Evaluation of malignancy in ring enhancing brain lesions on CT by thallium-201 SPECT

K Källén, M Heiling, A-M Andersson, A Brun, S Holtás, E Ryding, I Rosén

Abstract

Objective—To investigate patients with cystic enhancing lesions on CT and to determine whether thallium-201 (201TI) SPECT adds to further preoperative information in differential diagnosis between gliomas and abscesses.

Methods—Twenty one patients with cystic ring enhancing CT findings were studied and uptake indices were compared with CT enhancement volumes, histopathology, and survival times.

Results—Fourteen high grade gliomas, three low grade gliomas, and four abscesses were found. Uptake was higher in the highly malignant glioma group (median thallium index (TI)=2.1), than in the low grade glioma group (median TI=1.4) or among the abscesses (median TI=1.6). Overlapping indices were found between high and low malignant cystic gliomas as well as between either one of the glioma groups and the infectious lesions, and there were no significant differences between groups. There was a level at the value 2, where TI\geq2 correlated with tumour diagnosis. One low grade tumour had an extremely high index and a very high enhancement volume. Indices correlated significantly with CT enhancement volumes (P=0.005). There was no significant correlation between TI indices and patient survival times among the high grade gliomas. One patient with a highly malignant tumour but low TI uptake <2, had a survival >five years.

Conclusions—It is concluded that high 201TI uptake in enhancing cystic lesions is an indicator of highly malignant glioma. However, the differentiation between the high malignant gliomas and abscesses or low malignant gliomas by 201TI SPECT is only partial with an overlap between these groups.

Methods

PATIENTS

Over a three year interval, 67 patients with suspected malignant glioma as judged from CT underwent brain 201TI SPECT. In an earlier study all of these patients with histologically defined gliomas were analysed. The present study selectively included all those 21 patients with cystic lesions with ring enhancement on CT.

Patients’ (10 female and 11 male) ages ranged from 11 to 74 years. All included patients had their CT and SPECT examinations performed preoperatively. Within an interval of 35 days from SPECT and CT examinations all patients were operated on and the final histological diagnosis was determined. Two patients underwent diagnostic biopsy, 15 patients underwent tumour resection. In four patients an infectious abscess was suspected. The cystic cavity was extirpated or punctured in two patients; the infectious diagnosis was verified by positive leucocyte SPECT in the other two cases.

Malignant gliomas were originally classified according to the histological classification method of Kernohan et al. This system includes four grades of primary astrocytoma, oligodendroglioma, or mixed oligoastrocytoma (I, II, III, IV) but gliomas with heterogeneous growth and areas of varying malignancy grades are common, when the most malignant part decides the grading level. Tumours grade I and grade II are grouped together as low grade gliomas, tumours II-III, III, and IV are grouped together as high grade gliomas. With reference to the World Health Organisation (WHO) classification this means that high grade gliomas in this study comprise anaplastic astrocytomas, anaplastic oligodendrogliomas, and glioblastomas, the others being low grade gliomas.

The clinical course of the patients was followed up for a minimum of three years and a maximum of six years. All patients with...
highly malignant tumours, except for one who is alive, were followed up until their death.

**Table 1 Patients’ age and sex**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>Tumour grade</th>
<th>Lesion position</th>
<th>Survival (weeks)</th>
<th>Size (ml)</th>
<th>Enh (ml)</th>
<th>Histology</th>
<th>R</th>
<th>B</th>
<th>TI index</th>
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* Patient with tumour located in the midline with a false too low TI (1.0). In this case TI was defined as the tumour uptake relative to the uptake in the lateral part of the hemisphere. For tumour grading L = low grade; H = high grade; Abs = abscess. For lesion position lt = left; rt = right; temp = temporal; front = frontal; par = parietal; occ = occipital. Enh = enhancement. For histology R = resected tissue; B = biopsy specimen.

**TECHNIQUES**

The $^{201}$Tl SPECT measurements were made with a brain dedicated dedicated SPECT camera (Tomo- matic 564). Each patient was given an intravenous injection of 75 MBq $^{201}$Tl in isotonic sodium chloride. Children were given 1 MBq $^{201}$Tl/kg body weight. The patients were positioned in the SPECT camera five minutes after TI administration. The $^{201}$Tl uptake was recorded in 10 transaxial contiguous 1 cm thick slices from 1 cm below the orbito-meatal line and superiorly. The intraslice resolution was about 1 cm (full width, half maximum). Images were acquired with a three turns per minute continuous rotation for five minutes. We used a 47-87 keV energy window around the 70 keV photo peak. The reconstruction was done in a 64×64 image matrix. The images were reconstituted with filter back projection and a linear attenuation correction in the axial plane. The attenuation coefficient used was 16%.

Preoperative CT was used as an anatomical guide. The $^{201}$Tl uptake was measured in the slice corresponding to the location of the cystic enhancing lesion identified on CT. Without knowledge of the histology of the lesion, a cross sectional profile was drawn through the part of the cystic lesion with the highest $^{201}$Tl uptake. The average value of the three adjacent pixels with the highest Tl uptake was used. For each patient we determined a $^{201}$Tl index of the uptake within the cystic lesion relative to the mean of three homologous pixels on the contralateral side (TI=tumour uptake/contralateral uptake). In one patient, the lesion was in the midline and consequently the TI was 1.0. In that case the tumour uptake was compared with the uptake in a low uptake region in the lateral part of one hemisphere.

All patients had a preoperative CT examination before and after administration of contrast. Different modern CT scanners were used. The time interval between the SPECT and CT examination never exceeded six weeks (median 13 days). The slices were parallel to the orbito-meatal line and the thickness varied between 4-10 mm in the posterior fossa and 8-10 mm supratentorially. Contrast enhancement was achieved by a bolus injection of 100 ml iohexol (300 mg/ml) or 1.5 ml/kg body weight in patients with a body weight ≤ 60 kg. Total volume of the mass and the volume of the tissue with blood-brain barrier damage was measured by the same neuroradiologist in every patient. The total volume measured consisted of the area with blood-brain barrier damage; including areas with necrosis or cysts.

The presence of blood-brain barrier damage was determined by visual comparison of precontrast and postcontrast images.

To measure the volume of the cystic lesions and their enhancement, a 5×10 cm grid was drawn on a disposed transparent x ray film using a cm scale, indicated on the image. The grid was placed on the lesion and areas of enhancement in every slice of the mass lesion and the area of enhancement or lesion volume were measured. The total volume was then calculated by multiplying the area of each slice with the slice thickness, and the volumes on each slice with pathology were added together.

**STATISTICAL ANALYSIS**

The results are expressed as medians and ranges. The relation between $^{201}$Tl indices and enhancement volumes of high or low grade gliomas or infectious lesions were analysed with an unpaired t test. The non-parametric Mann-Whitney U test was used. The level of significance was set at 0.05. Associations between $^{201}$Tl indices and enhancement volumes were assessed by the Spearman rank correlation test. The computer program StatView 4.0 was used in the analyses.

**Results**

Fourteen patients had histopathologically verified cystic high grade gliomas and three patients had cystic low grade gliomas. Four patients had intracerebral infectious lesions. Table 1 shows the characteristics of patients and lesions.

One patient, a 22 year old woman, had a tumour showing contradictory features of high and low malignancy (table 1 patient 16). She presented with a two month history of fatigue, change in mental state, and severe headache. Her initial CT was in September 1992 and it indicated high grade glioma as the probable diagnosis (fig 1). Because of spots of calcification in the middle of the tumour it was assumed to be a mixed oligodendroastrocytoma of high malignancy grade. The highly malignant character of the tumour was further confirmed by $^{201}$Tl SPECT examination (fig 1). An operation was performed 19 days after the initial CT. Tumour growth was well demarcated from normal brain tissue and the tumour seemed to be radically extirpated. Histopathologically the tumour had a mixed and varied appearance with small areas of an...
oligodendroglial-like type including calcifications, but mainly a pleomorphic cell population with small to large cells with distinct cell membranes and irregular, sometimes multiple, nuclei and often a loose, granular cytoplasm. All of these cell varieties were positive to antibodies against glial fibrillar acidic protein. There were no necroses, only a rare vessel with a thickened wall, and a rare mitosis, features mitigating against a malignancy hinted at by the pleomorphic cell picture (fig 2). Against this background the process was diagnosed as a pleomorphic xanthoastrocytoma with a likely oligodendroglial component and of low grade malignancy. The patient did not receive any primary adjuvant therapy. Initially she had a benign postoperative course with no sign of clinical deterioration, then she developed epilepsy with rare partial complex seizures. During the spring of 1995 she experienced an increase in seizure frequency and a CT examination disclosed a recurrent tumour located in the right frontal lobe—that is, in the same region as the original tumour was located. She was reoperated on in September 1995 with tumour resection and surgery was followed by radiation treatment. Her post-treatment CT has so far shown no signs of either residual tumour or tumour recurrence.

Indices of Tl uptake had a wide range in cystic high grade gliomas (table 2). One ring enhancing low grade glioma had an extremely high 201Tl index. There was an overlap in 201Tl indices between high grade and low grade gliomas and infectious lesions. There was no significant difference in 201Tl uptake indices between high grade gliomas versus low grade gliomas or infectious lesions. There was an index level at the value 2.0, where TI>2.0 correlated with tumour diagnosis as all infectious lesions had a TI<2. There was no clear level between high grade and low grade gliomas.

In a second analysis low grade gliomas and abscesses were put together as one group. The reason behind putting these two groups together was that both are suspected of having a low Tl uptake. Even in this case, no significant difference between groups was found.

In a third analysis the pleomorphic xanthoastrocytoma (patient 16) was considered an extreme outlier and was excluded from the group of low grade tumours. The tumour was atypical, and was measured and evaluated by different methods at separate times (fig 3A and B). In this case neither the abscesses nor the low grade gliomas had any TI values exceeding 1.9. Again, when assessing the difference between the high grade gliomas versus the low grade and infectious lesions, no significant difference between groups was found.

Contrast enhancement volume on CT had a wide range in cystic high grade gliomas as well as in low grade gliomas. The pleomorphic xanthoastrocytoma had the highest contrast...
enhancement volume (table 2 and fig 3 B). Tested by the Mann-Whitney U test enhancement volumes were significantly higher in high grade than in low grade gliomas only if the extreme outlier was excluded (U=19.5 tied P=0.038). There was an extensive overlap between enhancement volumes in high grade gliomas and infectious lesions and no demonstrable significant difference between the two groups. Among the high grade, low grade, and abscess lesions there was a highly significant correlation between 201Tl indices and CT contrast enhancement volumes with the outlier included (tied P=0.005) as well as without the outlier (tied P=0.012).

Table 2  201Tl indices and CT estimated enhancement volumes for cystic high grade gliomas, cystic low grade gliomas, and abscesses

<table>
<thead>
<tr>
<th></th>
<th>High grade (n=14)</th>
<th>Low grade (n=3)</th>
<th>Abscess (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>201Tl index</td>
<td>2.1 (1.0–4.2)</td>
<td>1.4 (1.3–6.2)</td>
<td>1.6 (1.0–1.9)</td>
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<tr>
<td>CT enhancement volume (ml)</td>
<td>20.5 (4.0–47.0)</td>
<td>4.0 (3.0–84.0)</td>
<td>9.5 (4.0–21.0)</td>
</tr>
</tbody>
</table>

Values are median (range).

Table 3 Survival time for patients with cystic high grade gliomas

<table>
<thead>
<tr>
<th></th>
<th>All high grade gliomas n=14</th>
<th>Low 201Tl uptake n=7</th>
<th>High 201Tl uptake n=7</th>
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</thead>
<tbody>
<tr>
<td>Survival time (weeks)</td>
<td>23.5 (3.0–260.0)</td>
<td>32.0 (8.0–260.0)</td>
<td>21.0 (3.0–39.0)</td>
</tr>
</tbody>
</table>

Values are medians (range). High uptake tumours, TI index > 2; low uptake tumours, TI index < 2.

Discussion

Thallium-201 SPECT has been proposed as a method for assessment of malignancy grade in gliomas.6–7 There is a selective uptake of 201Tl in highly malignant glioma cells. The mechanism behind intracellular TI uptake is probably an active transport by less selective ion channels in malignantly transformed glial cells.19–21 The cellular uptake is not solely related to cell biology in the tumour. The uptake is multifactorial, depending also on blood flow in the tumour, extent of pathological vessel invasion, and extent of blood-brain barrier breakdown.

In a recent study we evaluated the accuracy in preoperative glioma malignancy grading on the basis of 201Tl uptake indices, CT findings, and histopathology.22 We found a significant correlation between CT enhancement volumes and 201Tl uptake indices in high grade gliomas. Uptake of 201Tl in non-enhancing gliomas was very low, independent of tumour malignancy grade. A disrupted blood-brain barrier seems to be a prerequisite for intracerebral penetration of TI and its uptake in gliomas. This is expected as the TI ion is polar and may only penetrate into the CNS when there is a disrupted blood-brain barrier. False negative scans were found as a result of shielding by the intact blood-brain barrier. Enhancement volumes correlated with 201Tl uptake indices in this as well as in our previous report. The

One of the patients with a cystic high grade glioma with low TI uptake (patient 4, table 1) was alive at the end of the follow up time. His tumour was histologically classified as a glioblastoma multiforme, or according to the classification of Kernohan et al5 a glioma grade III-IV. The patient underwent whole brain irradiation to a dose of 58 000 cGy in the tumour bearing hemisphere and adjuvant combined chemotherapy consisting of procarbazine, vincristine, and lomustine (CCNU) in accordance with the local treatment regime. This case now has a follow up time of >five years. His latest CT was in May 1996 and showed no sign of tumour recurrence.
importance of cell biology (malignancy grade) for Tl uptake seems to be of a more complicated nature than previously understood. The low grade malignant gliomas with small or moderate enhancement volumes had low 201Tl uptake. The abscesses as a group seem to fall into the same category as the low grade gliomas.

In our previous report we found some cystic tumours of high malignancy grade to have low Tl uptake despite a disrupted blood-brain barrier. There is a risk for underestimation of tumour malignancy grade when using 201Tl SPECT in cases of extensive presence of necrotic tumour areas in combination with moderate surrounding enhancement. Because cystic features on CT can be signs of a highly malignant glioma but also are characteristic of an infectious lesion—for example, a bacterial abscess. 201Tl SPECT has been hypothesised to distinguish between the two diagnoses. In both cases there is a disrupted blood-brain barrier and a CT enhancement but factors facilitating a selective intracellular Tl uptake only exist when malignantly transformed cells are present. However, our results indicate that 201Tl only allows a partial discrimination between cystic highly malignant gliomas and infectious lesions as partly overlapping 201Tl indices exist between the two groups.

Ruiz et al suggested that 201Tl SPECT was of value in discriminating lymphomas from infectious processes in patients with AIDS with intracranial mass lesions, as none of the patients with infectious lesions had a 201Tl uptake. Other authors have reported 201Tl uptake in infectious lesions. Abnormal intracerebral Tl localisation in a bacterial brain abscess was found by Krishna et al. Distribution of Tl in tumour tissue and inflammatory lesions has been studied in rats by Ando et al. Their results indicated that Tl accumulated mainly in tumour tissue but also to a lesser extent in subcutaneous inflammatory tissue specifically at sites where leucocytes and macrophages were crowded.

In our material there is a case similar to that described by Krishna et al. Patient 20 (table 1) had a moderately intense 201Tl uptake in a cystic brain lesion that was found to be a bacterial abscess (fig 4). The Tl is at the same level as that of a high grade glioma with a moderate enhancement volume. It must be stressed that many factors contribute to the intracerebral Tl uptake. Uptake of 201Tl is an indicator of highly malignant tumour but Tl accumulation is also found to some extent in inflammatory or infectious tissue. In our material there is an index level at the value 2.0, were Tl≥2.0 correlates with tumour diagnosis.

The case with a low grade tumour with high 201Tl uptake and high enhancement volume is puzzling and shows that high 201Tl uptake might also be found in occasional benign tumours of uncommon cell type and with blood-brain barrier damage. Findings from CT and Tl uptake in this case were both imitating the findings of a highly malignant glioma. The tumour showed contradictory features of a high and low malignancy character but was judged to be of low malignancy. This is in agreement with the WHO practice and the relatively benign postoperative course shown by the patient. In a previously published study early and late retention of Tl was measured. The authors found that early high and rapid uptake combined with slow reduction of Tl indicated a hypervascular malignant tumour. However, early high and rapid uptake but rapid reduction of Tl indicated a hypervascular benign tumour, such as a meningeoma. In this study we only evaluated early Tl retention and we do not know in what way the relatively benign pleomorphic xanthoastrocytoma would have reacted if late retention had been been measured. This single case confirms the need for caution when evaluating preoperative CT as well as 201Tl SPECT.
In the clinical follow up there was one case with a glioblastoma and an unexpectedly long survival. Even with aggressive therapy, the survival of adults with high grade astrocytomas is very limited. Virtually no one is cured from their illness. The median survival time is 18 months for patients with anaplastic astrocytomas and 12 months for patients with glioblastoma multiforme. However, there are other well known prognostic factors with significant impact on survival time such as age younger or older than 50 years and Karnofski performance greater or less than 70. The median survival time of those with the best prognostic variables was 58 months in one published survival analysis of more than 1500 patients with high grade astrocytomas who entered clinical trials. A published meta-analysis for patients treated with both chemotherapy and radiation therapy found a median survival time of 12 months, with a range from seven to 46 months. Our patient with definite long term therapy found a median survival time of 30 months.31 Our patient with definite long term therapy found a median survival time of 12 months. Our patient with definite long term therapy found a median survival time of 12 months.

We conclude that in cystic brain lesions20Tl SPECT allows a partial differentiation between high grade gliomas and low grade gliomas or infectious abscesses. Enhancing CT findings and high20Tl uptake in cystic lesions are both indicative of highly malignant gliomas but false negative as well as false positive findings exist with both methods. Diagnostic biopsy still seems necessary to establish a correct histological diagnosis in these cases.

The study was supported by the Swedish Cancer Fund, grant No 0233-B94-03X-BB, and by the Swedish medical research council, grant No B95-14X-00084-31B. We thank Magnus Lindgren for statistical advice, and Professor LG Salford, Lindgren for statistical advice, and Professor LG Salford, with both methods. Diagnostic biopsy still seems necessary to establish a correct histological diagnosis in these cases.

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