Clinical Study

Use of $^{201}$Tl SPECT imaging to assess the response to therapy in patients with high grade gliomas

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Key words: high grade glioma, chemotherapy, $^{201}$Tl SPECT, computed tomography, magnetic resonance imaging

Summary

Purpose. To assess the potential role of $^{201}$Tl single photon emission tomography (201-Thallium SPECT) when compared to other imaging modalities in the evaluation of the response to therapy in high grade gliomas.

Materials and methods. Twenty patients with histologically proved high grade glioma have been included: 15 with glioblastoma (GBM), 3 with anaplastic astrocytoma (AA) and 2 with anaplastic oligoastrocytoma (AOA). Patients were assessed by $^{201}$Tl SPECT, computed tomography (CT) and magnetic resonance imaging (MRI) at (a) either at the moment of maximum response to first line chemotherapy, or after the completion of radiotherapy and chemotherapy if post-surgical residual disease was present, and (b) after the completion of second line chemotherapy if disease persisted, or either a relapse or disease progression was confirmed. Final response was evaluated according to the McDonald criteria, and by comparing SPECT, CT and MRI results.

Results. According to the McDonald criteria, clinical response after first line chemotherapy was 5 partial response, 7 stable disease and 8 progressive disease. Evaluation by $^{201}$Tl SPECT was in agreement with such criteria in nearly all patients (90%). MRI findings closely agreed with the clinical follow-up. CT findings clearly differed from those observed by SPECT and MRI. After second line therapy, 10 patients progressed, 3 had stable disease and 7 had partial response. $^{201}$Tl SPECT agreed with the clinical status in 89% cases, whereas MRI and, specially CT, fared significantly lower.

Conclusion. Compared to conventional neuroimaging, $^{201}$Tl SPECT added valuable information in the assessment of the response to therapy in our patient population; whenever findings were not conclusive and in the case of disagreement between CT and MRI findings.

Introduction

Malignant gliomas of astrocytic origin account for almost half of the primary central nervous system (CNS) malignant tumors [1]. According to the World Health Organisation (WHO) classification, high grade gliomas include grade III anaplastic astrocytoma (AA) and grade IV glioblastoma (GBM) multiforme. Anaplastic forms of oligoastrocytomas and oligodendrogliomas may also be included into grade III [2]. Despite advances in diagnostic techniques and therapy, the prognosis for patients with glioma remains poor.

Multimodality therapy consists of intended maximal surgical resection, radiation therapy and nitrosourea-based combined chemotherapy. Despite aggressive treatment, malignant gliomas almost invariably recur. Therapy for recurrent glioma is similar to that used for the intact tumor (typically re-resection, in approximately 20% of patients, and either procarbazine, cisplatin or nitrosourea-based chemotherapy) [3]. Combination of procarbazine, CCNU and vincristine (PCV) has shown to be effective in patients with recurrent AA or with anaplastic oligodendroglioma [4]. Outstanding among recent advances in chemotherapy is Temozolamide (TMZ), a promising new drug for the treatment of malignant gliomas, and the first available dacarbazine-analogue to be used orally. On the basis of its in vitro activity against glioma cell-lines and good cerebrospinal fluid penetration, TMZ has been shown to produce
objective tumor regression after the first relapse [5,6].

Unfortunately, recurrence is the main problem in the management of patients with glioma. When clinical recurrence is suspected, radiological diagnosis (computed tomography (CT) or magnetic resonance imaging (MRI)) may not be fully reliable for the differential diagnosis between tumor necrosis, scar or actual recurrence [7,8]. In such cases, radionuclide imaging with 201-Thallium single photon emission tomography ($^{201}$Tl SPECT) may be used to separate response to therapy from tumoral growth [9,10].

The unique functional properties of this tracer have prompted its use in clinical oncology, specially in glial tumors [9–12]. Thallium uptake depends on cell membrane ATP-ase pump activity, tumoral vascularization and cell proliferation. Unlike tumor viable cells, reactive glial cells are not accompanied by increased ATP-ase activity [13–14]. Although blood–brain barrier breakdown is the most important mechanism leading to contrast-enhancement in CT scans and MRI, it is much less important for $^{201}$Tl uptake [15].

Here we report on a prospective study which was designed to establish the role of $^{201}$Tl SPECT in the assessment of the response to chemotherapy in patients with high grade gliomas as compared with other imaging modalities (CT and MRI).

**Patients and methods**

Twenty consecutive patients (aged 36–74 years, 17 male) admitted to the neurosurgery department of our hospital with a suspicion of CNS high grade glioma were included in the study. Patients had either undergone surgery with intended total tumor resection ($n=10$) or partial resection ($n=9$), or had been diagnosed by stereotactic biopsy ($n=1$). Final histopathologic diagnosis was: 15 GBM, 3 AA, and 2 anaplastic oligoastrocytoma (AOA). Patients were imaged by CT scan, MRI and SPECT before surgery and within the first five days post-surgery.

Post-operatively, follow-up of the patients was carried out within the setting of a multidisciplinary Neuro-oncology committee. Patients received different chemotherapy regimes: (a) BCNU (carmustine) was used in 11 patients with GBM and without measurable residual post-surgical disease; in 10 of them it was given in association with radiotherapy, (b) BCNU plus CDDP (cisplatin) and radiotherapy was used in one case of GBM with measurable residual disease; both as first line therapy, (c) PCV (procarbazine, CCNU, vincristine) was used in 5 cases (3 AA and 2 AOA) as primary line combined with radiotherapy, and (d) TMZ plus CDDP (cisplatin) was used as primary treatment in 3 GBM cases.

A second line of treatment was required in 17 patients in whom tumor persisted, relapsed or had progressed at the end of first line therapy: (a) TMZ was used in 13 patients with relapse (10 GBM, 3 AA), (b) TMZ combined with CDDP was given to one patient with GBM showing progressive disease after completion of first line with BCNU, and (c) VP16 (etoposide)+ CDDP was used in two patients with AOA who did no show response to a first course with PCV. TMZ was also used in one of such patients with AOA after failure of both first line (PCV) and second line therapy (VP16+ CDDP).

As previously described, 17 patients received 3-D planned external beam radiotherapy (60 Gy) either before or concurrently with chemotherapy.

During the course of adjuvant therapy, patients were reassessed by SPECT, MRI and CT. Interval among techniques was less than two weeks. Assessment was done at the moment of maximal clinical response, which could be either (a) after 3–4 cycles of chemotherapy or completion of radiotherapy, or (b) after chemotherapy if residual post-surgical disease was still present. Similarly, response was evaluated after second line chemotherapy. Patients with partial response to first line therapy were evaluated every three months by SPECT, MRI and CT.

Final response for each branch (summarized in Table 1) was evaluated by (a) the McDonald criteria, which were used as the standard, (b) $^{201}$Tl SPECT and (c) TC and MRI.

**McDonald criteria**

McDonald et al. [16] postulated the response criteria for citotoxic agents in supratentorial malignant gliomas based on clinical status, need of steroid therapy, and radiological findings. Today this system is widely accepted among neuro-oncologists.

The scheme includes four response categories: complete response (CR): disappearance of all enhancing lesion by MRI or CT, off steroids, or neurologically stable or improved. Partial response (PR): evidence of $\geq50\%$ reduction in tumor size (by RMI or CT), steroids stable or reduced, patient neurologically stable.
<table>
<thead>
<tr>
<th>Id</th>
<th>Tumor location</th>
<th>Histology</th>
<th>Surgery</th>
<th>1st line therapy</th>
<th>Response</th>
<th>Response (McDonald) (m)</th>
<th>TTP (months) (m)</th>
<th>2nd line therapy</th>
<th>Response</th>
<th>Final Exitus (m)</th>
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<tbody>
<tr>
<td>1</td>
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<td>GBM</td>
<td>Partial BCNU + RT</td>
<td>SD SD SD SD</td>
<td>SD SD SD SD</td>
<td>P (14 m)</td>
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<td>GBM</td>
<td>Complete BCNU + RT</td>
<td>SD SD SD SD</td>
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<td>P (16 m)</td>
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<td>Partial BCNU + RT</td>
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<td>4</td>
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<td>GBM</td>
<td>AA Biopsy CCDP + RT</td>
<td>SD SD SD SD</td>
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<td>Frontal R</td>
<td>GBM</td>
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<td>Complete GC + RT</td>
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<td>17</td>
<td>Frontal R</td>
<td>GBM</td>
<td>Complete GC + RT</td>
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<td>P (16 m)</td>
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<td>GBM</td>
<td>Complete GC + RT</td>
<td>SD SD SD SD</td>
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<td>P (16 m)</td>
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Notes: (–): non-conclusive (non-specific inflammatory post-treatment reaction); (+): mass effect and increased edema without changes in tumor size; REC: recurrence; CR: complete response; PR: partial response; P: progression; (PR+): significant decrease of thallium uptake in tumor area; TMZ: temozolomide; BCNU: carmustine; CCDP: cisplatin; PCV: CCNU, procarbazine and vincristine; VP16: etoposide; RT: radiotherapy; RN: radionecrosis; L: left; R: right.
or improved. **Progressive disease (PD)**: 25% increase in tumor size or any new tumor, steroids stable or increased, neurologically worse. **Stable disease (SD)**: all other situations.

201⁻TI SPECT

Thallium SPECT imaging [9,14] was performed in every patient. Patients were injected with 4 mCi (148 MBq) 201⁻TI chloride and 2 h later delayed SPECT was acquired using a single-head rotating gamma-camera (GE camstar) equipped with a LEAP (low energy all purpose) collimator; 64 views were obtained for 25 sec each on 64 × 64 word matrix. A 57–80 KeV energy window was selected. Acquired images were reconstructed by filtered backprojection (ramp filter) and a Butterworth filter (0.4 cycles/pixel of cut-off frequency, order 10) without attenuation correction. Transaxial, coronal and sagittal slices were visually inspected on a colour scale display, slice thickness being 6.4 mm.

SPECT images were evaluated by visual analysis. In order to meet correlation with the clinical and radiological findings, consensus criteria for therapy response were as follows: **CR** was suggested if images did not show any abnormal uptake at the tumor area. **PR** was considered if uptake had decreased to at least 50% compared with the baseline study, and **SD** if no changes had been observed. **Tumor progression (P)** was defined if uptake was increased, even if only slightly so (25%), compared with the baseline study.

**Computed Tomography**

Imaging included scans obtained both prior to and after intravenous injection of iodinated contrast material. Axial slices of the pre-contrast scan provided a baseline density for the lesion relative to the normal brain, which was used to determine the degree of contrast enhancement.

CT follow-up examinations were assessed for response, stability or progression taking into account changes in tumor size, extent and degree of contrast enhancement, mass effect and edema. Unfortunately, not every patient could be evaluated for response by CT: 2 patients after the first line and 4 cases after the second line of chemotherapy were not imaged.

**Magnetic Resonance Imaging**

Magnetic resonance imaging studies included spin-echo T1–T2-weighted axial images which were obtained before the intravenous administration of gadolinium-DTPA. Post-contrast T1-weighted axial slices were also performed.

Like with CT, the status of the disease defined by MRI was as overall progression or regression as judged by tumor size and/or degree of gadolinium enhancement, mass effect or surrounding edema.

Four response categories were established here also according to the McDonald criteria, on both CT and MRI studies: **CR**: disappearance of all enhancing lesion. **PR**: evidence of ≥50% reduction in tumor size or enhancing lesion. **PD**: 25% increase in tumor size or any new tumor. **SD**: all other situations. New tumor masses or new hemorrhagic focus, adjoining or at a distance from post-operative cavities were defined as PD on both CT and MRI scans.

The time interval for the CT, MRI and SPECT examinations did not exceed two weeks.

**Results**

**Evaluation after first line chemotherapy**

Response to therapy could be evaluated in all patients (see Table 2). 201⁻TI SPECT agreed with the clinical status in 18 out of 20 assessed patients (90%). Also, MRI findings closely agreed with the clinical follow-up, whereas CT findings clearly differed from the other modalities, as follows: (a) 201⁻TI SPECT correctly

<table>
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<tr>
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<th>SPECT</th>
<th>CT</th>
<th>MRI</th>
<th>McDonald</th>
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<tr>
<td>Progressive disease</td>
<td>8 P</td>
<td>5 P</td>
<td>7 P</td>
<td>8 P</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 SD</td>
<td>5 SD</td>
<td>6 SD</td>
<td>6 SD</td>
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<tr>
<td>Partial response</td>
<td>5 PR</td>
<td>3 PR</td>
<td>3 PR</td>
<td>4 PR</td>
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<tr>
<td>Complete response</td>
<td>1 CR</td>
<td>1 NC</td>
<td>1 PR</td>
<td>1 PR</td>
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<td>Non conclusive</td>
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<td>(n = 20)</td>
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CT: computed tomography; MRI: magnetic resonance imaging; SPECT: Single photon emission tomography; SD: stable disease; PR: partial response; CR: complete response; NC: non-conclusive; P: progression. (*): patient 20 (Figure 2) had partial response by MRI (tumor size decreased more than 50% and a residual nodule persisted). 201⁻TI SPECT showed disappearance of tumor uptake. Symptoms improved and anti-edema therapy was not needed.
identified all patients \((n = 8)\) with progression according to the McDonald criteria (see Figure 1), whereas MRI could only identify seven. In the remaining patient, MRI imaging was non-conclusive because of post-treatment changes (patient 7). As for CT scans, progression was seen in 5 patients, and the result was uncertain in another patient (patient 7). In two cases CT was not performed. (b) Six patients had stable disease, and both \(^{201}\text{TI}\) SPECT and MRI findings agreed with the McDonald criteria. Five patients were classified as stable disease by CT scan, and one patient was thought to have partial response (patient 6). (c) Five patients had partial response as judged by \(^{201}\text{TI}\) SPECT. In four such patients the McDonald criteria established a partial response. Stable disease was found in the remaining case. MRI and CT findings showed partial response in 3 of the patients, and stable disease in one patient, respectively. In one case, both MRI and CT were non conclusive for partial response (patient 8). (d) A complete response was defined by \(^{201}\text{TI}\) SPECT even though it was considered as partial response by clinical criteria an MRI (patient 20, Figure 2). In this patient tumor size had decreased more than 50% although persisted as a residual nodule. CT scan could not determine the degree of response. Thallium uptake had totally disappeared.

**Findings at the completion of second line chemotherapy**

Second line chemotherapy was given to 16 patients (see Table 3): 15 with progression due to relapse or progressive residual disease (11 GBM, 2 AA, 2 oligoAA) and one patient with stable disease (1 AA). One patient received radiotherapy at progression. Mean time to progression was 7.5 months (range 3–18 months).

Temozolamide was used in 14 patients: 12 with progression, one with stable disease, and one case of AOA after failure of CDDP + VP16. Temozolamide in association with CDDP was proposed in another case of GBM with progression.

Follow-up evaluation was available for 15 patients after completion of chemotherapy (18 studies). While writing the manuscript, one patient was still in the course of therapy. After second line therapy, \(^{201}\text{TI}\) SPECT agreed with clinical status in 89% cases (16 out of 18 evaluated studies).

Three patients did not receive second line therapy: two of them had partial response after first line therapy, and the remaining patient died 3 months after surgery. A clinical status of partial response was maintained in these two patients (patients 5 and 8) for a long time (13 and 12 months respectively).

If all follow-up studies are considered, overall agreement between \(^{201}\text{TI}\) SPECT and McDonald criteria was 90% (19/21 studies). MRI and, specially, CT differed significantly from \(^{201}\text{TI}\) SPECT findings, as follows: (a) eight patients had clinical symptoms of progression and were consistent with \(^{201}\text{TI}\) SPECT images. Radiological imaging was discordant as follows. One of the patients had confusing CT and MRI findings and a differential diagnosis between progression versus radionecrosis could not be established (patient 15 after CDDP + VP16 therapy). A partial response was observed by CT in one patient with clinical progression. In two patients, CT and MRI showed radiological signs of progression, such as increased edema and mass effect. These two patients, with tumor stability by \(^{201}\text{TI}\) SPECT improved significantly after steroid therapy (patients 2 and 6). (b) \(^{201}\text{TI}\) SPECT images did not change from the previous study in two patients, who were considered as having stable disease. These two patients kept clinically stable and one of them did not show changes in MRI. The remaining patient initially had neurological worsening caused by increased edema around a tumor which did not increase in size. Patient improved after steroid therapy (patient 14). Unfortunately, CT scan was performed in only one patient and revealed stable disease. (c) Partial response with faint to moderate decreased thallium uptake in the tumor

### Table 3. \(^{201}\text{TI}\) SPECT compared to TC and/or MRI during follow-up in second line therapy

<table>
<thead>
<tr>
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<th>SPECT</th>
<th>CT</th>
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<th>McDonald</th>
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<tr>
<td>Progressive disease</td>
<td>8 P</td>
<td>5 P</td>
<td>6 P</td>
<td>8 P</td>
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<td>(–)</td>
<td>1 P*</td>
<td>1 P</td>
<td>1 P</td>
<td>1 P*</td>
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<tr>
<td>Partial response</td>
<td>7 PR</td>
<td>3 PR</td>
<td>5 PR</td>
<td>7 PR</td>
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<td>(–)</td>
<td>1 PR+</td>
<td>2 P*</td>
<td>3 P*</td>
<td>21 P*</td>
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<td>Complete response</td>
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<td>Non-conclusive</td>
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<td>((n = 18))</td>
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<td>16</td>
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Refer footnote of Table 2 for explanation of symbols; (*) patients with increased perilesional edema without tumor size changes. (PR+) significant decrease of thallium uptake in tumor area.
area was seen in 8 patients. In one such patient, partial response was significant by SPECT (PR+: patient 4, AA). Clinically, seven of them had partial response to chemotherapy, and the remaining one showed apparent progression, due to increased edema and mass effect without changes in tumor size. MRI imaging showed partial response in five patients, and revealed apparent progression in three. CT correctly classified three patients with partial response, while another patient with partial response was deemed to have stable disease. CT could not be performed in two cases. (d) Complete response was not observed in any case. (e) There were no cases of non-conclusive examination.

**Discussion**

In patients with brain tumors, a diagnosis of recurrence is usually reached by CT and MRI. However, with these morphologic imaging techniques it is often difficult to differentiate histologically active tumoral growth from post-treatment changes, which have similar degree of contrast-enhancement and anatomical
appearance [14]. Radiation necrosis is known to mimic tumor recurrence [17]. Therefore, findings of CT or MRI are not always conclusive. In such cases SPECT with $^{201}$TI may provide useful information. Thallium is taken up by neoplastic glial cells [9–12]. Uptake is not only dependent on the breakdown of blood–brain barrier, as is the case with contrast agents, but is also related to cell growth.

Knowledge of specific structural changes as revealed by CT and MRI is necessary for surgical planning and other therapeutic decision-making [18–20]. Furthermore, neuroimaging evaluation during
treatment is needed to identify the cause of clinical worsening such as true tumor progression, development of hydrocephalus or other causes of mass effect. However, conventional imaging methods do not always allow for a distinction between tumor progression and side effects such as inflammatory or glial reaction, or radionecrosis [20]. In this context, it has been suggested that $^{201}$TI SPECT may be clinically useful and reliable for the differential diagnosis between viable tumor and necrotic tissue or post-surgical changes [18,19]. Moreover, $^{201}$TI SPECT results are comparable to PET (position emission tomography) [21,22], but PET is not widely available.

In our study, the final response to therapy was evaluated according to the McDonald criteria [16], which are based both on clinical and radiological findings. Worsening of the clinical status in many of these patients limit the availability of histological confirmation.

A comparison of radiological and nuclear medicine diagnostic modalities for the assessment of the response to therapy in patients with high grade gliomas has not been widely reported. Specifically, the use of $^{201}$TI SPECT has seldom been reported to our knowledge for the evaluation of therapy in high grade gliomas [20,25]. Roesdi et al. [25] studied ten patients using $^{201}$TI SPECT findings as a response parameter for PCV chemotherapy in recurrent glioma. Källen et al. [20] published a preliminary study comparing $^{201}$TI SPECT, MRI and MR spectroscopy during astrocytoma chemotherapy. Also, $^{201}$TI SPECT was shown to be useful for the diagnosis of suspected astrocytoma recurrence [10,28–30] and to differentiate radiation necrosis from tumor regrowth [31].

Contrary to the opinion of Källen et al. [27], we support the use of $^{201}$TSPECT during the course of therapy to help establish the degree of response, in accordance with MRI and clinical status in most cases, especially when MRI is non conclusive (patient 7). In our experience, $^{201}$TI SPECT changes are in agreement with MRI results, both in cases of regression (partial or complete) or progression. In addition, our data suggest that treatment induces thallium tumor uptake variations that may precede anatomic changes on MRI. Sometimes, neuroimaging studies may not be conclusive because of post-surgery or post-treatment changes in brain tissue. In any case, for those patients with suspected recurrent glioma after therapy, $^{201}$TI SPECT detected tumoral growth better than TC or even MRI.

At the time of recurrence, all our patients showed increased $^{201}$TI uptake in the surgical area as a undeniable sign of tumoral growth, while this could not be established in three patients on CT and in two patients on MRI. In two patients, $^{201}$TI SPECT showed partial response while on clinical progression. However, such patients improved after anti-edema therapy. Edema may cause neurological deterioration that leads to an underestimation of the response by the McDonald criteria. Steroids used in these patients as an anti-edema treatment do not modify thallium uptake, although their influence on MRI findings is well known [32]. Also, it is important to underline that some patients, even with partially controlled tumor findings (by SPECT) may develop progressive brain damage at the end stage of their disease due to demyelination (as observed by RMI and CT). In such patients, it is likely that polytherapy lengthens survival at the expense of progressive cognitive and neurological worsening that may mimic progression.

Temozolamide, which seems prolong survival in high grade glioma patients when other therapy modalities have failed, has not been assessed by $^{201}$TI SPECT. In our limited number of patients, temozolomide showed promising results.

Our preliminary study is limited by the few number of patients, and by the fact that not all patients were evaluated simultaneously by CT along with SPECT and MRI. For the purpose of glioma treatment evaluation, MRI offers higher sensitivity and specificity than CT, and nowadays MRI is the key follow-up examination. Nevertheless, both CT and MRI, have limitations that leave an important role for $^{201}$TI SPECT.

We conclude that thallium SPECT adds valuable information in the evaluation of the response to therapy in high grade gliomas, specially compared to CT scan, in cases where it is not fully reliable or in the case of disagreement with MRI. Intensity of response according to $^{201}$TI SPECT correlates with the clinical follow-up and the McDonald criteria. We believe that $^{201}$TI SPECT is useful because it provides an estimation of the outcome after therapy in these patients. Nevertheless, a large number of patients will be necessary to strengthen these statements. The study continues.

References


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