Effect of radiotherapy on brain glucose metabolism in patients operated on for low grade astrocytoma

M Bruehlmeier, U Roelcke, B Amsler, K H Schubert, O Hausmann, K von Ammon, E W Radü, O Gratzi, C Landmann and K L Leenders


Updated information and services can be found at:
http://jnnp.bmjjournals.com/cgi/content/full/66/5/648

These include:

References
This article cites 27 articles, 7 of which can be accessed free at:
http://jnnp.bmjjournals.com/cgi/content/full/66/5/648#BIBL

Rapid responses
You can respond to this article at:
http://jnnp.bmjjournals.com/cgi/eletter-submit/66/5/648

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

- Other Neurology (3147 articles)
- Radiotherapy (69 articles)

Notes

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to Journal of Neurology, Neurosurgery, and Psychiatry go to:
http://www.bmjjournals.com/subscriptions/
SHORT REPORT

Effect of radiotherapy on brain glucose metabolism in patients operated on for low grade astrocytoma

M Bruehlmeier, U Roelcke, B Amsler, K H Schubert, O Hausmann, K von Ammon, E W Radü, O Gratzl, C Landmann, K L Leenders

Abstract

Objective—To assess the effect of postoperative radiotherapy on brain glucose metabolism (CMRGlu) of operated patients with low grade astrocytomas.

Methods—PET and 18F-fluorodeoxyglucose was used to measure absolute CMRGlu in patients with fibrillary astrocytoma (WHO II) of the frontal lobe, who did (n=7) or did not (n=12) receive radiotherapy subsequent to first debulking tumour resection. In addition, statistical parametric mapping (SPM95) was applied to assess the pattern of relative CMRGlu associated with the frontal tumour. Data were compared with 12 healthy controls.

Results—A global reduction of absolute CMRGlu was found when either patients with or without radiotherapy were compared with controls (ROI analysis). Brain areas of relative CMRGlu reduction were found in the brain ipsilateral and contralateral to the tumour, comparing both patient groups with controls by SPM (“tumour diaschisis effect”). Superimposed, absolute CMRGlu in the contralateral frontal, parietal, occipital cortex as well as in the white matter was on average 17% lower in patients receiving radiotherapy than in patients who did not.

Conclusions—The data discriminate a tumour effect from a radiotherapy effect, and support the view of adverse effects of radiotherapy on brain not directly involved by tumour.

(J Neurol Neurosurg Psychiatry 1999;66:648–653)

Keywords: low grade astrocytoma; brain glucose metabolism; radiotherapy

Patients and methods

Depending on location and size, circumscribed brain lesions may suppress remote CMRGlu and blood flow (diaschisis9). To minimise the diaschisis effect which could arise from various tumour locations, we included only tumours which were confined to the frontal lobe of one brain side (according to MRI). In addition, only tumours which at the time of the PET study did not show MRI criteria of malignancy (contrast enhancement, peritumoral oedema) were
A second diameter was determined (y). Tumour size was then calculated as elliptical area as:
\[
\text{Area} = \frac{\pi \times x \times y}{2}
\]
for CMRGluc. For CMRGluc Y=arterial blood samples available.

### Table 1 Clinical data

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Resection type</th>
<th>Interval (months)</th>
<th>Tumour size (mm²)</th>
<th>CMRGluc</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>M</td>
<td>P</td>
<td>25</td>
<td>314</td>
<td>N</td>
</tr>
<tr>
<td>72</td>
<td>F</td>
<td>P</td>
<td>22</td>
<td>225</td>
<td>N</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>GT</td>
<td>17</td>
<td>174</td>
<td>N</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>P</td>
<td>28</td>
<td>440</td>
<td>Y</td>
</tr>
<tr>
<td>39</td>
<td>F</td>
<td>P</td>
<td>24</td>
<td>226</td>
<td>Y</td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>P</td>
<td>14</td>
<td>121</td>
<td>Y</td>
</tr>
<tr>
<td>37</td>
<td>F</td>
<td>P</td>
<td>42</td>
<td>660</td>
<td>Y</td>
</tr>
</tbody>
</table>

**RadN**=non-irradiated patients; **RadY**=irradiated patients; **GT**=gross total (macroscopically complete); P=partial resection. Interval=interval between tumour resection, with or without radiotherapy) and PET study. Tumour size was assumed to correspond to the area calculated from the axial plane (CTT or MRI, available as films) which showed the greatest diameter of resident/ recurrent tumour. From that plane, the largest diameter was determined (x). Vertical to that line, a second diameter was determined (y). Tumour size was then calculated as elliptical area as: \( \pi \times x \times y / 2 \). For CMRGluc Y=arterial blood samples available.

PET DATA ACQUISITION

FDG PET was performed using a 933/04–16 tomograph (CTT, Knoxville, four rings, seven planes, 8 mm full width at half maximum (FWHM)). The FDG was prepared as previously described. The head of the subjects was positioned parallel to the orbitomeatal line and was placed in an individually moulded thermoplastic head support to minimise movement during scanning. After two 10 minute transmission scans by means of a Ga-68/Ge-68 ring source, 140 to 298 MBq FDG were administered intravenously over 3 minutes using a constant infusion pump. In 11/19 patients, and in all healthy subjects, arterial blood samples were available for the determination of plasma radioactivity and glucose concentration. A protocol comprising one dynamic (48 minutes) and one static (5 minutes) emission scan was used covering the whole brain at two positions, yielding a total of 14 adjacent planes with a plane to plane distance of 8 mm. These slices were then interpolated to 26 planes of the standard stereotactic atlas coordinate system of Talairach and Tournoux. Radioactivity concentrations of the resulting images were given in counts/pixel.

**Radiotherapy**

The decision to treat patients with radiotherapy did not depend on clinical or neuroradiological criteria, but was defined by the policy of the referring clinical department. Whereas patients from Zürich were not irradiated, all patients from Basel received radiotherapy. Patients were immobilised with a thermoplastic head fixation to ensure reproducible position. CT based dose planning was done on a Philips TPS. The preoperative tumour volume with a 2 cm margin was chosen as the planning target volume. Opposing fields were used in five patients, two patients received wedged angled fields. The tumour enclosing isodose was normalised to 2 Gy. All fields were treated Monday to Friday on a 6MeV Philips Linac SL6 with 2 Gy single fractions up to a median total tumour dose of 56 Gy (54–60 Gy). The following range of doses was estimated to distribute over non-tumorous brain: contralateral frontal (minimum–maximum, mean (SD): 36 (19) to 46 (12) Gy; contralateral parieto-occipital: 5 (9) to 19 (16) Gy; ipsilateral parieto-occipital: 1(2) to 13 (13) Gy. Patients visited the radiation oncologist weekly during and 6 weeks after treatment to evaluate acute side effects. Thereafter, patients were seen by the referring physician for long term follow up.

**Statistical Parametric Mapping (SPM95)**

SPM95 provides a means to investigate specific patterns of radioactivity distributions—for example, associated with brain lesions. We used SPM95 to assess the pattern of cerebral FDG uptake (as a measure of glucose metabolism) associated with a left frontal lesion (tumour) of non-irradiated and irradiated patients. For this purpose, images of patients with right sided tumours were flipped to have the lesions of all patients on the left side. Images of these patients were then compared with the images of healthy subjects and stereotactically normalised, using a series of linear and non-linear steps (SPM95). Because digitised MR images were not available, we used a standard PET template and the subjects’ PET images for stereotactic normalisation. This procedure may potentially be compromised by the brain lesion itself. However, (1) no patient had a significant space occupying lesion as judged on MRI films, (2) there was no midline shift in any patient, (3) the lesion volumes were comparable in both groups, and (4) our SPM results do not consider the tumour quadrant itself. As judged by visual inspection, PET images of all patients were consistently transformed without introducing artifacts. The images were then smoothed with a gaussian filter with FWHM corresponding to the spatial resolution of the scanner. Between subject variations in global FDG uptake were removed by normalising individual global FDG uptake to an arbitrary mean by proportional scaling of the count images. By computing a t statistic, images of
non-irradiated patients and normal subjects were then compared on a pixel by pixel basis. Pixels exceeding the threshold of $p=0.01$ were displayed in axial, sagittal, and coronal projections of a statistic parametric map (for methodological details see Friston et al. 13).

REGIONS OF INTEREST (ROI) ANALYSIS
Because SPM95 does not rely on absolute values of CMRGlu, nor does it take changes of global CMRGlu into account, absolute CMRGlu was determined in the 11 patients in whom arterial blood samples were available, and in the 12 normal subjects. For this purpose, firstly, CMRGlu (in units of $\mu$mol/100ml/min) was calculated on the PET image sets using the original model of Sokoloff et al.14 with its modification for humans.15 Secondly, a standard template of elliptical ROIs was created on the stereotactically normalised PET images to compute CMRGlu profiles. The focus of this part of the study was brain contralateral rather than ipsilateral to the tumour side, because metabolism in the cortex and subcortical white matter surrounding low grade tumours can be reduced to a similar degree as in tumours themselves, which makes it difficult to exactly differentiate non-tumorous brain from tumour. In addition, contralateral brain was to a lesser amount exposed to radiotherapy than tumour itself. Thus, CMRGlu reduction in the contralateral brain of irradiated patients would strongly support the hypothesis of radiation induced side effects. The following brain regions contralateral to the tumour side were evaluated: frontomedial, frontoprefrontal, frontolateral, parietal, and occipitomedial cortex; white matter at the level of the centrum semiovale; and hemisphere contralateral to the tumour side. The ROIs were placed at the appropriate locations throughout the whole brain in an axial direction. For each subject, the resulting CMRGlu values were plotted against the relative plane offset ($z$ value, in mm) related to the thalamus ($\text{thalamus}=0$), thus yielding individual ROI CMRGlu profiles.

Profile values for ROI CMRGlu were then averaged for each subject to result in one mean CMRGlu value per ROI per subject. In addition, ROI profiles were averaged for each

Table 2  Brain areas with relative CMRGlu reductions due to left frontal tumor

<table>
<thead>
<tr>
<th>Side</th>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Size</th>
<th>Decrease</th>
<th>z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral</td>
<td>Cingulate gyrus (BA 32)</td>
<td>−2</td>
<td>6</td>
<td>44</td>
<td>109</td>
<td>−18%</td>
<td>4.52</td>
</tr>
<tr>
<td></td>
<td>Middle temporal gyrus (BA 39)</td>
<td>−50</td>
<td>−64</td>
<td>24</td>
<td>253</td>
<td>−15%</td>
<td>4.03</td>
</tr>
<tr>
<td>Contralateral</td>
<td>Inferior parietal lobulus (BA 40)</td>
<td>56</td>
<td>−34</td>
<td>32</td>
<td>231</td>
<td>−19%</td>
<td>4.14</td>
</tr>
<tr>
<td></td>
<td>Cingulate gyrus (BA 23)</td>
<td>2</td>
<td>−26</td>
<td>32</td>
<td>447</td>
<td>−13%</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td>Middle frontal gyrus (BA 6)</td>
<td>26</td>
<td>6</td>
<td>56</td>
<td>157</td>
<td>−16%</td>
<td>3.63</td>
</tr>
</tbody>
</table>

BA=Brodman area; X, Y, Z=pixel coordinates of peak difference; size=area size (number of voxels, voxel size=2×2×4 mm); decrease=% reduction in patients for the respective peak coordinates; z score=score of peak difference (transformed $t$ value).

(SPM95, patients v controls: significance level $p=0.01$).

Figure 1  Statistical parametric mapping (SPM95) projections showing areas with significantly ($p=0.01$) lower relative CMRGlu in 12 non-irradiated patients compared with 12 controls. Differences are displayed on sagittal, coronal, and transverse projections. VPC/VAC=vertical line through anterior/posterior commissure; R=right side of brain.
group (radiated, non-irradiated, controls) to result in one mean CMRGlu profile per location.

**Statistics**

Due to the few patients in each group, the non-parametric Kruskal-Wallis test was applied for group to group comparisons of CMRGlu ROI values. A possible relation between CMRGlu and the interval between operation with or without radiotherapy and the time of the PET study was tested using the Spearman’s rank test.

**Results**

**Statistical Parametric Mapping (SPM95)**

The comparison between the 12 non-irradiated patients and 12 healthy controls disclosed a specific pattern of relatively reduced CMRGlu in patients (fig 1). This “lesion induced suppression” of CMRGlu particularly comprised the frontal brain contralateral to the tumour side, and the parietal lobe of both brain sides. In the left frontal brain, no differences between non-irradiated patients and controls were found, which we attribute to the varying tumour locations within the frontal brain. Similar results were also obtained when irradiated patients were compared with controls (data not shown), whereas no differences in the relative CMRGlu pattern were found when non-irradiated and irradiated patients were compared. In addition, no relative increases in CMRGlu were found when patients were compared with controls. As no differences in the CMRGlu pattern were found between non-irradiated patients and controls or irradiated patients and controls, the results of the analysis as presented in table 2 are derived from the comparison between all patients (n=19) and the control subjects (n=12).

**ROI Analysis**

Figure 2 A–D shows the group profiles of absolute CMRGlu values for the four irradiated and seven non-irradiated patients contralateral to the tumour, and for the 12 control subjects. For the irradiated patients, all ROIs were within the radiation field (see methods, radiotherapy). When compared with controls, the CMRGlu profiles of non-irradiated patients were shifted towards the left side (lower CMRGlu). Compared with non-irradiated patients, the profiles of irradiated patients were further shifted towards lower CMRGlu values.

The mean group CMRGlu values for each ROI are presented in table 3 and reflect the profile shifts seen in fig 2A–D. The mean

---

**Table 3 Absolute CMRGlu values (µmol/100 ml/min)**

<table>
<thead>
<tr>
<th>ROI</th>
<th>RADY</th>
<th>RADN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontomedial</td>
<td>33.7 (1.6)</td>
<td>$-14%$</td>
<td>39.1 (1.9) $-23%$</td>
</tr>
<tr>
<td>Frontolateral</td>
<td>34.5 (1.7)</td>
<td>$-15%$</td>
<td>40.6 (2.0) $-22%$</td>
</tr>
<tr>
<td>Frontoprefrontal</td>
<td>33.8 (1.8)</td>
<td>$-22%$</td>
<td>43.1 (3.1) $-13%$</td>
</tr>
<tr>
<td>Parietal</td>
<td>37.5 (2.0)</td>
<td>$-20%$</td>
<td>47.0 (2.9) $-13%$</td>
</tr>
<tr>
<td>Occipitomedial</td>
<td>37.5 (2.0)</td>
<td>$-20%$</td>
<td>47.0 (2.9) $-13%$</td>
</tr>
<tr>
<td>White matter</td>
<td>23.9 (1.0)</td>
<td>$-16%$</td>
<td>28.5 (1.5) $-9%$</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>28.8 (1.2)</td>
<td>$-18%$</td>
<td>35.0 (2.0) $-18%$</td>
</tr>
</tbody>
</table>

Values are mean (SEM). RADN=non-irradiated patients (n=7); RADY=irradiated patients (n=4); in patients all regions refer to the brain side contralateral to the tumour. Per cent values express the CMRGlu difference between the respective groups; group differences are significant.
CMRGlu reduction in non-irradiated patients versus controls averaged over all ROIs was 17%, the mean difference between CMRGlu in non-irradiated patients and irradiated patients was also 17%. No correlation between the time elapsed since operation with or without radiotherapy and CMRGlu was found (Spearman’s rank test for all ROIs: r<0.1, p>0.1).

**Discussion**

Neuropsychological impairment is often found in children and adults after therapeutic cranial irradiation of brain tumours.10-12 Also prophylactic cranial irradiation—for example, of patients with small cell lung cancer—may cause neuropsychological disturbances. In many cases, however, it is difficult to differentiate between effects of the primary disease state and concurrent therapies.13 We used CMRGlu as a possible indicator of radiotherapy induced adverse effects in patients with operated LGAs. Our data allow the differentiation of the disease state from the radiotherapy effect. Firstly, they disclose an overall CMRGlu reduction in patients with LGAs compared with healthy subjects. This can in part be attributed to metabolic suppression of normal brain due to the presence of residual/recurrent tumour and brain damage induced by operation (diaschisis14). Metabolic suppression of remote brain was evident from the SPM95 data, which showed a similar pattern for both irradiated and non-irradiated patients, and which is likely to reflect the lesion effect on remote brain glucose metabolism. Superimposed on the pattern of relative glucose metabolism, irradiated patients furthermore showed widespread reductions of absolute CMRGlu—an average of 17% compared with non-irradiated patients. Whereas lower contralateral frontal CMRGlu in irradiated patients could represent a direct consequence of radiotherapy because this brain area was also largely exposed to irradiation, that remote brain such as contralateral parietal or occipital cortex showed this reduction was unexpected. These data suggest that “localised” external beam radiotherapy applied to the treatment of frontal low grade astrocytomas may exert spatially non-confined effects.

Several neuropathological changes may underlie this CMRGlu reduction. Radiation toxicity may occur as early (within months after completion of radiotherapy) or delayed (after years) effects. Early effects are considered to correspond to transient oedema or white matter demyelination; patients may present with somnolence, mood, or memory disturbances. Delayed effects may persist and seem to be mediated by cerebrovascular changes, demyelination, and autoimmune triggered brain injury.15 Apart from frontal cortical CMRGlu reduction, CMRGlu of the contralateral white matter was also reduced in irradiated patients. Together with the CMRGlu reductions in the parietal and occipital cortex, these findings may indicate a primary damage to the white matter, which is considered the cerebral element most vulnerable to irradiation,16 and a secondary trans-synaptic suppression of adjacent or remote cortex.

Metabolic radiotherapy effects have also been shown by nuclear magnetic resonance spectroscopy. Usenius et al17 found a lower concentration of N-acetyl-L-aspartate (a neuron specific metabolite) in tumour adjacent brain of irradiated patients with glioma. It still needs to be determined whether these changes are primarily caused by the tumour or by the radiotherapy. Wang et al18 found a less suppressed metabolism of non-tumorous brain after radiotherapy of metastatic and primary brain tumours, which was most likely due to the therapeutic effect of radiotherapy on the tumour with a consequently reduced diaschisis of remote brain areas. Our results clearly discriminate between a tumour effect and a radiotherapy effect and support the view of significant remote effects of radiotherapy on brain not directly involved by the tumour.

One important factor to be considered is the time between radiotherapy and the assessment of neuropsychological functions or brain energy metabolism. Vigliani et al19 found attention and memory disturbances to be frequent at 6 months after radiotherapy, although these disturbances seemed to recover over subsequent years. On the contrary, Armstrong et al20 reported memory impairment 2 to 3 years after postoperative radiotherapy. In our series, the difference in absolute CMRGlu between both patient groups was 17% at a mean interval of 46 (irradiated patients) and 48 (non-irradiated patients) months. In addition, we found no relation between the time elapsed since operation, with or without radiotherapy, and absolute CMRGlu. Although our results are derived from only a few patients, they suggest that the radiotherapy induced effects on cerebral glucose metabolism apparently occur early after completion of radiotherapy. It is not yet clear how our metabolic findings relate to the time characteristics of the above mentioned neuropsychological reports. To clarify the exact time course of brain glucose metabolism, within subject follow up studies are required.

Our results raise the question whether decreases in CMRGlu, either regional or global, are clinically relevant, and whether they may correspond to the impaired neuropsychological performance reported in several studies of irradiated patients with low grade gliomas.18-20 PET studies in patients with Alzheimer’s disease,18,21 brain injury,22 multiple sclerosis23, and elderly healthy subjects24 showed a close relation between reductions of cerebral energy metabolism on the one hand, and the degree of subjective complaints or measurable decline in neuropsychological test performance on the other. These data thus underline the fact that measurement of cerebral energy metabolism provides a correlate of brain function. For our patient groups, it is noteworthy that CMRGlu in irradiated patients was on average 17% lower than in non-irradiated patients. In turn, CMRGlu in non-irradiated patients was of similar magnitude lower than the mean CMRGlu of controls. This gradual decrease of CMRGlu from healthy subjects through non-irradiated...
Radiotherapy on brain glucose metabolism in low grade astrocytoma

This study was in part supported by the Swiss Cancer League, grant No FOR 491.


