy (40 Gy) and neutron therapy (10 Gy). Twenty-one of these underwent a PET examination after photon therapy and 12 also were studied after the end of combined therapy. Forty-four patients with recurrent colorectal carcinoma were treated with photon therapy and 12 patients with and 12 also were studied after the end of combined therapy.

PET Studies of Fluorodeoxyglucose Metabolism

PET Studies in these patients in order to assess the therapy-induced changes in tumor metabolism.

Patients and Methods

Forty-four patients (age between 41 and 80 yr, male-to-female ratio 1:1) with histologically proven recurrent colorectal carcinoma were examined after previously curative surgery. The patients had received no chemotherapeutic or radiation therapy prior to the combined photon-neutron radiation. Six of the 44 patients had distant metastases prior to therapy. The decision for the mixed-beam schedule was made by the oncologic panel of the University of Heidelberg. All 44 patients had a baseline PET examination (prior to the radiation therapy); 23 had only the baseline PET study, 9 also were examined after photon therapy, and 12 underwent three PET examinations (PET prior to therapy, after photon therapy, 6 wk after neutron therapy). In seven cases, we performed studies 7 or 14 days after the onset of photon therapy.

The combination treatment consisted of 40 Gy photons, given in 2-Gy fractions (five fractions per week), followed by 10-Gy neutrons (1-Gy fractions, three fractions per week, 14 MeV neutrons from a deuteron-tritium generator). The neutrons were applied as a boost by use of an arc therapy technique with a safety margin of 1.5-2 cm (12,13). Informed consent was given by all patients.

Pelvic CT was performed with a Siemens Somatom DRH. Eight-millimeter thick continuous sections were acquired and skin markings were performed for correlative positioning of PET over the tumor area. The PET examinations were carried out using a PC2048-7WB scanner (Scanditronix, Uppsala, Sweden) and two detector rings (512 bismuth germanate-gadolinium orthosilicate detectors). Therefore a simultaneous acquisition of
two primary and one cross-section is possible. The slice thickness is approximately 11 mm. The mean sensitivity of the system is 12,500 cps/μm/cm² for the primary sections and 17,500 cps/μm/cm² for the cross section. Transmission scans with more than 10 million counts per section were performed prior to emission scanning. PET images were acquired 1 hr after intravenous administration of 9–12 mCi ¹⁸F-fluorodeoxyglucose (FDG). The acquisition time was 10 min. The total number of counts per slice exceeded one million.

Fluorine-18-FDG was produced using the method described by Oberdorfer et al. (18). Radiochemical purity was measured using high-performance liquid chromatography and exceeded 98% (18).

PET images were generated with an iterative reconstruction program (19) on a VAX 11/750 (Digital Equipment, Maynard, MA) computer system. The image matrix was 128 × 128 and interpolated to 256 × 256 for display. The spatial resolution was 5.1 mm. The pixel size was 4 × 4 mm in all reconstructed images. A correction for attenuation and scattering was done.

The identification of anatomic structures was done by comparing the PET sections with the CT images. For quantitative evaluation, regions of interest (ROIs) were positioned in tumor and normal soft tissue (gluteal muscles) with a region size exceeding 32 pixels in all cases. FDG uptake was expressed as the standardized uptake value (SUV): SUV = tissue concentration (nCi/g)/injected dose [nCi]/body weight [g].

The CEA plasma level was measured from EDTA-treated plasma samples taken immediately before the PET examination with an enzyme linked immunosorbent assay using streptavidin technology (Enzymun-Test® CEA measured on an ES 600, Boehringer, Mannheim, Germany). The measuring range of the test is 0.55 ng/ml with a lower detection limit of 0.5 ng/ml. The upper limit of the normal range is 5 ng/ml. Furthermore, the glucose-plasma level was measured by use of a standard clinical test. The correlation of the FDG uptake and the glucose-plasma level was evaluated and the regression function was calculated.

RESULTS

Eighty-four examinations in 44 patients were evaluated. The FDG uptake prior to therapy ranged from 1.14 to 4.9 SUV (median value = 2). Figure 1A shows the FDG uptake pattern in 20 of the 44 patients, which were evaluated prior and after photon therapy. We noted a decrease in FDG uptake in 11 cases, while 2 patients had an increase in FDG accumulation and 7 remained unchanged. There was a significant difference between the median uptake values prior and after photon therapy (u-test: p = 0.094). The data of 12 patients, which were evaluated prior and after combined therapy are shown in Figure 1B: six patients had a decrease in FDG uptake. Figure 1C shows the situation after photon therapy compared to the situation after the end of the combined therapy (n = 11). A further decrease was observed only in three cases, five patients had an increase and three patients had no change in FDG uptake. The uptake values for 12 patients, which were studied prior to therapy, after 40 Gy photons, and after the end of combined therapy are given in Table 1.

An example of a patient prior and after therapy is shown in Figures 2 and 3. On the CT image (Fig. 2A) a large pre-sacral mass is noted. This was the situation 6 mo after surgery prior to radiation therapy. The corresponding PET-image (Fig. 2B) shows the pre-sacral mass with an intense FDG accumulation. The situation 5 mo after the onset of the treatment is shown in Figure 2C-D. There was a significant decrease in FDG accumulation. However, there was residual metabolism present in the lesion. We noted an enhanced FDG uptake in the fatty tissue of the irradiated field (Fig. 2D). The CEA plasma values in this patient remained within the normal range for 119 days (Fig. 3).

The PET FDG data were compared with the CEA values in 41 cases prior and during therapy. Normal CEA levels were associated with increased FDG uptake in 14 of the 41 examinations, while in only two cases was CEA increased and FDG uptake was within the limits for normal soft tissue (Fig. 4). The glucose-plasma levels varied between 61 mg/100 ml and 217 mg/100 ml (median

![FIGURE 1.](image)

(A) Standardized FDG uptake (SUV) in 20 patients prior to therapy (median = 2) and after 40 Gy photon therapy (median = 1.8). Three patients had a SUV of 2 prior to therapy and of 1.8 after photon therapy. Line = line of identity. (B) FDG uptake (SUV) in 11 patients prior to therapy and after the combination of photon and neutron therapy (median = 1.8). (C) FDG uptake (SUV) in 11 patients after photon therapy and after the end of the combined therapy.

1486 The Journal of Nuclear Medicine • Vol. 32 • No. 8 • August 1991
value = 112). We noted only a low correlation with \( r = 0.46 \) (polynomial regression, \( p = 0.002 \)) between FDG uptake and glucose-plasma levels in 47 cases (Fig. 5).

**DISCUSSION**

It is well known since the early studies of Warburg (20,21) that aerobic glycolysis is elevated in neoplastic tissue. While the most data exist for hepatomas, increased activities of the key enzymes of glycolysis have also been observed in human colon tumors (22). FDG as a glucose analog is transported into the cell and trapped in its phosphorylated form (23,24). This principle of metabolic trapping can be used for oncological studies. Strauss et al. (25) showed that PET with FDG is a useful method for the differentiation between scar tissue and recurrent neoplastic disease in colorectal tumors. Furthermore, PET FDG data have been correlated with histologic malignancy grading in brain tumors (26–29). This is in line with results of Sweeney et al. (30), showing that the acceleration of glycolysis corresponds to the tumor's growth rate. Alavi et al. suggested that these data can be used to predict survival rates (31). DiChiro et al. observed a dependence of the recurrence of intracranial meningiomas on the glycolytic rate as estimated by PET (27).

The possibility to obtain quantitative, reproducible data...
about the metabolic state of tumors permits the application of PET in the evaluation of the treatment response in tumors. In our study, a complete or partial palliative effect was achieved in all patients. However, in only 2 of 12 cases with three or more examinations were FDG uptake values for normal soft tissue reached. Moreover, only in about 50% of the patients we noted a decrease in FDG uptake after therapy. In a study with head and neck tumor patients, Minn et al. (33) observed a difference in FDG uptake in radiosensitive and radioresistant tumors. They used a conventional gamma camera with the consequence that the tumor-to-tissue ratio in their evaluation could neither be corrected for blood activity nor for the activity of the under- or overlying tissue. However, they found that nonresponders to radiotherapy showed no decrease in FDG accumulation. Abe and Isoslevsky (33,34) found a reduction of the amount of uptake of radiopharmaceuticals after therapy in animal studies, indicating that there was less viable tissue in the tumor masses. These data were observed for the first two days (33) and up to 20 days (34) after therapy. Ogawa et al. (35) reported a decrease in four of five cases in a study with five patients undergoing combined chemo- and radiotherapy. The differences in response between these studies and our results may depend on the tumor types as well as the different treatment protocols.

The fact that there was no further significant decrease in FDG uptake after neutron therapy is still puzzling. There are two possible explanations for this finding: first this may be due to inflammatory effects caused by radiation. It is well known that these effects occur and may last for the first half year after the end of the therapy (36). Inflammation may also be the cause for the finding that only 50% of the patients had a significant decrease after the combined therapy compared to the initial situation. Therefore, the observation interval may still be 3 mo, but it must include an examination 6–9 mo after the end of the therapy. In some patients, we noted a radiation effect in the soft tissue in the irradiated field. These patients showed increased radiopacity in CT scans and a moderately enhanced FDG uptake (Fig. 2D), which is indicative for a noninfectious inflammation. Furthermore, inflammatory tissue may mimic recurrent tumor. A patient initially considered for radiation therapy showed a questionable lesion and an increased FDG uptake (SUV-2) in the pelvic region, while endoscopy and histology revealed an inflammation with multiple fistulas (Fig. 6A-B). This patient was not included in the study population. The data show that increased FDG uptake in tumor patients can be caused both by residual tumor metabolism as well as by inflammation.

The second explanation may be that there is indeed no curative benefit of neutron therapy. The only benefit is a palliative one. This statement is supported by the preliminary results of Engenhart et al. (37), who showed that incomplete and complete pain relief was achieved in 28 patients treated with a mixed-beam schedule, while no curative therapy was observed in these patients.

Both explanations agree well with the finding that in most of the patients we observed a satisfactory palliative effect. PET provides mean values for a definite tissue volume including possible inflammatory regions and residual tumor cells. Reparatory and inflammatory events together with residual tumor tissue may be responsible for an unchanged or decreased but still elevated FDG uptake in the irradiated area. The fraction of inflammatory tissue is dependent on the follow-up interval, therefore long-term follow-up studies should reflect mainly scar and/or residual tumor tissue.

The concept of heterogeneity of radiation response in tumors is one of the most promising for the explanation of tumor recurrences after radiation. Radioresistant cells have been found in recurrent irradiated head and neck cancer and in clones of an epidermoid cell line (38,39). This fact may complicate predictive assays for the clinical use. In detecting residual tumor tissue, PET can contribute to the clinicians decision for curative and/or additive measures.

Yamada and others (40) showed in animal experiments that the uptake in the brain decreased linearly with increasing blood glucose. The FDG uptake in rat hepatomas was not correlated with the plasma-glucose level. In our study, the FDG uptake in colorectal tumors showed only a low correlation to the plasma-glucose level. The glucose level was measured from samples taken immediately before the injection of FDG. We measured the uptake values with PET one hour after the injection. So we had to assume

![FIGURE 5. Glucose-plasma level and FDG uptake value 1 hr after tracer injection (n = 47); polynomial regression: y = a + bx + cx² with a = 5.218936, b = 0.060381, and c = 0.000267; variance = 0.96562, STD = 0.982663 (p = 0.002).]
that there was no dramatic change in glucose level during this time interval.

Tumor markers have been proposed as a means for the monitoring of patients undergoing therapy. According to the results of Davey et al. (41), the pre-treatment CEA plasma levels are a predictor for treatment response. The authors defined response in terms of regression of palpable disease. In our study, we found a normal CEA level in 14 of 41 cases concomitant with an elevated FDG-SUV. Since all these patients had a recurrent tumor, the FDG uptake is a more sensitive parameter for the follow-up of irradiated recurrences than the CEA plasma level. Similar results were found by Nagata et al. (42) in liver tumors. They observed in a few cases a good visualization of the tumors in the absence of elevated tumor markers. Dexter and others (43,44) described heterogenous cell lines from colon carcinomas with different DNA content and different sensitivities to chemotherapeutic agents. Moreover, Kimball (45) isolated a subpopulation in which CEA production could not be demonstrated. This cell line showed an increased resistance to 5-FU and was metastatic when injected in mice. Finally, Balles (46) found an influence of radiotherapy on the plasma CEA level, resulting in different critical values for the detection of a recurrence as compared to patients undergoing no radiotherapy. Taken together, these data indicate that the CEA plasma level is not an accurate parameter (especially in radio-nonresponders) for therapy control.

In conclusion, we can state that PET using FDG is a sensitive method for the measurement of early effects after radiotherapy of recurrent colorectal cancer. A problem in the evaluation of the measured value is the fact that PET obtains mean values of a considerably larger tissue volume, which may consist of a population of inflammatory cell and residual tumor cells. It is doubtful that this can be overcome by interpreting maximal values in the ROI since this must be done under the assumption of a clear cut difference between the metabolic needs of inflammatory areas and the metabolism of residual tumor tissue.

Furthermore, there remains the lack of a "normal" value for scar tissue to get a definitive measure of what is going on in the irradiated area and clonogens clearly cannot be detected by the method. However, it is possible to perform follow up studies. Most of the inflammatory effects will be gone 6 mo after therapy (36) and a recurrent tumor can be detected. This is the link to another clinical application of PET: the task to optimize and individualize a therapeutic scheme. As we know from many studies, each tumor has to be seen as an individual, both concerning the initial metabolic status and the extent of response to therapy. In irradiated colorectal recurrences, this will require in some cases longer observation intervals.

ACKNOWLEDGMENTS

The authors thank H. Marx, H. Trojan, H. Gasper, W. Konowalczyn, K. Weber, W. Weber, S. Obrecht, and E. Bender for their help in performing this study.

REFERENCES


PET Studies of Fluorodeoxyglucose Metabolism in Patients with Recurrent Colorectal Tumors Receiving Radiotherapy

Uwe Haberkorn, Ludwig G. Strauss, Antonia Dimitrakopoulou, Rita Engenhart, Franz Oberdorfer, Hermann Ostertag, Jürgen Romahn and Gerhard van Kaick


This article and updated information are available at:
http://jnm.snmjournals.org/content/32/8/1485

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml