Evaluation of Single Photon Emission Computerised Tomography (SPECT) using Tc99m-Tetrofosmin as a Diagnostic Modality for Recurrent Posterior Fossa Tumours

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Abstract:

BACKGROUND: Brain Single Photon Emission Computerised Tomography (SPECT) has been established as a potentially useful tool for the assessment of recurrent brain tumours. Though brain SPECT is exquisitely sensitive in detecting viable tumour tissue in the supratentorial region, its efficacy has not been evaluated till date in case of infratentorial posterior fossa tumours. AIM OF THE STUDY: To evaluate the diagnostic utility of brain SPECT in differentiating recurrence of tumour from post-radiation gliosis in the posterior fossa of the brain. SUBJECTS AND METHODS: Twenty-one patients with primary malignant posterior fossa brain tumour were evaluated by brain SPECT with Tc99m-Tetrofosmin as the tumour-seeking agent. Clinical behaviour of the tumour observed for a minimum period of one year after the SPECT study was taken as the gold standard. STATISTICAL ANALYSIS: The Chi-square test has been used to note the significance of the association between the clinical outcome and the SPECT finding. In addition, the sensitivity and specificity of brain SPECT were also calculated. RESULT: Brain SPECT in 4 patients revealed increased tracer concentration over the primary tumour bed, which was consistent with recurrent tumour. The clinical course was consistent with tumour recurrence in 13 of the 21 patients, which included 3 patients with positive SPECT study and 10 patients with negative SPECT study. Brain SPECT revealed recurrent tumour in 4 patients whereas clinical follow-up suggested recurrence in 13 patients. The clinical course was consistent with radiation necrosis in the remaining 8 patients. In 1 brain SPECT positive patient the clinical course was consistent with post-radiation gliosis. CONCLUSION: This study demonstrates that brain SPECT is not a sensitive diagnostic modality to differentiate recurrent tumour from post-radiation gliosis in the posterior fossa of the brain. (J Postgrad Med 2003;49:316-21)

Key Words: Posterior fossa, Tetrofosmin, Fanbeam collimator, Post-radiation gliosis.

Accurate neuroimaging can assist in the diagnosis, management and follow-up of patients with posterior fossa brain tumour. Brain SPECT has been established as a potentially useful tool for the assessment of recurrent brain tumours. Though brain SPECT is exquisitely sensitive in detecting viable tumour tissue in the supratentorial region, its efficacy has not been evaluated till date in case of infratentorial posterior fossa tumours. We undertook a pilot study and evaluated 21 patients of malignant posterior fossa tumour by brain SPECT with Tc99m-Tetrofosmin as the tumour-seeking agent. The aim of the study was to evaluate whether brain SPECT is a reliable modality for differentiating recurrent tumour from post-radiation gliosis in posterior fossa tumours.

Subjects and Methods

Brain SPECT with Tc99m-Tetrofosmin and contrast-enhanced computerised tomography (CT) were performed in 21 patients of histologically proven malignant posterior fossa brain tumour in the age range of 5-51 years. Twelve patients were under the age of 18. There were 6 females and 15 males in the group. All of them had received postoperative radiotherapy 8-36 months prior to the brain SPECT. The histological type was medulloblastoma in 10 patients, ependymoma in 4 and high-grade glioma (WHO grade 3 and 4) in the remaining 7 patients (Table 1). All eligible patients were sequentially enrolled and followed up in the cancer clinic and imaged between 1998 and 2002. All the patients underwent a contrast enhanced computed tomography (CECT) scan of the brain within 1 week of brain SPECT study, with the majority of study pairings being completed within 72 hours. Seven patients also underwent an additional magnetic resonance imaging (MRI) of brain. Clinical behaviour of the tumour observed for a minimum period of one year after the SPECT study was taken as the gold standard. The study design was approved by the institute’s ethical committee. Informed consent was obtained from all patients or legal guardians.

Brain SPECT was acquired one-hour post intravenous administration of 185-1000 Mega Bequeral (MBq) Tc99m-Tetrofosmin, using a dual-head single photon emission computed tomography system (Varicam, Elscint, Israel) fitted with a low-energy ultrahigh resolution fan beam coll...
The absence of any abnormal tracer uptake over the site of the primary tumour bed was considered indicative of viable tumour. The intensity of tracer concentration in the tumour mass was expressed as tumour to background ratio (Tetrofosmin index).

Two experienced nuclear medicine physicians evaluated the scan findings independently and were blinded from the SPECT finding. The lesions were interpreted as post-radiation gliosis if their HU-values were close to CSF-density with no evidence of any mass-effect, whereas lesions showing effacement of adjacent sulcal spaces (mass-effect) with or without contrast-enhancement were reported as recurrent tumour.

An irregular region of interest (ROI) was drawn around the tumour, encircling it completely. The ROI was drawn on the transverse slice with the highest radiotracer concentration and the average pixel count in the ROI was obtained. A similar ROI was drawn on the corresponding area of the contralateral side by computer-assisted software and the average pixel count in the ROI was obtained. The ratio of the two average pixel counts was obtained and defined as the Tetrofosmin Index.

Thus, the Tetrofosmin retention index was calculated as follows:

\[ \text{Tetrofosmin index} = \frac{\text{Average pixel count in the ROI}}{\text{Average pixel count in the ROI on the contralateral side}} \]

No ROI was drawn in patients who did not show Tetrofosmin concentration and Tetrofosmin index was not calculated in them.

The sensitivity and specificity analysis for brain SPECT was performed considering the clinical behaviour of the disease as the gold standard. The Chi-square test was applied to see the significance of association between the SPECT finding and the clinical course of the disease.

### Result

In this study, brain SPECT in 4 patients revealed increased tracer concentration over the primary tumour bed, which was consistent with recurrent tumour (Figure 1 & Figure 2). The Tetrofosmin retention index was 5.26±1.64. The remaining 17 patients did not reveal any abnormal tracer concentration over the site of primary tumour (Figure 3 & Figure 4).

CECT was consistent with recurrence in 13 of the 21 patients. This included 3 patients with positive SPECT study, but the fourth patient with a positive SPECT study had a normal CT brain. On the other hand CT brain was consistent with post-radiation gliosis in 8 out of the 21 patients.

The clinical course was consistent with tumour recurrence in 13 of the 21 patients, which included 3 patients with positive SPECT study and 10 patients with negative SPECT study (Table 2). One patient with a positive brain SPECT study remained clinically asymptomatic during follow-up and had a normal CT brain constituting a false positive SPECT study.
Figure 1: Transverse slice of CT showing a well-defined cerebellar medulloblastoma

Figure 2: Corresponding slice in SPECT showing intense tracer accumulation

Figure 3: Transaxial section of MRI showing a well-defined brainstem glioma

Figure 4: Corresponding slice in SPECT showing no tracer accumulation

Table 2: Follow-up and pre & post-SPECT therapy details

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Debulking Surgery</th>
<th>Radiotherapy</th>
<th>Chemotherapy before SPECT</th>
<th>Provided Outcome of Clinical follow-up</th>
<th>SPECT Finding</th>
<th>Therapy offered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Performed</td>
<td>60Gy</td>
<td>Not Given</td>
<td>Recurrence</td>
<td>Recurrence</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>2</td>
<td>Performed</td>
<td>60Gy</td>
<td>Not Given</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Phenytoin And steroid</td>
</tr>
<tr>
<td>3</td>
<td>Performed</td>
<td>56Gy</td>
<td>Carboplatin and etoposide</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>4</td>
<td>Performed</td>
<td>60Gy</td>
<td>Not Given</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>5</td>
<td>Performed</td>
<td>60Gy</td>
<td>Not Given</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>Phenytoin And steroid</td>
</tr>
<tr>
<td>6</td>
<td>Performed</td>
<td>60Gy</td>
<td>Carboplatin and etoposide</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>7</td>
<td>Only Biopsy</td>
<td>60Gy</td>
<td>Carboplatin and etoposide</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>8</td>
<td>Performed</td>
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<td>Recurrence</td>
<td>Gliosis</td>
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<tr>
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<td>Gliosis</td>
<td>Recurrence</td>
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<tr>
<td>10</td>
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<td>60Gy</td>
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<td>Gliosis</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>11</td>
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<td>60Gy</td>
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<td>Recurrence</td>
<td>Gliosis</td>
<td>Phenytoin And steroid</td>
</tr>
<tr>
<td>12</td>
<td>Performed</td>
<td>60Gy</td>
<td>Carboplatin and etoposide</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>13</td>
<td>Performed</td>
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<td>Not Given</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>Phenytoin And steroid</td>
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<tr>
<td>14</td>
<td>Only Biopsy</td>
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<td>Carboplatin and etoposide</td>
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<td>Gliosis</td>
<td>PCV regimen</td>
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<td>Carboplatin and etoposide</td>
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<td>Phenytoin</td>
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<td>Recurrence</td>
<td>Gliosis</td>
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<td>Carboplatin and etoposide</td>
<td>Gliosis</td>
<td>Gliosis</td>
<td>Phenytoin And steroid</td>
</tr>
<tr>
<td>18</td>
<td>Performed</td>
<td>60Gy</td>
<td>Carboplatin and etoposide</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>19</td>
<td>Performed</td>
<td>60Gy</td>
<td>Carboplatin and etoposide</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>20</td>
<td>Performed</td>
<td>60Gy</td>
<td>Not Given</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
<tr>
<td>21</td>
<td>Only Biopsy</td>
<td>60Gy</td>
<td>Carboplatin and etoposide</td>
<td>Recurrence</td>
<td>Gliosis</td>
<td>PCV regimen</td>
</tr>
</tbody>
</table>

PCV regimen - Procarbazine, expand and Vincristine regimen
The clinical course was consistent with radiation necrosis in the remaining 8 patients. The Chi-square test did not reveal any significant association between the SPECT findings and the clinical outcome with a P of 1.00.

In the paediatric age group (< 16 years, n= 11), brain SPECT was able to detect 1 of the 7 patients with recurrence of tumour as suggested by the clinical follow-up. It was false positive in one patient and was true negative in 4 patients. Amongst the adult patients (> 16 years, n=10) brain SPECT was able to detect 2 of the 6 patients with recurrence of tumour as suggested by the clinical follow-up. It was not false positive in any patient and was true negative in 3 patients.

The results of brain SPECT as a whole and according to age are compared in Table 3.

**Discussion**

Tetrofosmin was introduced as a myocardial perfusion agent, which can differentiate ischaemic but viable myocardium from scarred myocardium. Initial results suggest that Tetrofosmin concentrates in solid malignancies like thyroidal carcinoma, non-Hodgkin’s lymphoma and hepatocellular carcinoma. This principle was applied to image brain tumours with Tetrofosmin. Various investigators have reported its utility in imaging recurrent brain tumours. However; no study has evaluated posterior fossa tumours exclusively. Usually, there is little or no Tetrofosmin uptake in normal brain tissue. Tetrofosmin shows intense physiological uptake in the choroid plexus of ventricles, extra ocular muscles and temporalis muscle. Therefore Tetrofosmin brain SPECT is not suitable for the evaluation of tumours close to these structures, but otherwise it allows good visualisation of tumour margins.

The main observation of this study is the poor sensitivity (23.07%) of brain SPECT for the detection of tumour recurrence in the posterior fossa in contrast to the high sensitivity of SPECT reported in the case of supratentorial tumours. The sensitivity in the paediatric group was 16.6% whereas it was considerably better in the adult group (28.5%)(Table 5).

The mechanism of Tc99m-Tetrofosmin accumulation has been studied in myocardial cells, and it seems to be dependent on cellular metabolism because mitochondria take up the tracer with a process that is dependent on their membrane potential and their coupling state (i.e. their ability to couple oxidative phosphorilation). In the present study no Tetrofosmin uptake was noted in normal brain tissue, so the breakdown or increased permeability of the blood brain barrier (BBB) seems to be a condition necessary for uptake in the tumour. Nevertheless, it is known that in a tumour cell line, the uptake mechanism, intracellular distribution and washout kinetics of Tetrofosmin are influenced by compounds that interfere with metabolic processes and that the mechanism by which the tracer enters the cells depends upon both the cell membrane (Na+K+ pump) and the mitochondrial potential. Endothelial cells of the BBB express the multidrug resistance 1 gene, the product of which is an adenosine triphosphatase membrane pump extruding a variety of toxins from the cells. Tc99m-Tetrofosmin is one of these substrates. The inhibition of multidrug resistance has been shown to delay the excretion of Tc99m-Tetrofosmin. Without inhibition the pump prevents the tracer from reaching the interstitial space. The choroid plexus tissue, the vasculature of which expresses neither tight junctions nor multidrug resistance 1 gene, accumulates Tc99m-Tetrofosmin, supporting this concept. In this study, 3 patients who showed Tetrofosmin uptake have not received chemotherapy before the SPECT study and in all cases the histological type was medulloblastoma.

Secondly, the posterior fossa of the brain is a compact anatomical space, which provides relatively less space for the tumour to grow without compressing the neuronal structures. Thus a tumour smaller than 1 cm can produce considerable clinical symptoms without being detected on SPECT, as the resolution of brain SPECT is around 1 cm. There are relatively more venous sinuses in relatively less space in the posterior fossa, and frequently these sinuses contain high amounts of retained radioactivity, which sometimes mask an adjacent tumour having equal or less tracer intensity. Lastly, it is possible that when brain SPECT was performed, some lesions may have been gliosis and showed no Tetrofosmin accumulation.

**Table 5: Comparison of results in the paediatric and adult age groups as well as both groups combined**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Brain SPECT (Overall)</th>
<th>Brain SPECT in children (n=11)</th>
<th>Brain SPECT in adults (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>23%</td>
<td>16.6%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Specificity</td>
<td>87%</td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>75%</td>
<td>50.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>41%</td>
<td>44.4%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Percentage of false negative test</td>
<td>77%</td>
<td>83.3%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Percentage of false Positive test</td>
<td>12%</td>
<td>20.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
After SPECT study, during the long follow-up period, the lesion, which was gliosis, may have changed into tumour or tumour recurrence.

One 12-year-old male patient with desmoplastic medulloblastoma had a false positive brain SPECT study. The primary tumour was situated in the cerebellum in the midline, close to the confluence of sinuses. The venous blood of the brain drains out via the confluence of sinuses, which consequently retain high amount of radioactivity inside them. The high amount of retained radioactivity at a small place can induce SPECT reconstruction artifact, which can mimic a tumour mass.

**Conclusion**

Although Tetrofosmin brain SPECT is an excellent modality for diagnosing tumour recurrence at supratentorial locations, this study demonstrates that brain SPECT is not so sensitive in case of posterior fossa tumours. Therefore any negative brain SPECT study in suspected patients of posterior fossa tumour recurrence should be treated with caution and should be correlated with another imaging modality for optimum patient care.

**References**


**Expert Imaging in Brain Tumours**

Malignant gliomas account for 60% of all primary brain tumours and patients with this tumour type have a dismal prognosis; the mean survival is only from 2 to 3 months to 1 year. With the development of aggressive therapeutic trials, an increasing number of patients are presenting after treatment with symptoms and signs that may be secondary to residual or recurrent tumour, or solely due to radiation-induced changes. Results of both CT scan and MRI performed after the cranial irradiation are difficult to interpret because of the inflammation resulting from surgery or radiation therapy and offer only an imperfect definition of tumour viability. Functional imaging with thallium-201 brain SPECT is now known to be useful in determining the presence of recurrent glioma after radiation therapy. For this purpose it has been shown to have an accuracy similar to that of 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission tomography. However, in primary brain tumours, 99mTc-MIBI brain SPECT demonstrated a better specificity than thallium-201 studies, due to the physical properties of 99mTc (140 keV gamma-ray energy, higher photon flux, higher tumour to background ratio).
The authors report here the results of a prospective study, the aim of which was to evaluate the diagnostic utility of $^{99m}$Tc-Tetrofosmin brain SPECT in differentiating recurrence of tumour from post-radiation gliosis in the posterior fossa of the brain. This is the first time that such a nuclear imaging for infratentorial tumours has been done. Sadly, the results of this study were not those we expected. Some comments that need to be made on this study are as follows: acquisition of images was not sufficient (after 1 hour), 4 hours later would have been better, especially when radiation therapy was previously given; the study pools paediatric and adult series, although the results were separated; the histological population was heterogeneous, 14 cases concerned medulloblastomas and ependymomas and in 11 cases, these tumours were located in the cerebello-pontine angle and in the brainstem.

Despite this criticism, such studies should be encouraged. The best histological types and a more suitable population could be selected. Nuclear imaging could, in the future, be a great help for the management of patients with glioma.

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References