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

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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. CEA plasma levels were measured from blood samples taken immediately before the PET study. A significant decrease in FDG uptake despite good palliative results were observed in only 50% of the patients. This may be explained by inflammatory reactions caused by radiation injury. Inflammation and metabolically active residual tumor tissue cannot be distinguished. It is concluded that an observation interval longer than 6 mo may more effectively detect residual tumor activity. In 14 of 41 examinations, an increased FDG uptake was associated with a normal CEA value, and in only two cases were normal FDG uptake values and increased CEA levels found, suggesting that PET is more sensitive than the measurements of CEA plasma levels for tumor recurrence.

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Recurrent colorectal cancer occurs in 20%–40% of patients within the first two years after potentially curative surgery (1,2). In these patients, radiation therapy can result in tumor control or convert an inoperable tumor to an operable status. Furthermore, palliative effects such as survival rate and pain relief (*3–9*) can be improved. Combinations of radiation and chemotherapy achieved no improvement in survival rate, complete remission rate, or local failure rate as compared to radiation alone (*10*). Neutron therapy seems to have some benefit because of its lower dependence on the tissue oxygen extraction function (*11*). In the literature (*12–14*), an improvement of the local control rate in patients treated with combined photon-neutron therapy as compared to photon therapy alone is reported. However, the difficulty to establish an accurate estimation of therapy response exists in spite of the tumor evaluation with new modalities. Assays testing the radiosensitivity of tumor samples have several major difficulties: low cell yield, preparatory problems with single cell suspensions and contamination (*15*). Computed tomography (CT) has interpretation problems resulting in a discrepancy between subjective parameters such as pain relief and morphologic changes (e.g., tumor size). In most cases, CT demonstrates remaining presacral masses after therapy (*16,17*) leaving the possibility that there is residual active tumor tissue. In contrast, PET has the possibility to determine noninvasively whether the therapy causes a significant change in the tumor physiology and can be used as a predictor of therapy response. We performed PET studies in these patients in order to assess the therapy-induced changes in tumor metabolism.

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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 chemo- 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 deuterium-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/cm^3 for the primary sections and 17,500 cps/μm/cm^3 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 ^{18}F-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-TestR 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

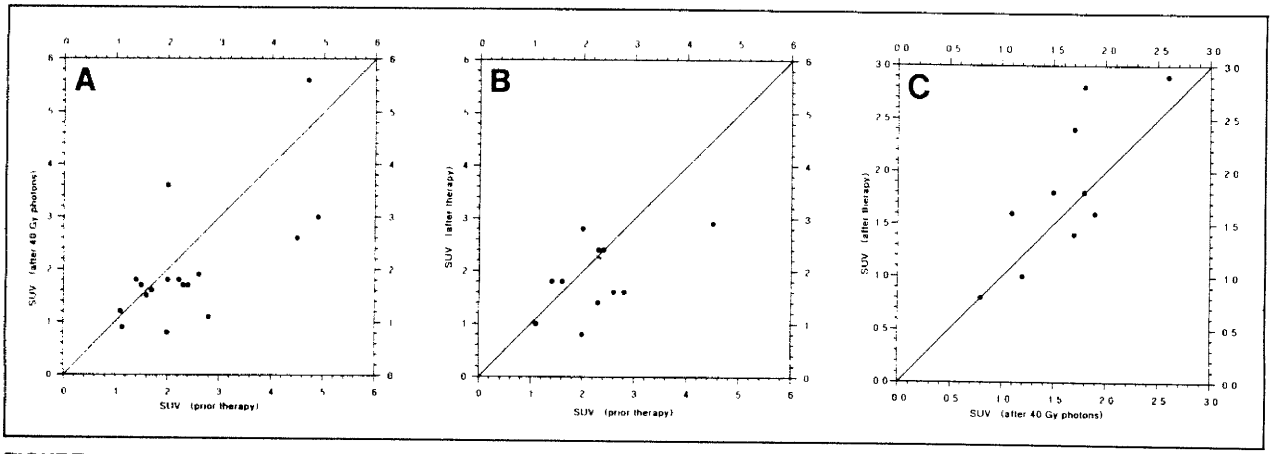

FIGURE 1. (A) Standardized FDG uptake (SUV) in 20 patients prior to therapy (median = 2) and after 40 Gy photon therapy (median = 1.8). Three patients had a SUV of 2 prior to therapy and of 1.8 after photon therapy. Line = line of identity. (B) FDG uptake (SUV) in 11 patients prior to therapy and after 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.

TABLE 1
Standardized FDG Uptake Values in 12 Patients Prior to Therapy, After Photon Therapy, and After Combined Therapy (n.e. = not evaluable)

Patient no.	Baseline	Photon therapy	Combined therapy
1	2	0.8	0.8
2	2.8	1.1	1.6
3	1.1	1.2	1
4	2	1.8	2.8
5	2.6	1.9	1.6
6	2.3	n.e.	2.4
7	2.4	1.7	1.4
8	2.3	1.7	1.4
9	1.4	1.8	1.8
10	4.5	2.6	2.9
11	1.6	1.5	1.8
12	4.9	3	3.2

value = 112). We noted only a low correlation with r = 0.46 (polynomal regression, p = 0.002) between FDG uptake and glucose-plasma levels in 47 cases (Fig. 5).

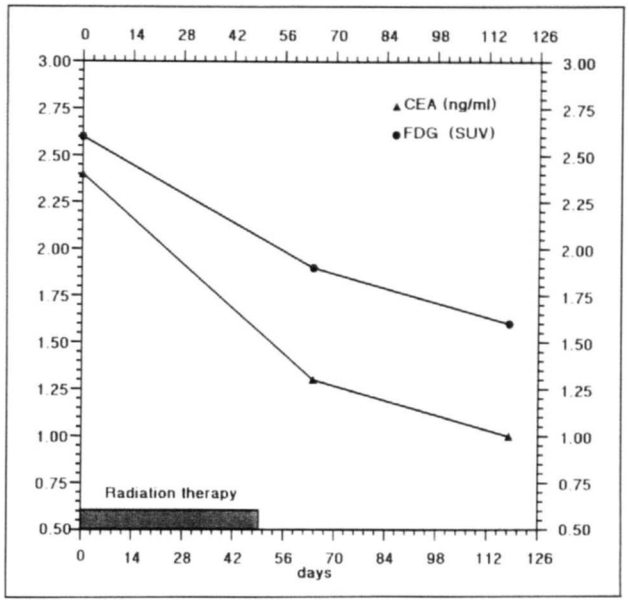

FIGURE 3. FDG uptake and CEA plasma level of the same patient in Figure 2 prior to therapy and up to 119 days after the onset of the therapy.

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

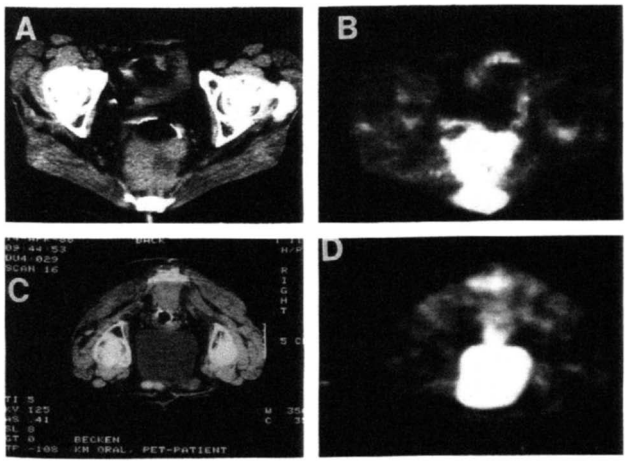

FIGURE 2. CT (A) and PET (B) images of a patient with recurrent colorectal carcinoma prior to therapy. CT (C) and PET (D) image of the same patient 15 days after the onset of therapy.

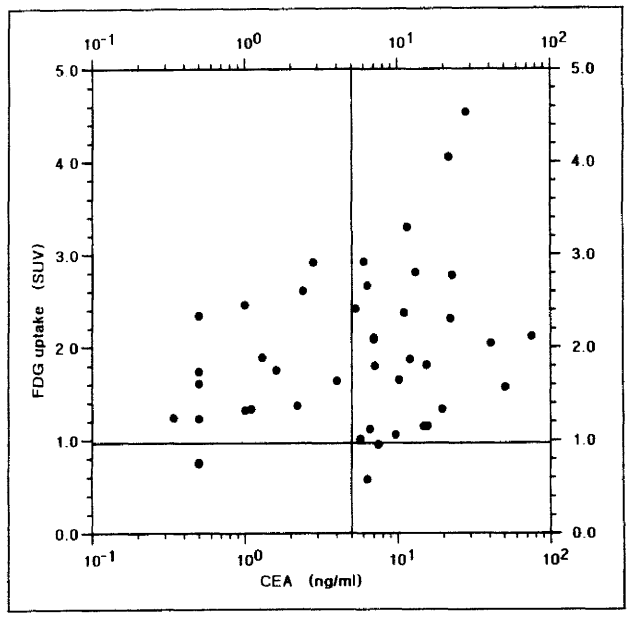

FIGURE 4. CEA plasma concentration and FDG uptake values 1 hr after tracer injection in 41 cases. Normal range: CEA = 0-5 ng/ml; FDG < 1.0 SUV.

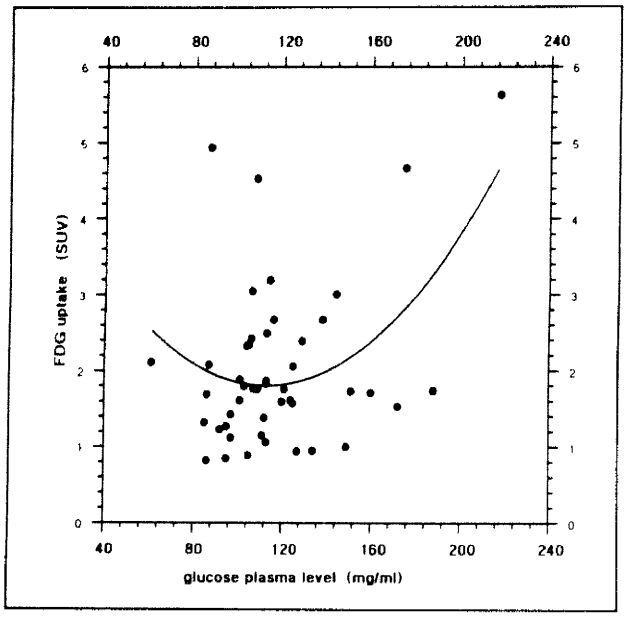

FIGURE 5. Glucose-plasma level and FDG uptake value 1 hr after tracer injection (n = 47); polynomal regression; $y = a + bx + cx^2$ with a = 5.218936, b = 0.060381, and c = 0.000267; variance = 0.96562, STD = 0.982663 (p = 0, 002).

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. (*32*) observed a difference in FDG uptake in radioresponsive 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 Iosilevsky (*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 curation 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

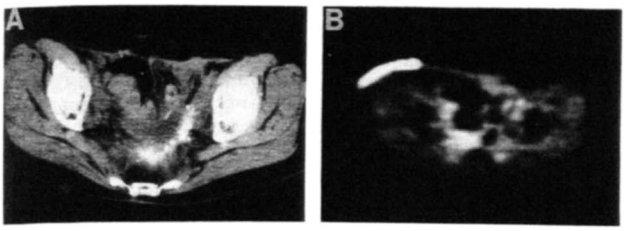

FIGURE 6. CT (A) and PET (B) images of a patient with a lesion in the pelvic region (SUV = 2). Histology revealed an inflammation with multiple fistulas. The intense accumulation on the ventral side of the patient is caused by a FDG-filled anus praeter.

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, Balslev (*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.

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REFERENCES

1. Philipshen SJ, Heilweil M, Quan SH, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. *Cancer* 1984;53:1354–1362.
2. Rich T, Gunderson LL, Lew R, Galdibini JJ, Cohen AL, Donaldson G. Patterns of recurrence of rectal cancer after potentially curative surgery. *Cancer* 1983;52:1317–1329.
3. Allum WH, Mack P, Priestman TJ, Fielding JW. Radiotherapy for pain relief in locally recurrent colorectal cancer. *Ann R Coll Surg Engl* 1987;69:220–221.
4. Beart RW, Martin JW, Gunderson LL. Management of recurrent rectal cancer. *Mayo Clin Proc* 1986;61:448–450.
5. Dobrowsky W, Schmid AP. Radiotherapy of presacral recurrence following radical surgery for rectal carcinoma. *Dis Colon Rectum* 1985;28:917–919.
6. Herzog J, Schmidt B, Fassbender T, Hübener KH. Die Stellung der Strahlentherapie in der Behandlung von Lokalrezidiven bei Rektumkarzinomen. *Strahlenther Onkol* 1988;164:121–128.
7. Pacini P, Cionini L, Ciatto S, Tucci E, Sebaste L. Symptomatic recurrences of carcinoma of the rectum and sigmoid—the influence of radiotherapy on the quality of life. *Dis Colon Rectum* 1986;29:865–868.
8. Schmidt H, Müller RP, Hildebrand D. Ergebnisse der Strahlenbehandlung bei Rezidiven kolorektaler Tumoren. *Strahlenther Onkol* 1984;160:288–292.
9. Wannenmacher M. Strahlentherapie bei Tumorrezidiven im Gastrointestinaltrakt. *Chirurg* 1985;56:499–502.
10. Rominger CJ, Gunderson LL, Gelber RD, Conner N. Radiation therapy alone or in combination with chemotherapy in the treatment of residual or inoperable carcinoma of the rectum and rectosigmoid or pelvic recurrence following colorectal surgery. *Am J Clin Oncol* 1985;8:118–127.
11. Field SB, Fowler JF. The biological basis for neutron therapy. *J Eur Radiother* 1984;5:170–175.
12. Engenhart R, Kimmig B, Marin-Grez M, Höver KH, Flentje M, zum Winkel K. Combined neutron-photon-therapy of locally recurrent rectosigmoidal tumors. *Strahlenther Onkol* 1989;165:327–329.
13. Kimmig B, Engenhart R, Flentje M, Marin-Grez M, Hover KH. Strahlentherapie mit Photonen und Neutronen bei Rezidiven kolorektaler Tumoren. *Röntgenblätter* 1989;42:47–50.
14. Breteau N, Destembert B, Favre A, Sabattier R, Schlienger M. An interim assessment of the experience of fast neutron boost in inoperable rectal carcinomas in Orleans. *Bull Cancer (Paris)* 1986;73:591–595.
15. Peters LJ. Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response. *Radiotherapy and Oncology* 1990;17:177–190.
16. Flentje M, Frey M, Kuttig H, Kimmig B. Strahlentherapie bei Lokalrezidiven kolorektaler Tumoren. Prognostische Faktoren, Verlaufsdiagnostik und Ergebnisse. *Strahlenther Onkol* 1988;164:402–407.
17. Bohndorf W, Richter E, Aydin H. CT—Diagnostik und Strahlentherapie lokaler Rezidive nach Operation eines Rektumkarzinoms. *Strahlentherapie* 1984;160:318–323.
18. Oberdorfer F, Hull WE, Traving BC, Maier-Borst W. Synthesis and purification of 2-deoxy-2-^{18}fluoro-D-glucose and 2-deoxy-2-^{18}fluoro-D-mannose: characterization of products by ^{1}H- and ^{19}F-NMR spectroscopy. *Int*

J Appl Radiat Isot 1986;37:695–701.
19. Schmidlin P, Kubler WK, Doll J, Strauss LG, Ostertag H. Image processing in whole body positron emission tomography. In: Schmidt HAE, Csernay L, eds. *Nuklearmedizin* Stuttgart: Schattauer;1987:84–87.
20. Warburg O, Wind F, Negelein E. On the metabolism of tumors in the body. In: Warburg O, ed. *The metabolism of tumors*. London: Constable; 1930:254–270
21. Warburg O. Über den Glukosestoffwechsel der Carcinomzelle. *Klin Wochenschr* 1925;4:534–536.
22. Weber G, Lui MS, Takeda E, Denton JE. Enzymology of human colon tumors. *Life Sci* 1980;27:793–799.
23. Bessell EM, Thomas P. The effect of substitution at C-2 of D-glucose 6-phosphate on the rate of dehydrogenation by glucose 6- phosphate dehydrogenase (from yeast and from rat liver). *Biochem J* 1973;131:83–89.
24. Coe EL. Inhibition of glycolysis in ascites tumor cells preincubated with 2-deoxy-2-fluoro-D-glucose. *Biochim Biophys Acta* 1972;264:319–327.
25. Strauss LG, Clorius JH, Schlag P, et al. Recurrence of colorectal tumors: PET evaluation. *Radiology* 1989;170:329–332.
26. DiChiro G, DeLaPaz R, Brooks R, et al. Glucose utilization of cerebral gliomas measured by (^{18}F) fluorodeoxyglucose and positron emission tomography. *Neurology* 1982;32:1323–1329.
27. DiChiro G, Hatazawa J, Katz DA, Rizzoli HV, DeMichele DJ. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. *Radiology* 1987;164:521–526.
28. Kornblith PL, Cummins CJ, Smith GH, Brooks RA, Patronas NJ, DiChiro G. Correlation of experimental and clinical studies of metabolism by PET scanning. *Prog Exp Tumor Res* 1984;27:170–178.
29. Mineura K, Yasuda T, Kowada M, et al. Positron emission tomographic evaluation of histological malignancy in gliomas using oxygen-15 and fluorine-18-fluorodeoxyglucose. *Neurological Res* 1986;8:164–168.
30. Sweeney MJ, Ashmore J, Morris HP, et al. Comparative biochemistry of hepatomas. IV. Isotope studies of glucose and fructose metabolism in liver tumors of different growth rates. *Cancer Res* 1963;23:995–1002.
31. Alavi JB, Alavi A, Chawluk J, et al. Positron emission tomography in patients with glioma. A predictor of prognosis. *Cancer* 1988;62:1074–1078.
32. Minn H, Paul R, Ahonen A. Evaluation of treatment response to radiotherapy in head and neck cancer with fluorine-18-fluorodeoxyglucose. *J Nucl Med* 1988;29:1521–1525.
33. Abe Y, Matsuzawa T, Fujiwara T, et al. Assessment of radiotherapeutic effects on experimental tumors using ^{18}F-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 1986;12:325–328.
34. Iosilevsky G, Front D, Bettman L, Hardoff R, Ben-Arieh Y. Uptake of gallium-67-citrate and (2-^{3}H)deoxyglucose in the tumor model, following chemotherapy and radiotherapy. *J Nucl Med* 1985;26:278–282.
35. Ogawa T, Shishido F, Inugami A, et al. Assessment on changes of blood flow and metabolism in patients with cerebral gliomas following radiochemotherapy. In: Matsuzawa T, ed. *Proceedings of the international symposium on current and future aspects of cancer diagnosis with positron emission tomography*. Sendai: Tohoku University; 1985:69–74.
36. Perez CA, Brady LW, eds. *Principles and practice of radiation oncology*. Philadelphia: Lippincott; 1987:1–48.
37. Engenhart R, Kimmig B, Marin-Grez M, Hover KH, Strauss LG, Kaick G. Prospective clinical trial of patients with unresectable locally recurrent rectosigmoidal tumors treated with combined neutron-photon therapy. *Radiology* 1988;169(P):320.
38. Weichselbaum RR, Beckett MA, Dahlberg W, Dritschilo A. Heterogeneity of radiation response of a parent human epidermoid cell line and four clones. *Int J Radiation Oncology Biol Phys* 1988;14:907–912.
39. Weichselbaum RR, Beckett MA, Schwartz JL, Dritschilo A. Radioresistant tumor cells are present in head and neck carcinomas that recur after radiotherapy. *Int J Radiation Oncology Biol Phys* 1988;15:575–579.
40. Yamada K, Matsuzawa T, Endo S, et al. Differences in glucose metabolism among brain, myocardium and tumor. In: Matsuzawa T, ed. *Proceedings of the international symposium on current and future aspects of cancer diagnosis with positron emission tomography*. Sendai: Tohoku University; 1985:28–33.
41. Davey P, Arnott SJ, Sturgeon CM. Carcinoembryonic antigen as a prognostic indicator in the radiotherapeutic management of rectal cancer. *Eur J Surg Oncol* 1987;13:17–20.
42. Nagata Y, Yamamoto K, Hiraoka M, et al. Monitoring liver tumor therapy with F-18-FDG positron emission tomography. *J Comp Asst Tomog* 1990;14:370–374.
43. Dexter DL, Spremulli EN, Fligiel Z, et al. Heterogeneity of cancer cells from a single human colon carcinoma. *Am J Med* 1981;71:949–956.
44. Petersen SE, Bichel P, Lorentzen M. Flow-cytometric demonstration of tumour-cell subpopulations with different DNA content in human colorectal carcinoma. *Eur J Cancer* 1978;15:383–386.
45. Kimball P, Brattain MG. Isolation of a cellular subpopulation from a human colonic carcinoma cell line. *Cancer Res* 1980;40:1574–1579.
46. Balslev IB, Pedersen M, Teglbjaerg PS, et al. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. *Cancer* 1986;58:22–28.