Metabolic and Hemodynamic Evaluation of Brain Metastases from Small Cell Lung Cancer with Positron Emission Tomography

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ABSTRACT

Brain metastases from small cell lung cancer respond to chemotherapy, but response duration is short and the intracerebral concentration of chemotherapy may be too low because of the characteristics of the blood-brain barrier. Positron emission tomography has been applied in a variety of tumors for studies of metabolic and hemodynamic features. This study was performed to determine regional cerebral metabolic rate of glucose (rCMRg1u), regional cerebral blood flow (rCBF), and regional cerebral blood volume (rCBV) in brain metastases from small cell lung cancer and the surrounding brain. Tumor rCMRg1u, rCBF, and rCBV exerted a broad variability, but were higher than the corresponding values in white matter and higher than or similar to those of gray matter. Tumor rCMRg1u and rCBF were highly correlated (P < 0.01, r = 0.79). No correlation between survival and metabolic or hemodynamic parameters could be demonstrated. After radiotherapy, mean tumor rCMRg1u decreased from 0.40 to 0.31 μmol/g/min (not significant), and rCBF and rCBV remained unchanged. However, cortical rCBF demonstrated a trend of increased values after radiotherapy from 0.37 to 0.49 ml/g/min (P = 0.13). No change in rCMRg1u was observed in gray or white matter after radiotherapy. Global CBF seems to be reversibly depressed by the metastases, but local hemodynamic changes in the tumor could not be detected with positron emission tomography in this study. An association between high tumor rCMRg1u and rCBF as an indicator of hypoxia was not observed. Other methods for noninvasive in vivo analysis of tumor hemodynamics are needed, especially for discrimination between tumor necrosis and hypoxia.

INTRODUCTION

Brain metastases frequently develop in patients with SCLC. Despite the high sensitivity to chemotherapy and radiotherapy, the cumulative risk of developing brain metastases is 50–80% (1–4). The brain is considered a pharmacological sanctuary because of the blood-brain barrier with inadequate concentrations of most cytostatic drugs in the cerebrospinal fluid compared with plasma concentrations (5). However, this is opposed by the fact that the response rate of chemotherapy of brain metastases from SCLC is equal to extracranial distant metastases (6). Both WBRT and chemotherapy result in response rates from 25–70% depending on the time interval and result of primary chemotherapy (7, 8). Basically, the treatment of CNS relapse is palliative, and WBRT and chemotherapy are optional (9).

Other approaches have been applied to reduce the devastating complication that may have major implications for the quality of life of the patients. Prophylactic cranial irradiation has been studied in several randomized trials and a significant reduction in the frequency of CNS relapse has been encountered (7). However, this treatment results in a variety of side effects such as dementia and insomnia, and the impact on survival is debatable (10, 11). Prophylactic cranial irradiation is optional but not standard for patients in complete remission after chemotherapy in most comprehensive cancer centers.

Metabolic and hemodynamic characteristics of brain metastases from SCLC may provide new information that can improve the understanding of CNS failure and lead to better therapeutic approaches. Tumor blood flow, vascular density, and nutrient supply may influence the response to both chemotherapy and radiotherapy (12). Various techniques have been applied for studies of tumor metabolism and hemodynamics, including PET.

On the basis of the increased glycolysis in cancer cells, PET-FDG has been studied in a variety of tumors (13–15). A high sensitivity to PET-FDG in lung cancer has been determined, and the method seems to be superior to CT and mediastinoscopy in the staging of mediastinal lymph nodes (16, 17).

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3 The abbreviations used are: SCLC, small cell lung cancer; PET, positron emission tomography; FDG, [18F]fluorodeoxyglucose; PET-FDG, PET with FDG; WBRT, whole brain radiotherapy; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; rCBV, regional cerebral blood volume; rCBF, regional cerebral blood flow; rCMRg1u regional cerebral metabolic rate of glucose.
PET has also been applied in a few metastatic brain tumors. However, it seems that the usefulness is limited because increased accumulation of FDG is seen in only 68% of the metastatic brain lesions (18). Hemodynamic properties have been studied in gliomas (19, 20) and breast cancer (21).

CT and MRI are considered standard diagnostic procedures for brain metastases, but multiple small (but symptomatic) lesions may be difficult to detect. The spatial resolution of MRI and CT is superior to PET but gives no functional information (22). Tumors often express substantial inherent heterogeneity, and changes in metabolic and hemodynamic patterns within the tumors may reflect altered sensitivity to chemotherapy or radiation. The present study was undertaken to study regional cerebral glucose metabolism and hemodynamics in brain metastases from SCLC and the surrounding brain tissue.

MATERIALS AND METHODS

Patients

From January 1995 to March 1997, six patients with MRI-verified brain metastases from SCLC entered the study. Eligibility criteria were stable extracranial disease, age 18–70, WHO performance status 0–2, no prior cranial surgery or radiotherapy, and signed informed consent. All of the patients had received chemotherapy according to an ongoing randomized Phase-III trial including platinum compounds, epipodophyllotoxins, vincristine, doxorubicin, and cyclophosphamide. One patient presented with a brain metastasis at the time of diagnosis. He received standard chemotherapy, resulting in extracranial complete remission and initially remission of neurological symptom. After 3 months, the patient again had seizures indicating cerebral progression and entered this study. The rest of the patients had CNS relapse at a median of 3 months (range 2.5–11 months) after completion of chemotherapy, and all of them had obtained extracranial complete remission. One patient had only one visible tumor according to MRI. All of the other patients had multiple metastases, and a total of 12 tumors were studied with PET (Table 1). Repeating PET scans were performed 6–8 weeks after treatment.

PET

PET was performed with a GE 4096 tomograph (General Electric Medical Systems, Milwaukee, WI) producing 15 slices with a spacing of 6.5 mm. The axial field of view is approximately 10 cm and the central spatial resolution (full width half maximum, FWHM) is 5 mm in the transaxial plane (23).

The PET session included measurements of rCBV followed by rCBF and rCMR$_{\text{glu}}$. A 10-min transmission scan using a rotating $^{68}$Germanium pin source was performed for attenuation correction before rCMR$_{\text{glu}}$ whereas the decay of $^{15}$O was awaited, and all of the acquisitions were corrected for random events, dead time, and scatter. All of the patients were in a fasting state for at least 6 h before the session. Patients were placed in the scanner with the canthomeatal line (CM) as landmark for positioning. The patients were in the scanner for a total of approximately 2 h. A molded head holder of polystyrene foam was used for individual head fixation.

A silicone catheter was placed in the radial artery, and the plasma activity was counted and corrected for decay using a scintillation well counter or computerized sampling to calculate the input function. The absolute tracer activity was reconstructed in images with the activity in kBq/cc, and the tomograph and the scintillation counter or sampler were calibrated.

Table 1 Structural, metabolic, and hemodynamic characteristics of the brain metastases

<table>
<thead>
<tr>
<th>Patient and tumor location</th>
<th>ROIa size (pixelsb)</th>
<th>Tumor type</th>
<th>Tumor rCMR$_{\text{glu}}$ (peak value)</th>
<th>Blood glucose (mean value)</th>
<th>Tumor rCBF (mean value)</th>
<th>Tumor rCBV (mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Left paraoccipital region</td>
<td>245</td>
<td>Solid</td>
<td>0.34</td>
<td>8.0</td>
<td>0.28</td>
<td>1.9</td>
</tr>
<tr>
<td>1: Left temporal lobe</td>
<td>465</td>
<td>Solid</td>
<td>0.47</td>
<td>8.0</td>
<td>0.37</td>
<td>4.0</td>
</tr>
<tr>
<td>1: Left cerebellar hemisphere</td>
<td>613</td>
<td>Solid</td>
<td>0.41</td>
<td>8.0</td>
<td>0.37</td>
<td>4.0</td>
</tr>
<tr>
<td>2: Left frontal lobe</td>
<td>634</td>
<td>Cystic</td>
<td>0.30</td>
<td>5.3</td>
<td>0.18</td>
<td>1.8</td>
</tr>
<tr>
<td>2: Centrally right cerebral hemisphere</td>
<td>691</td>
<td>Cystic</td>
<td>0.31</td>
<td>5.3</td>
<td>0.19</td>
<td>1.4</td>
</tr>
<tr>
<td>3: Right occipital lobe</td>
<td>900</td>
<td>Cystic</td>
<td>0.35</td>
<td>7.4</td>
<td>0.25</td>
<td>2.1</td>
</tr>
<tr>
<td>4: Left cerebellar hemisphere</td>
<td>280</td>
<td>Solid</td>
<td>0.48</td>
<td>5.9</td>
<td>0.57</td>
<td>6.2</td>
</tr>
<tr>
<td>4: Vermis cerebellum</td>
<td>112</td>
<td>Solid</td>
<td>0.51</td>
<td>5.9</td>
<td>0.57</td>
<td>2.7</td>
</tr>
<tr>
<td>4: Right parietal region</td>
<td>97</td>
<td>Solid</td>
<td>0.43</td>
<td>5.9</td>
<td>0.44</td>
<td>2.0</td>
</tr>
<tr>
<td>5: Left temporal lobe</td>
<td>132</td>
<td>Solid</td>
<td>0.38</td>
<td>20.9</td>
<td>0.38</td>
<td>2.6</td>
</tr>
<tr>
<td>5: Right occipital lobe</td>
<td>116</td>
<td>Solid</td>
<td>0.39</td>
<td>20.9</td>
<td>0.61</td>
<td>3.4</td>
</tr>
<tr>
<td>6: Left paraoccipital region</td>
<td>909</td>
<td>Cystic</td>
<td>0.20</td>
<td>5.7</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

a ROI, region of interest; NA, not analyzed.
b Pixel size, 2 × 2 mm.

Treatment

Patients were allocated to palliative treatment according to the severity of symptoms. Most patients received high-dose glucocorticosteroids for immediate symptom relief after the diagnosis of the brain metastases. If this resulted in complete symptom relief, patients were allocated to elective WBRT within 2–3 weeks. Before this, the patients underwent staging procedures, including bronchoscopy and abdominal ultrasound with liver biopsy and bilateral bone marrow aspiration and biopsy. If the patients were without extracranial disease, radiotherapy was given in a total dose of 50.4 Gy in 28 fractions of 1.8 Gy. Patients with minor or no symptomatic relief after treatment with high-dose glucocortic-steroids and extracranial disease were allocated to WBRT, 20 Gy in 4 fractions, 5 Gy per fraction.
rCBV. The patients were instructed to inhale air with a concentration of no more than 0.5% stable carbon monoxide with a total of 30 mCi (1 GBq $^{15}$CO) for 2 min. After a 2-min delay to obtain steady state of the distribution, a static emission scan was performed for 6 min. Blood samples from the radial artery were collected by a computerized blood sampler from the initiation of tracer inhalation until the end of the emission in all of the patients to measure the input function for quantification of the tracer. The sampled data were integrated and multiplied with a calibration factor for the scanner and corrected for the relative cerebral hematocrit (0.85). rCBV was then assessed as the ratio between the image activity (kBq/cc) and this product (ml/100 ml).

rCBF. A 5-ml bolus of $H_2O$ with 30 mCi (1 GBq) $H_2^{15}$O was injected into the cubital vein contralateral to the catheter of the radial artery. Simultaneously, 3-min dynamic acquisition was performed with continuous computerized blood sampling from the radial artery at a rate of 1 ml/s. Calculation of the flow was performed by the autoradiographic methods. Correction for the dispersion in the measured arterial radioactivity-time curve was applied to avoid overestimation (24).

$rCMR_glu$. Starting simultaneously with a slow (30-s) injection of 5–7 mCi (185–260 MBq) FDG in the contralateral cubital vein, dynamic emission scan was performed for 60 min. Patients were blindfolded for the first 20 min, and the surroundings were kept comfortable and quiet. To measure the tracer input function, blood samples were collected from the radial artery. This was done manually at intervals of 10 s (for the first 3 min), 30 s (for 2 min), 1 min (for 5 min), 2 min (for 10 min), and 5 min (for 40 min, i.e., between 20 and 60 min after the injection). Blood glucose concentrations were sampled at time 0, 10, 30, and 60 min after the injection of FDG. The graphical method developed by Patlak et al. (25) and Gjedde et al. (26) was used for image quantification and calculation of $rCMR_{glu}$. The time interval from 20–60 min was used for the linear fit with an operational lumped constant of 0.55.

Image Analysis

The region of interest was defined by computerized alignment with MRI using the computerized brain atlas software package (27). Both PET images and MRI were coregistered to a brain surface mask and resliced (normalized) to a stereotactic standard brain. This is based on the digitized Talaraich brain atlas (28). The precision of this procedure is 1–2 mm (27). The calculated $rCMR_{glu}$ of the tumor was normalized by comparison with an area of the same size in the contralateral white matter. Peak and mean values were calculated. Additionally $rCMR_{glu}$ of cortical areas of maximal activity were calculated for utilization ratio of the gray-white matter (GM:WM). Mean values of three areas contralateral to the tumor were used. For patients with bilateral tumors, the mean value of bilateral temporal gray and white matter was applied.

Statistical Analysis

The metastatic lesions were analyzed individually, and Pearson’s correlation was used to describe relationships between different variables, although the metabolic and hemodynamic features of different lesions in one patient could be related. Wilcoxon’s signed rank test was used to compare the metabolic and hemodynamic values in different areas and before and after treatment.

RESULTS

Tumor $rCMR_{glu}$ was higher than $rCMR_{glu}$ of white matter and, in the majority of tumors, also higher than $rCMR_{glu}$ of cortex. Both peak and mean tumor $rCMR_{glu}$ was highly correlated to tumor rCBF (Fig. 1A; $P = 0.001$, $r = 0.80$) and tumor rCBV. However, in three cystic tumors, $rCMR_{glu}$, rCBF, and rCBV as expected were significantly lower compared with solid tumors; and, in a separate analysis of only solid tumors, the correlation between tumor FDG and rCBF was no longer significant at the 5% level.

Three patients had repeating PET analysis after therapy. When these studies were included in the correlation analysis, a statistically significant correlation between peak tumor $rCMR_{glu}$ and tumor rCBF was observed (Fig. 1B; $P = 0.015$, $r = 0.74$).

The peak values along the rim of the cystic lesions were higher than the contralateral cortical values. $rCMR_{glu}$, rCBF, and rCBV of the solid tumors exerted a broad variability independent of the region-of-interest sizes. The majority of the tumors had a higher FDG uptake compared with the contralateral cortex, and all of the tumors had a higher uptake than the contralateral white matter. Also rCBF and rCBV were generally higher in the tumors than in the cortex (Table 2).

The blood glucose levels were measured in all of the patients; and in one patient, steroid-induced hyperglycemia (blood glucose 20.9 mmol/liter) was detected at the time of the PET scan. All of the other patients had normal blood glucose levels (Table 1). The absolute values of tumor $rCMR_{glu}$ were not affected in this patient, but the cortical $rCMR_{glu}$ was decreased (0.17 μmol/g/min) compared with the mean value for all of the cases (0.25 μmol/g/min; SD, 0.05). Consequently, the tumor cortex uptake ratios of $rCMR_{glu}$ were increased to 2.23 and 2.26, respectively, compared with a mean value of 1.48 (SD, 0.50).

Two patients had repeating PET after WBRT and a total of four tumors were analyzed both before and after radiotherapy (Table 3). Fig. 2 shows PET scans before and after radiotherapy of one of these patients. All of the tumors regressed after radiotherapy according to MRI and symptom control. This correlates to $rCMR_{glu}$, which decreased in the tumors from 0.36 (±0.11) μmol/g/min to 0.31 (±0.12) μmol/g/min (mean values ± SD). However, this decrease was not statistically significant ($P = 0.47$, by Wilcoxon correlation). No changes in $rCMR_{glu}$ was observed in the gray or white matter after radiotherapy. Cortical rCBF increased significantly after WBRT from 0.40 ± 0.09 ml/g/min to 0.49 ± 0.08 ml/g/min ($P = 0.13$), whereas rCBF and rCBV remained unchanged in tumors and white matter after therapy.

DISCUSSION

Tumor hypoxia may be associated with poor prognosis, and it has been shown in cancer cell lines that FDG uptake increases with hypoxia (29, 30). In the present study, some of the analyzed metastases were cystic with central necrotic areas. These lesions had lower mean values of rCBF, rCBV, and $rCMR_{glu}$. The solid lesions all had higher values, and a significant correlation be-
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The correlation between tumor rCMR_glu and rCBF was found. However, the values varied within the tumors, within different lesions in the same patients, and within the patients. This reflects the large tumor heterogeneity.

The tumor rCMR_glu and rCBF were higher than or equal to cortical values and higher than corresponding areas in the white matter. After radiotherapy, tumor rCMR_glu tended to decrease, whereas tumor rCBF remained unchanged. Remote rCMR_glu and rCBV were unaffected, but rCBF increased in cortex and white matter after radiotherapy. Whether this was caused by tumor-related depression of rCBF before radiotherapy or by elevated values after radiotherapy is unknown. In a study of mainly high grade gliomas, Beaney et al. (31) demonstrated a significant cortical depression of oxygen metabolism and rCBF compared with patients without brain tumors. This could be caused by increased intracranial pressure (32). The fact that cortical rCBF in our study increased after radiotherapy whereas tumor rCMR_glu decreased indicates that tumor regression normalizes global CBF. Ogawa et al. (19) found similar results in a study of hemodynamic and metabolic changes after radiochemotherapy in patients with gliomas. Tumor rCMR_glu decreased...
in all of the patients after treatment, but tumor hemodynamics were not significantly altered. Simultaneously, rCBF increased in the contralateral gray matter. The small number of patients in this study limits the interpretation of these data; a higher number of patients would be required to demonstrate significant correlations.

The wide range of tumor values of rCMRglu was comparable to the range of the values of high grade gliomas, which also have a broad variability (Ref. 12; 0.12–0.88 μmol/g/min; Table 4). The tumor values of rCBF seemed to be somewhat lower than previously reported values for high grade gliomas (0.18–0.61 ml/g/min and 0.26–1.02 ml/g/min, respectively), but comparable to reported values from brain metastases (Ref. 12; Table 4). The values of the cortex and white matter in this study are similar to previously reported values (12).

A broad variability of blood flow and glucose consumption has been observed in human malignancies. It has been assumed that glucose uptake is proportional to the availability and, thereby, the flow rate during normoglycemia (12). Increased glucose uptake seems to be associated with the grade of malignancy, but within highly malignant tumors, a substantial variability has also been observed. This may be due to a variable distribution of blood flow with heterogeneous microcirculation and necrotic areas.

The lack of observed hemodynamic changes in the tumors after treatment may be an artifact of the poor spatial resolution of PET. This is mainly due to poor statistics, i.e., the energy of $^{15}$O is high, and the axial spatial resolution with this tracer is more than 8 mm. Therefore, the calculated values represent averages of larger areas, and, because of this partial volume effect, small areas with a low regional blood flow are not detected. At present, microcirculatory heterogeneity and continuous circulatory alterations, due to various factors, cannot be detected in vivo. Other tracers to study tumor hemodynamics and hypoxia are warranted. In lung cancer and gliomas, $^{18}$F-labeled misonidazole has been associated with hypoxia (33, 34), and various other methods have been applied (35).

The time intervals between the treatment and the PET scan are likely to influence the results. Increased FDG uptake has been described immediately after radiotherapy. In this study, the posttreatment PET scans were performed 6–8 weeks after radiotherapy.

The calculation of rCMRglu in tumors with FDG has some limitations that may bias the results: (a) on average, FDG uptake in most tumors does not differ from that of normal cortex; therefore, delineation with PET may be uncertain and image coregistration with MRI is necessary; and (b) the method for quantification of rCMRglu varies among different laboratories, and the optimal method has not been determined. The original autoradiographic method described by Sokoloff and et al. (36) may not be feasible for malignancies. This method is well

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**Table 4** Global, regional, and tumoral CMRglu and CBF

<table>
<thead>
<tr>
<th>Tissue</th>
<th>CMRglu (μmol/g/min)</th>
<th>CBF (ml/g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>0.30–0.40</td>
<td>0.50–0.55</td>
</tr>
<tr>
<td>Gray matter</td>
<td>0.25–0.51</td>
<td>0.25–0.78</td>
</tr>
<tr>
<td>White matter</td>
<td>0.08–0.28</td>
<td>0.08–0.33</td>
</tr>
<tr>
<td>Grade I–II astrocytomas</td>
<td>0.14–0.43</td>
<td>0.03–1.01</td>
</tr>
<tr>
<td>Grade III–IV astrocytomas</td>
<td>0.12–0.88</td>
<td>0.26–1.02</td>
</tr>
<tr>
<td>Brain metastases</td>
<td></td>
<td>0.03–0.72</td>
</tr>
<tr>
<td>Present study</td>
<td>0.18–0.52</td>
<td>0.18–0.61</td>
</tr>
</tbody>
</table>

*CMRglu metabolic rate of glucose.

*a Modified from Vaupel et al. (12).
established for the study of normal brain, but, because of tumor heterogeneity and variations in the applied rate constants, this method may be inaccurate in malignant tissue (37). Both increased blood-brain barrier permeability and overexpression of glucose transporters in tumors (38, 39) alter the pharmacokinetics of glucose and FDG.

Initially, we used a revised autoradiographic model with correction for dephosphorylation of deoxy-glucose \( k_p \) (Ref. 40). This includes an operational lumped constant of 0.55. However, in one patient with hyperglycemia caused by steroid-induced diabetes, this model using standard values for the rate constants \( k_p \) resulted in negative values of rCMR\(_{gLu}\), for white matter. We, therefore, used the graphical method developed by Patlak et al. (25) and Gjedde et al. (26). This method can be applied to both homogeneous and heterogeneous tissue and assumes that linear correlation of FDG uptake and arterial tracer concentration is obtained between 10 and 40 min after FDG injection. The optimal time to equilibration is probably as long as 60 or 120 min (41) but is probably not feasible in this group of patients with poor conditions; therefore, we used the time curve from 20–60 min.

The blood glucose level could possibly be an important parameter in the relative uptake in brain tumors but may not affect the absolute values. In the patient with hyperglycemia (blood glucose, 20.9 mmol/liter), the tumor:corpus cortex uptake ratios in the two metastases were 2.23 and 2.26, respectively, whereas the mean value for all of the tumors was 1.48 (SD, 0.50). The absolute rCMR\(_{gLu}\) in the two metastases was 0.38 \( \mu \)mol/g/min and 0.39 \( \mu \)mol/g/min, which corresponded to the mean value of 0.36 \( \mu \)mol/g/min (SD, 0.11).

Multitracer studies are time-consuming and uncomfortable for the patients. The general prognosis of SCLC is poor, and, although a CNS response is observed after WBRT, the majority of the patients will have an extracranial relapse. This was also the case in the present study, and, because of poor performance, less than half of the included patients had repeating scans after therapy.

In conclusion, the present study showed that brain metastases from SCLC in general have a similar or higher rCMR\(_{gLu}\) and rCBF than the cortex. Regional CMR\(_{gLu}\) and rCBF in metastases seem to be correlated. As in primary malignant gliomas, global CBF is reversibly depressed by the tumor presumably because of increased intracranial pressure, but, after tumor reductive therapy, global CBF is normalized.

The present method could not detect an association between high tumor rCMR\(_{gLu}\) and low tumor rCBF as an indicator of hypoxia. However, this lack of detection may have been caused by insufficient spatial resolution and microcirculatory heterogeneity as well as by poor statistics due to too-few patients. As with other malignancies, these lesions are very heterogeneous and central necrotic areas are frequent. Other tracers for noninvasive in vivo analysis of tumor hemodynamics are needed, especially for discrimination between tumor necrosis and regional hypoxia.

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