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A prospective PET study of patients with glioblastoma multiforme

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Objective – To study the post-surgical metabolic and structural cerebral changes in patients with glioblastoma multiforme (GBM). *Materials and methods* – We examined ten patients prospectively with newly diagnosed GBM. All patients were primarily treated with surgery, followed by chemotherapy (carmustine, cisplatine and etoposide) and radiotherapy. Positron emission tomography (PET) was used to measure tumor- and cerebral metabolism. CT or MRI was used to estimate tumor volume by measurements of tumor area. *Results* – Tumor metabolism was not increased during chemotherapy ($P = 0.71$), but increased during radiotherapy ($P = 0.01$). CT/MRI showed similar results with no increase in tumor area during chemotherapy ($P = 0.33$) but increase during radiotherapy ($P = 0.002$). During the entire study, tumor metabolism and area increased evenly ($P = 0.01$). *Conclusions* – Our study did not show a gain of PET compared with structural imaging in the prospective evaluation of GBM. We found a difference in metabolic increase and tumor growth between the two treatment regimens, although this finding has limited relevance due to the design of the study.

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Key words: brain tumor; chemotherapy; glioblastoma multiforme; neurooncology; PET, positron emission tomography; prospective study; radiotherapy

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Introduction

The long-term prognosis for patients with glioblastoma multiforme (GBM) is poor (1). However, the use of intensive multimodality treatment, using surgical resection followed by adjuvant radio- and chemotherapy, may have significant impact on survival (2).

In most clinical trials, the response of the tumor to adjuvant treatment is measured by monitoring tumor volume, using CT or MRI with and without contrast. Inability to distinguish between viable tumor cell mass, necrosis and scar tissue (3, 4), often impede the assessment of tumor response by structural criteria alone. Furthermore, concomitant use of steroids may influence the morphological appearance of the tumor (5, 6).

Additional information of tumor response can be obtained by indirect measurements of tissue function, using positron emission tomography (PET) with ^{18}fluoro-deoxyglucose (FDG). The potential of this technique has been used to assess brain tumor malignancy (7), differentiate tumor recurrence from necrosis (8–10) and as a prognostic indicator (11). FDG uptake in tumor has been shown to correlate with cell density (12) and malignancy (7). It has also been shown that FDG-PET may be used as an indicator of prognosis in patients with primary brain tumors (11, 13), although evaluation of treatment outcome is still not reliable (14–16). Evaluating acute tumor response 24 h after chemotherapy with FDG-PET, has shown opposing results, since post-treatment increased glucose metabolism has correlated both positively (17) and negatively (18) with patient survival. Assessing tumor response a week or more after adjuvant therapy has also been described (19–21), but results are ambiguous, presumably caused by heterogeneity in study design (difference in tumor histology, time schedule for treatment and imaging, previous treatment and actual treatment).

In order to enlighten some of these issues, we aimed at describing the post-surgical changes in tumor size, metabolism and normal appearing brain regions, using prospective FDG-PET measurements of patients with *de novo* diagnosed GBM. Furthermore, we used these data to explore on efficacy of post-surgery chemotherapy and radiotherapy, in patients with GBM.

Materials and methods

Patients

All patients were recruited from the Department of Neurosurgery, The Neuroscience Centre, Rigshospitalet, Copenhagen University Hospital. The inclusion criteria were: *de novo* histologically confirmed (WHO) (22) GBM located supratentorially, age ≥18 and < 70 years, no prior chemo- or radiotherapy, a post-surgery WHO performance status of 0–2 and normal bone marrow, renal and hepatic function.

Thirteen patients (Table 1), 2 females and 11 males with an average age of 48 years (range 25–66), were included in the study. The surgical treatment included macroradical resection in one case, partial resection in ten cases and open biopsy in two cases. Following this, the patients were treated at the Department of Oncology, Section for Neuro-Oncology.

Treatment

Chemotherapy was initiated with a median of 22 days (range 18–35) after surgery, and was administered over a period of 5 days, every five weeks in three cycles. Each of these included intravenous (i.v.) infusion of a three-drug combination of BCNU 200 mg/m^2 on day 1, cisplatin 20 mg/m^2/day i.v. on days 1–5 and etoposide (VP-16) 100 mg/m^2/day i.v. on days 1–5.

Subsequent localized external beam radiotherapy (RT) was initiated with a median of 28 days (range 20–34) after the last cycle of chemotherapy, using a Clinac linear accelerator (Varian Medical Systems). A total dose of 60 Gy (energy 4–6 MV photons) was delivered in 30 fractions of 2 Gy/day, 5 days/week. A contrast-enhanced CT was performed for therapy planning, and this volume was used if it was greater than the preoperative volume. If the tumor volume included more than 50% of the brain, the radiotherapy was altered to whole-brain radiation in a reduced total dose, 20 Gy in four fractions of 5 Gy.

If the patients had progressive disease, based on clinical or radiological signs during the

Table 1 Patient characteristics and received therapy

Pt. no.	Age/sex	Tumor location	Surgery	WHO perfor-mance at inclusion	No. of chemocycles	Radiation (total/fraction size)	Time to progres-sion (months)[a]	Survival from surgery (months)[b]	AED	Cortico-steroids (mg)
1	54/M	Temp/sin	PR	1	1	60/2	2.0	11.5 Reop.[c]	Deprakine	–
2	53/M	Front-par/sin	PR	0	3[d]	60/2	8.4	11.6 Chemo.[e]	–	–
3	55/F	Front/dxt	OB	1	3	60/2	9.7	13.5	Oxcarba.	25–50
4	64/M	Par/sin	PR	0	3	60/2	15.6	20.8 Reop.[c]	–	–
5	49/M	Temp/dxt	PR	0	2	60/2	3.0	14.1	–	25–100
6	44/M	Front/dxt	PR	1	3	60/2	9.0	11.6	Oxcarba.	25
7	48/M	Temp-front/dxt	MR	0	3	60/2	13.2	19.2 Reop.[c]	Oxcarba.	–
8	31/M	Par/dxt	PR	0	3	60/2	7.9	8.4	–	5–10
9	44/M	Par/sin	PR	1	3	60/2	8.6	10.2	Oxcarba.	20–100
10	42/M	Front/sin	PR	1	3	60/2	7.9	11.6 Reop.[c]	Oxcarba.	25
11	66/M	Occ/sin	PR	1	(1)	–	–	0.8	–	25
12	52/F	Temp/dxt	PR	1	(1)	–	–	0.7	–	10
13	25/M	Temp-par/dxt	OB	2	(1)	20/5[f]	3.1	4.0	Oxcarba.	50

Abbreviations: M: Male; F: Female; front: frontal; temp: temporal; par: parieltal; occ: occipital; PR: Partial removal; OB: open biopsy; MR: macroradical removal; AED: antiepileptic drug; Oxcar: oxcarbazepine.

[a]Time to progression from surgery.

[b]Death caused by tumor progression in all patients except patients 11 and 12 (see text).

[c]Reoperation (second-line treatment) was performed after TTP.

[d]Chemotherapy was reduced 75% after the first chemocycle due to unacceptable toxicity.

[e]Experimental chemotherapy after TTP.

[f]Tumor bed >50% of brain volume cause reduced total dose.

chemotherapeutic treatment, the regime was interrupted and the patients were admitted to RT.

Patients who had experienced seizures received anticonvulsive therapy (Table 1). To minimize tumor and therapy-induced brain edema, corticosteroids were administered at the discretion of the physicians, although not maintained at constant dose during the study period (Table 1).

The Macdonald response criteria were used for treatment response evaluation (23), including structural imaging, neurological examination and medical records prior to and after each chemocycle and RT. A complete response (CR) requires disappearance of all contrast-enhancing tumor, neurologically stable or improved status and no use of steroids. Partial response (PR) is ≥50% reduction in tumor size, neurologically stable or improved status and stable or reduced steroids. Progressive disease (PD) is ≥25% increase in tumor size or neurological deterioration and steroids stable or increased. Stable disease (SD) reflects all other situations.

Each patient obtained the same structural imaging modality (CT or MR) as the presurgical study, with and without contrast. Prechemocycle structural imaging was obtained with a median of 6 days (range 3–10) before the start of the first chemotherapy cycle, and the corresponding FDG-PET scan with a median of 7 days (range 4–12) before the start of the first chemotherapy cycle. Post-chemocycle structural imaging was obtained with a median of 23 days (range 18–27) after the termination of the last chemotherapy cycle, and the corresponding FDG-PET with a median of 21 days (range 16–24) after the termination of the last chemotherapy cycle. Preirradiation structural imaging was performed with a median of 8 days (range 4–12) before start of radiotherapy, and FDG-PET scan with a median of 7 days (range 4–12) before start of radiotherapy. Post-irradiation imaging was performed with a median of 13 weeks (range 12–14) after completed RT for structural imaging and FDG-PET. Subsequently, the patients were followed regularly and imaging was repeated at deterioration.

Two patients (patients 11 and 12) deceased on the first day of chemotherapy, one with clinical signs of myocardial infarction and one with signs of cerebral incarceration. One patient (patient 13) developed status epilepticus during the first chemocycle and was admitted to whole-brain irradiation receiving a reduced total dose of 20 Gy in fractions of 5 Gy, because of extensive tumor growth.

The PET studies were performed according to protocols approved by the Ethical Committee of Copenhagen, Denmark. Prior to participation in the study, informed consent was obtained after written information for all subjects.

Positron emission tomography

We used a GE 4096-15 WB tomograph (24) yielding 15 consecutive image slices parallel to the canthomeatal (CM) line and separated by 6.5 mm. Spatial resolution in the image plane was approximately 7 mm and the axial field of view (FOV) 97.5 mm. The head was fixed using an individually molded head holder of polystyrene foam and positioned in the PET scanner. A transmission scan was performed immediately before tracer injection for attenuation correction. A dose of approximately 200 MBq FDG was administered as a slow bolus through an antecubital vein, and arterial blood samples were drawn manually from the distal part of the radial artery. Blood glucose was monitored throughout the examination.

Using a multiple-time graphical approach developed by Patlak et al. (25), the net influx constant of FDG (K_1) on a pixel-by-pixel basis was calculated from the interval between 30 and 60 min after injection. Negligible glucose-6-phosphatase activity (k_4) and equilibrium between tissue and plasma FDG were assumed to be present. The regional cerebral metabolic rate of glucose (rCMRglc; μmol/100 g tissue/min) in brain tissue was calculated as follows: $CMRglc = K_1 \times Glc_p/LC$. Glc_p denotes plasma glucose concentration and LC a lumped constant of 0.81, as estimated by Hasselbalch et al. (26).

Image analysis

PET image analysis was performed using a computerized brain atlas (CBA) (27). All PET images were co-aligned and the corresponding MRI/CT images were co-registered to the PET images.

A tumor mean (T-mean) value of rCMRglc was calculated by manual application of regions of interest (ROI) guided by the CT or MRI contrast-enhanced images. For patients with non-contrast-enhancing astrocytomas, delineation was based on MRI T_1, T_2 and proton weighted sequences. If the tumor extended across several slices, average weighted values were calculated.

In order to estimate rCMRglc in the hemisphere contralateral to tumor and in the cerebellum, PET images were normalized to a standard stereotactic space and thereby aligned to the intercommisural (AC–PC) line. ROI covering frontal-, temporal-, parietal- and occipital lobes were applied guided by the anatomical regions in the CBA. Weighted mean rCMRglc values were calculated for each lobe and the hemisphere.

Tumor area was assessed on CT or MR images using the following equation: $x/2 * y/2 * \pi$ (mm^2), where x and y are the largest perpendicular diameters in the axial plane. This approximated area was assumed to be proportional to tumor volume. A trained radiologist evaluated the CT/MRI and outlined the tumor visually. For contrast-enhancing tumors, the area of enhancement was considered to define the tumor. For non-enhancing tumors, density abnormalities on CT or intensity abnormalities on MRI were considered to define the tumor.

Statistical analysis

For each subject a regression line was calculated using the PET measurements as the dependent variable and time as the independent variable. The slope of the ten individual regression lines was compared with zero, using t-statistic. If the t-test of the individual regression lines were significantly different from zero, we concluded that there was a linear dependence between cerebral metabolism and time (28). A t –test of individual regression lines was also carried out for MRI/CT measurements with time as the independent variable. We used a Spearman correlation test to determine the association between changes in tumor MRI/CT area, mean CMRglc in tumor, contralateral cortex and contralateral cerebellum. Mean CMRglc tumor values and CT/MRI tumor area were analyzed as prognostic variables for time to progression (TTP) and survival from date of surgery using the Cox proportional hazards model for continuous variables (29). It is important to mention that the sample size of the study is small, which inevitably reduces the strength of the statistical evaluation.

Results

CT/MRI and FDG-PET were performed after each chemocycle to evaluate the chemotherapy response (Tables 2 and 3). Patient 6 refused to have a CT/MRI done for personal reasons and was not evaluated according to the Mcdonald criteria (Table 4). Two patients were excluded from the PET study after the first chemocycle: patient 1 had PD and patient 10 developed severe personality changes. Patient 5 had PD after the second chemocycle and was admitted to RT.

Ten patients were eligible for chemotherapy. No complete responder (CR) was found (Table 4) although one patient (patient 2) had PR after the first chemocycle, four patients (patients 3, 4, 8 and 9) had SD and four patients (patients 1, 5, 7 and 10) had PD. During the whole chemotherapy treatment period, five patients (patients 1, 5, 7, 9 and 10) had PD.

Eight patients were eligible for RT. Baseline imaging (post-chemotherapy or pre-RT) was performed, and after RT was terminated one patient had PR (patient 4), three patients had SD (patients 5, 7. and 9) and three patients had PD (patients 2, 3 and 8).

Assessed from the first day of chemotherapy, median TTP was 8.5 months (range 2.0–15.6 months) and median survival was 10.6 months (range 0.7–20.8 months) (Table 1).

Table 2 CT/MRI tumor area (mm^2) before and after each cycle of chemotherapy and the 30 fractions of radiotherapy

Pt. no.	1	2	3	4	5	6	7	8	9	10
Pre 1 cht.	11.8	3.5	27.5	9.6	7.1		21.6	20.4	9.6	5.5
Pre 2 cht.	19.6	1.6	22.0	6.9	29.4		30.6	18.8	8.2	11.0
Pre 3 cht.		2.4	18.8	4.7			28.3	20.4	9.7	
Post 3 cht.				4.7			28.3	20.4	17.7	
Pre rt.		7.1	18.8		31.4					
Post 1 rt.				1.6	37.7		33.0	27.5	19.4	
Post 2 rt.		14.1	31.4	16.6	37.7					

Abbreviations: Pt.: patient; cht.: chemotherapy; rt: radiotherapy. An empty space indicates missing value.

Table 3 Tumor mean values of cerebral metabolic rate of glucose (μmol/100 g tissue/min) before and after each cycle of chemotherapy and the 30 fractions of radiotherapy

Pt.no.	1	2	3	4	5	6	7	8	9	10
Pre 1 cht.	20.2	19.8	14.6	17.5	13.3	15.1	18.6	12.6	16.3	13.9
Pre 2 cht.	32.0	23.7	15.2	16.6	13.7	14.1	19.7	12.3	18.7	18.1
Pre 3 cht.		26.9	15.0	16.8		9.7	22.5	13.2	19.3	
Post 3 cht.				16.8		10.2	26.5	16.5	31.9	
Pre rt.		32.5	17.7		15.4					
Post 1 rt.				17.6	18.2	10.5	34.2	40.1	38.3	
Post 2 rt.		46.1	24.0	27.5	22.3					

Abbreviations: Pt.: patient; cht.: chemotherapy; rt: radiotherapy.
An empty space indicates missing value.

Table 4 Response evaluation according to the Macdonald criteria for nine of the ten patients during chemotherapy and seven of the eight patients during radiotherapy

	Chemotherapy	Radiotherapy
Complete response	0	0
Partial response	1	1
Stable disease	3	3
Progressive disease	5	3

Linear regression between rCMRglc and time was performed for each subject on data from the whole study, and during chemo- and radiotherapy.

There was a significant ($P < 0.01$) increase in tumor mean CMRglc and tumor area ($P < 0.01$) (Table 5) with time during the whole study. Data analysis of the two treatment periods, showed no significant time-related changes in CMRglc or tumor area during chemotherapy treatment, but a significant increase in CMRglc and tumor area during RT (Table 5, Figs 1 and 2). There was no association between CMRglc changes and time in the contralateral cortex or the contralateral cerebellum.

We found no significant intercorrelations between PET and CT/MRI data and there was no predictive value of PET or CT/MRI with regard to TTP or survival.

Discussion

This study is to our knowledge the first prospective PET study to be applied in patients with GBM. Our results show that measurements of post-surgery tumor glucose metabolism, is unchanged during chemotherapy, but increases significantly during radiotherapy.

Due to the design of the study, conclusions regarding efficacy of the two treatment regimens cannot be made, since they were applied in the same order (chemotherapy followed by radiotherapy). An important methodological consideration in this regard, is that the effect of the initial surgical treatment is most prominent in the time close to intervention, which was during chemotherapy for all patients. The risk of recurrence and tumor expansion increases with time, and was therefore relatively greater during radiotherapy. In this way the initial surgical tumor reduction may explain the non-significant change in tumor burden during chemotherapy and progression during radiotherapy. A randomized cross-over design would therefore be mandatory in order to reveal a possible difference in efficacy between the two treatment regimens in future studies.

Another methodological consideration is the small sample size that inevitably weakens the

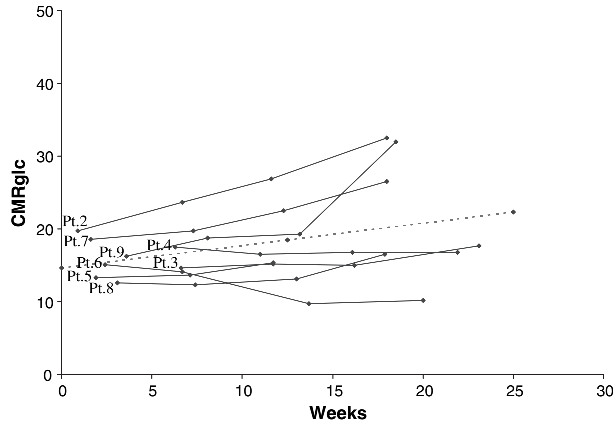

Figure 1. The relation between tumor mean values of cerebral metabolic rate of glucose (CMRglc; μmol/100 g tissue/min) and time is shown for each patient during chemotherapy. Furthermore, an average line is shown (*dashed line*). T_0 = day of tumor surgery.

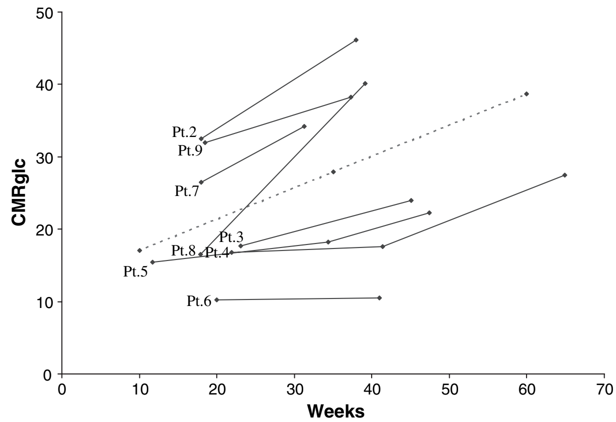

Figure 2. The relation between tumor mean values of cerebral metabolic rate of glucose (CMRglc; μmol/100 g tissue/min) and time is shown for each patient during radiotherapy. Furthermore, an average line is shown (*dashed line*). T_0 = day of tumor surgery.

Table 5 Time-related measurement changes.

Measurement	*t*	*P*
1 Tumor mean CMRglucose		
a. Whole study	3.06	0.01*
b. Pre-/post-chemotherapy	2.13	0.71
c. Pre/post-radiotherapy	3.52	0.01*
2 CT/MRI area		
a. Whole study	3.30	0.01*
b. Pre-/post-chemotherapy	1.05	0.33
c. Pre-/post-radiotherapy	5.49	0.002*
3 Contralateral cortex		
a. Whole study	1.50	0.17
b. Pre-/post-chemotherapy	1.60	0.16
c. Pre/post-radiotherapy	2.20	0.06
4 Cerebellar diaschisis		
a. Whole study	0.02	0.99
b. Pre/post-chemotherapy	0.43	0.67
c. Pre/post-radiotherapy	0.92	0.39

Changes in tumor mean values of cerebral metabolic rate of glucose (CMRglc; μmol/100 g tissue/min) (1), CT/MRI tumor area (mm^2) (2), CMRglc of contralateral cortex (3) and CMRglc of contralateral cerebellum (4), during the whole study (a) as well as before and after chemotherapy (b) and radiotherapy (c).

The changes are expressed by the *t*-value comparing the slope of the individual regression lines with zero. The *P* value is given and statistically significant changes with time are marked with an *asterisk*(*).

strength of the statistical evaluation. However, we did find a statistical difference in the regression analysis of PET and CT/MRI measurements, caused by a marked increase in tumor metabolism and area during radiotherapy. The correlation analysis is more sensitive to a reduced number of samples, since it does not incorporate all measurements of the study, and our results in this regard are negative. On the other hand, the time-related changes in tumor metabolism and area are almost similar (Table 5), which may reflect that the monitoring properties of PET and CT/MRI are comparable. In this way our study does not show a significant gain of PET vs CT/MRI in the prospective evaluation of GBM.

But do previous studies indicate that PET can be used to determine treatment efficacy in a clinical context?

Increased membrane glucose transportation has been shown to occur with neoplastic transformation using FDG-PET (30), but the response of malignant primary brain tumors to chemotherapy is still not clarified. Rozental et al. (18) found a general metabolic activation of GBM following carmustine treatment and patients with the largest relative change in FDG had the shortest survival, although neither baseline glucose uptake ratio, nor visual tumor grade accurately predicted survival length. In contrast to this, De Witte et al. (31) found that the response to carmustine treatment varied but a hypermetabolic reaction predicted a longer survival.

With regard to radiotherapy, a similar acute reaction of tumor metabolism was observed (16), which is believed to reflect a cellular reaction to irradiation as well as acute inflammation and breakdown of the blood–brain barrier. This initial reaction was followed by a relative reduction of tumor metabolism. In this way a possible induction of swelling and inflammation could be a pitfall when interpreting the observed temporal changes during radiotherapy.

It has been shown that post-surgery whole-brain radiotherapy in patients with malignant gliomas increased median survival from 14 to 36 weeks compared with surgery alone (32). It has also been shown that adjuvant chemotherapy significantly increases survival (33), and Lassen et al. (2) reported good clinical response to preirradiative chemotherapy in patients with GBM. Still, comparative studies using state of the art measurements of tumor size and metabolic activity cannot be found in recent literature.

In this way it has been demonstrated that there is an evident clinical relevance of PET in neuro-oncology, but whether PET is superior in determining treatment efficacy in patients with GBM is still ambiguous.

In conclusion, results of former PET studies are diverging and therefore less informative in the evaluation of treatment efficacy in GBM. In the current study, we find a different effect of chemotherapy and radiotherapy, although this finding bears little relevance due to the study design and the small patient sample size. We do not find a predictive value of PET measurements with regard to TTP, which could be caused by the small sample size. Still PET did monitor tumor progression in a qualitatively different but quantitatively similar way compared with volumetric estimates, and larger sample sizes are needed in order to decide if functional measurements are superior to structural.

References

1. Shapiro WR. Therapy of adult malignant brain tumors: what have the clinical trials taught us? Semin Oncol 1986;**13**:38–45.
2. Lassen U, Kristjansen PE, Wagner A et al. Treatment of newly diagnosed glioblastoma multiforme with carmustine, cisplatin and etoposide followed by radiotherapy. A phase II study. J Neurooncol 1999;**43**:161–6.
3. Forsyth PA, Petrov E, Mahallati H et al. Prospective study of postoperative magnetic resonance imaging in patients with malignant gliomas. J Clin Oncol 1997;**15**:2076–81.
4. Cairncross JG, Pexman JH, Rathbone MP. Post-surgical contrast enhancement mimicking residual brain tumour. Can J Neurol Sci 1985;**12**:75.
5. Cairncross JG, Macdonald DR, Pexman JH et al. Steroid-induced CT changes in patients with recurrent malignant glioma. Neurology 1988;**38**:724–6.
6. Watling CJ, Lee DH, Macdonald DR et al. Corticosteroid-induced magnetic resonance imaging changes in patients with recurrent malignant glioma. J Clin Oncol 1994;**12**:1886–9.
7. Di Chiro G, DeLaPaz RL, Brooks RA et al. Glucose utilization of cerebral gliomas measured by. Neurology 1982;**32**:1323–9.
8. Di Chiro G, Brooks RA. PET-FDG of untreated and treated cerebral gliomas. J Nucl Med 1988;**29**:421–3.
9. Glantz MJ, Homan JM, Coleman RE et al. Identification of early recurrence of primary central nervous system tumors by. Ann Neurol 1991;**29**:347–55.
10. Buchpiguel CA, Alavi JB, Alavi A et al. PET versus SPECT in distinguishing radiation necrosis from tumor recurrence in the brain. J Nucl Med 1995;**36**:159–64.
11. Alavi JB, Alavi A, Chawluk J et al. Positron emission tomography in patients with glioma. A predictor of prognosis. Cancer 1988;**62**:1074–8.
12. Herholz K, Pietrzyk U, Voges J et al. Correlation of glucose consumption and tumor cell density in astrocytomas. A stereotactic PET study. J Neurosurg 1993;**79**:853–8.
13. Patronas NJ, Brooks RA, DeLaPaz RL et al. Glycolytic rate (PET) and contrast enhancement (CT) in human cerebral gliomas. AJNR Am J Neuroradiol 1983;**4**:533–5.
14. Brock CS, Young H, O'Reilly SM et al. Early evaluation of tumour metabolic response using [18F]fluorodeoxyglucose and positron emission tomography: a pilot study following

the phase II chemotherapy schedule for temozolomide in recurrent high-grade gliomas. Br J Cancer 2000;**82**:608–15.
15. Rozental JM, Levine RL, Nickles RJ et al. Glucose uptake by gliomas after treatment. A positron emission tomographic study. Arch Neurol 1989;**46**:1302–7.
16. Rozental JM, Levine RL, Mehta MP et al. Early changes in tumor metabolism after treatment: the effects of stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 1991;**20**:1053–60.
17. De Witte O, Lefranc F, Levivier M et al. FDG-PET as a prognostic factor in high-grade astrocytoma. J Neurooncol 2000;**49**:157–63.
18. Rozental JM, Cohen JD, Mehta MP et al. Acute changes in glucose uptake after treatment: the effects of carmustine (BCNU) on human glioblastoma multiforme. J Neurooncol 1993;**15**:57–66.
19. Mineura K, Yasuda T, Kowada M et al. Positron emission tomographic evaluation of radiochemotherapeutic effect on regional cerebral hemocirculation and metabolism in patients with gliomas. J Neurooncol 1987;**5**:277–85.
20. Ogawa T, Uemura K, Shishido F et al. Changes of cerebral blood flow, and oxygen and glucose metabolism following radiochemotherapy of gliomas: a PET study. J Comput Assist Tomogr 1988;**12**:290–7.
21. Holtho VA, Herholz K, Berthold F et al. *In vivo* metabolism of childhood posterior fossa tumors and primitive neuroectodermal tumors before and after treatment. Cancer 1993;**72**:1394–403.
22. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol 1993;**3**:255–68.
23. Macdonald DR, Cascino TL, Schold SC Jr et al. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;**8**:1277–80.
24. Rota Kops E, Herzog H, Schmid A et al. Performance characteristics of an eight-ring whole body PET scanner. J Comput Assist Tomogr 1990;**14**:437–45.
25. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab 1985;**5**:584–90.
26. Hasselbalch SG, Madsen PL, Knudsen GM et al. Calculation of the FDG lumped constant by simultaneous measurements of global glucose and FDG metabolism in humans. J Cereb Blood Flow Metab 1998;**18**:154–60.
27. Greitz T, Bohm C, Holte S et al. A computerized brain atlas: construction, anatomical content, and some applications. J Comput Assist Tomogr 1991;**15**:26–38.
28. Matthews JN, Altman DG, Campbell MJ et al. Analysis of serial measurements in medical research. BMJ 1990;**300**:230–5.
29. Cox DR. Regression models and life-tables. J Royal Stat Soc B 1972;**34**:187–220.
30. Gallagher BM, Fowler JS, Gutterson NI et al. Metabolic trapping as a principle of oradiopharmaceutical design: some factors resposible for the biodistribution of. J Nucl Med 1978;**19**:1154–61.
31. De Witte O, Hildebrand J, Luxen A et al. Acute effect of carmustine on glucose metabolism in brain and glioblastoma. Cancer 1994;**74**:2836–42.
32. Walker MD, Green SB, Byar DP et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 1980;**303**:1323–9.
33. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 2002;**359**:1011–18.