Thallium-201 SPECT: the optimal prediction of response in glioma therapy

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Abstract. *Purpose:* The aim of this study was to estimate ^{201}Tl SPECT and CT-MRI cut-off values that lead to a validated prognostic classification for the end-point overall survival, in order to discriminate glioma patients with good and poor prognosis at an early stage during chemotherapeutic treatment.
Methods: We studied patients who underwent ^{201}Tl SPECT and CT-MRI before and after two courses of chemotherapy. Cut-off values were retrieved from the Cox model. Patients were classified according to the computed cut-off values, creating subgroups of patients with different prognosis in terms of survival [tumour regression (TR); stable disease (SD); tumour progression (TP)]. The differences between the subgroups were assessed by Kaplan-Meier analyses. The predictive performance of the classification procedure was evaluated by a leave-one-out cross-validation method.
Results: ^{201}Tl SPECT classified 41% of the patients as SD, 25% as TR and 34% as TP. CT-MRI classified 82% of the patients as SD, and only 4% and 14% as TR and TP, respectively. Of those patients with a relatively long overall survival (i.e. ≥16 months), cross-validation estimates of ^{201}Tl SPECT classification rates were 50% TR and 50% SD, and cross-validation estimates of CT-MRI classification rates were 7% TR, 72% SD, and 21% TP.
Conclusion: We constructed a ^{201}Tl SPECT model that makes it possible to identify glioma patients with a good or a poor prognosis at an early stage during chemotherapeutic treatment. With this model, accurate predictions can be made with regard to the expected duration of survival.

Keywords: Brain SPECT – Chemo-radiotherapy – Gliomas – Prognosis

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Introduction

Standard treatment of patients with newly diagnosed malignant glioma consists of surgery [1–3] and radiotherapy [4, 5], with or without adjuvant chemotherapy [6–8]. Despite multimodality treatment, malignant gliomas recur almost invariably, with a poor prognosis and few long-term survivors. Up to now, therapeutic options for patients with recurrent glioma have been limited. Second surgery, re-irradiation, chemotherapy, immune therapy and gene therapy are possible treatment modalities in case of tumour recurrence. Chemotherapy may be effective, particularly in tumours of oligodendroglial origin [9, 10], although response percentages are not high in recurrent malignant astrocytoma [11]. With limited response rates and potential toxicity of chemotherapeutic treatment, reliable and early response assessment is essential.

In 1990, Macdonald et al. [12] introduced the currently used imaging-based criteria for response assessment in clinical trials of supratentorial malignant glioma. These criteria were derived from those used in general oncology, based on major changes in tumour size on enhanced computed tomography (CT) or magnetic resonance imaging (MRI), in combination with steroid use and neurological findings. However, over time, it has become apparent that the Macdonald criteria have certain shortcomings [13]. They are not applicable to all clinical situations in which brain tumour response needs to be assessed. Moreover, quantitative evaluation of treatment response with CT or MRI is not without limitations [14–21], and has been proven to be susceptible to considerable inter-observer variability [22]. Functional brain imaging techniques, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET), are claimed to be more specific than structural imaging methods, such as CT and MRI, in the follow-up of glioma patients. During the

last decade, thallium-201 (^{201}Tl) SPECT has been used to differentiate tumour recurrence from radiation necrosis [23–27], and more recently, its role in the evaluation of glioma treatment response during chemotherapy has been explored [28–32].

In view of the limitations of structural brain imaging techniques and the growing interest in functional brain imaging techniques, we recently established the value of ^{201}Tl SPECT as a predictor of overall survival (OS) and response to chemotherapy in patients with recurrent glioma, as compared with that of conventional CT and MRI [28]. In that study, response classification on CT-MRI was derived from the criteria developed by Macdonald et al. [12], differentiating patients with tumour regression (TR) (≥50% reduction in tumour size), tumour progression (TP) (≥25% increase in tumour size), and stable disease (SD) (all other situations). As there are no comparable, generally accepted criteria for the classification of glioma treatment response on ^{201}Tl SPECT, ^{201}Tl SPECT response classification was also based on the −50/+25% criteria as constructed for CT-MRI. That study demonstrated that ^{201}Tl SPECT was superior to CT and MRI as an early predictor of OS and response to chemotherapy in patients with recurrent glioma. Especially maximal tumour intensity on ^{201}Tl SPECT appeared to be a powerful predictor of outcome, both at baseline and after two courses of chemotherapy.

The aim of the present study was to estimate ^{201}Tl SPECT cut-off values that lead to a validated prognostic classification for the end-point OS, in order to discriminate patients with a good and those with a poor prognosis at an early stage during treatment. To evaluate the validity of the Macdonald criteria for the prediction of OS, CT-MRI cut-off values were computed as well.

Materials and methods

Patients

Patients treated with paclitaxel or the combination of procarbazine, CCNU and vincristine (PCV) chemotherapy for recurrent glioma were identified in the brain tumour database of the VU University Medical Centre (Amsterdam, the Netherlands). Patients who had undergone adequate ^{201}Tl SPECT and CT or MRI (before and after contrast material administration) before and after two courses of chemotherapy were included. This applied to the same patients as described in (the follow-up analysis of) our previous study [28].

Imaging

SPECT was started 30 min after intravenous injection of 150 MBq ^{201}Tl-chloride, using a dual-head gamma camera (Genesys, ADAC, Milpitas CA). Projection data were acquired with a 64×64 matrix, 60 s per projection, collecting 64 projections. Images were reconstructed with a Hanning filter (cut-off frequency 0.56 cycles/cm), without attenuation correction. All CT scans were performed using a standard protocol including 3–5 mm slices for the posterior fossa and 8–10 mm slices for the remainder of the brain, before and after contrast material administration. All MRI scans were performed using a standard protocol including transverse T2-weighted images and T1-weighted images, before and after contrast material administration.

^{201}Tl SPECT scans were evaluated by one nuclear medicine physician, whereas CT and MRI scans were evaluated by one neuroradiologist; both were unaware of the patient's outcome and of the alternative imaging test results. ^{201}Tl SPECT analysis comprised measurement of the maximal tumour intensity at baseline (before chemotherapy) and at follow-up (after two courses of chemotherapy). Maximal tumour intensity was defined as the ratio of the mean tumour counts in the axial slice with the maximal tumour activity to the mean activity in the contralateral supratentorial hemisphere. Each baseline and follow-up CT and MRI scan was evaluated on the basis of the image slice on which the lesion showed the largest diameter, and tumour size was measured on this slice. Tumour size was defined as the product of the two largest perpendicular transverse enhancing tumour diameters on the post-contrast images. The diameters were measured on the hard copies, by reference to the centimetre scale printed on the film. The percentage change in maximal tumour intensity on ^{201}Tl SPECT, and in tumour size on CT-MRI, was calculated by dividing follow-up data by baseline data for every individual patient. With respect to the calculation of the change in ^{201}Tl SPECT maximal tumour intensity, a correction was made for the partial non-tumour-related change in intensity. As maximal tumour intensity is defined as the ratio of the mean tumour counts in the axial slice with the maximal tumour intensity to the mean activity in the contralateral supratentorial hemisphere, the maximal intensity of normal brain tissue is 1. In order to calculate only the tumour-related change in intensity, we subtracted 1 from all baseline and follow-up maximal tumour intensity data.

Statistical analysis

To compute ^{201}Tl SPECT and CT-MRI cut-off values for the prediction of OS, we performed Cox regression analyses in which OS was predicted by baseline ^{201}Tl SPECT maximal tumour intensity or CT-MRI tumour size and the percentage change after two courses of chemotherapy. Overall survival was defined as the interval (in months) from start of chemotherapy to death. Because of the proven impact of histology on prognosis in glioma [33], the prognostic value of histology was examined in additional regression analyses. Therefore, tumour histology was dichotomised [glioblastoma multiforme (GBM) versus non-GBM]. The cut-off values were subsequently determined by setting the Cox model chance of surviving 10 months (i.e. the median OS of the included patients) equal to $(50-Y)$% and $(50+Y)$%. The value of Y was chosen such that the differences in OS between the response groups, as measured by the log-rank statistic, were maximised, both for ^{201}Tl SPECT and for CT-MRI. Patients demonstrating a chance of at least $(50+Y)$% to survive 10 months were classified as "good prognosis patients"; in other words, these patients were predicted to demonstrate TR. Those with a chance of at most $(50-Y)$% to survive 10 months were classified as "poor prognosis patients"; these patients were predicted to demonstrate TP. Those with a chance over $(50-Y)$% and less than $(50+Y)$% to survive 10 months were classified as "intermediate prognosis patients"; these patients were predicted to demonstrate SD.

Thereafter, we classified our patients according to the computed cut-off values, creating subgroups of patients with different survival prognoses (TR; SD; TP). The differences between the three subgroups of patients with regard to OS were assessed by Kaplan-Meier analyses. The predictive performance of the classification procedure was assessed by a leave-one-out cross-validation method. Instead of using an external data set, prediction was mimicked by removing one patient from the data set, determining cut-off values on the basis of all other patients, and providing a prognosis for the removed patient. This prognosis was compared with the observed OS of the patient.

Results

Patient characteristics

From January 1994 to April 2001, 67 patients had been treated with PCV (procarbazine, CCNU, vincristine) or paclitaxel for recurrent glioma in the VU University Medical Centre. Forty-four of these 67 patients were included in the current study. Patient characteristics are shown in Table 1. Primary tumour histologies included GBM (n=27), anaplastic astrocytoma (n=7), (anaplastic) oligodendroglioma (n=9) and oligo-astrocytoma (n=1); altogether, there were 27 GBMs versus 17 non-GBMs. All patients had previously undergone cranial surgery and radiation therapy. Thirty-two patients had been treated with PCV, and 12 with paclitaxel. The median OS was 10 months (range 3–47 months).

Computation of cut-off values

Cox regression analyses (results not tabulated) demonstrated that ^{201}Tl SPECT maximal tumour intensity, and particularly the percentage change after two courses of chemotherapy (baseline P=0.01; change P<0.01), was strongly related to OS. Tumour size on CT-MRI (baseline P=0.05; change P=0.01) had an effect on OS as well. We found no significant association between histology and survival in addition to ^{201}Tl SPECT maximal tumour intensity (P=0.20) or CT-MRI tumour size (P=0.07). Therefore, we decided to construct cut-off values that were not adjusted for histology. The cut-off values for ^{201}Tl SPECT and CT-MRI are graphically displayed in Fig. 1. As can be read from Fig. 1, prognosis depended on both baseline and follow-up data, as for a certain change in ^{201}Tl SPECT maximal tumour intensity or CT-MRI tumour size, prognosis was better if the baseline maximal tumour intensity was lower, or its size smaller (and vice versa). For TP, the chance of surviving 10 months was equal to or less than 33%, and for TR, the chance of surviving 10 months was at least 67%. The patients classified as SD had an intermediate prognosis. The chances 33% and 67% led to maximum differences in OS between the response groups as measured by the log-rank statistic, both for ^{201}Tl SPECT and for CT-MRI. An important difference between Fig. 1a and Fig. 1b is that the vertical distance between the lines in Fig. 1b is much larger. This suggests a less powerful performance of CT-MRI in separating patients with regard to OS in comparison with ^{201}Tl SPECT.

The results of the Kaplan-Meier analyses are demonstrated in Fig. 2, and indicate that both ^{201}Tl SPECT (P<0.01; Fig. 2a) and CT-MRI (P<0.01; Fig. 2b) could distinguish all three subgroups of patients (TR, SD, TP),

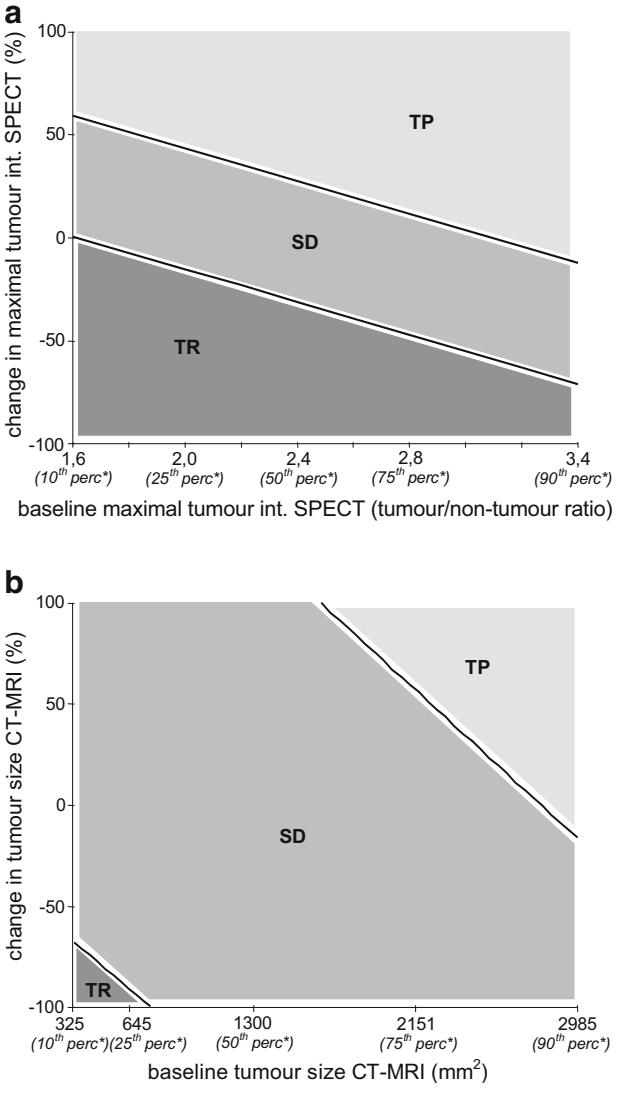


Fig. 1. Cut-off values for the prediction of OS. *TR* tumour regression, defined as ≥67% chance of surviving 10 months; *SD* stable disease, defined as >33% and <67% chance of surviving 10 months; *TP* tumour progression, defined as ≤33% chance of surviving 10 months. *Applies to the 10th, 25th, 50th, 75th and 90th percentiles of all baseline measurements. **a** ^{201}Tl SPECT; **b** CT-MRI

Table 1. Patient characteristics

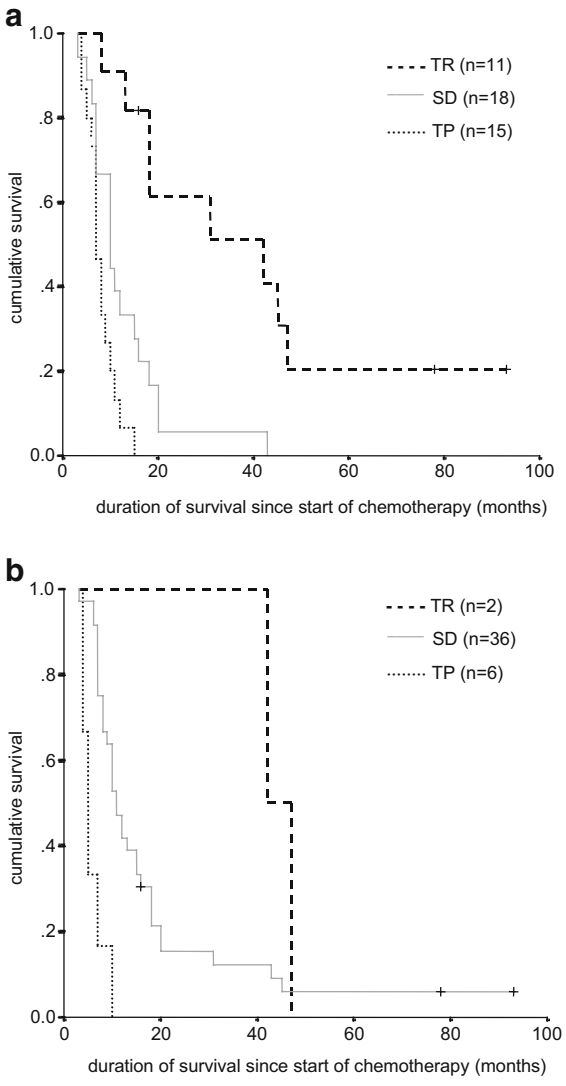
Characteristic	No. of patients or value
Male/female	31/13
Median age (years)	46.9 (25–68)
Median KPS [a]	80 (60–100)
(Initial) operation: resection/biopsy	40/4
(Initial) mean radiotherapy dose (Gy)	51.1 (28–66)
Tumour histology: GBM/non-GBM	27/17
Chemotherapy: paclitaxel/PCV	12/32
Scan type: CT/MRI	26/18
Median OS [b] (months)	10.0 (3–47)

Values in parentheses are ranges

KPS Karnofsky performance score, *GBM* glioblastoma multiforme, *PCV* procarbazine, CCNU, vincristine, *OS* overall survival

[a]At the time of tumour recurrence

[b]From the start of chemotherapy



◀ **Fig. 2.** Kaplan-Meier survival curves, constructed according to the computed cut-off values. **a** ^{201}Tl SPECT (log-rank test: $P<0.01$). **b** CT-MRI (log-rank test: $P<0.01$)

who differed significantly with regard to OS. The median OS in the TR, SD and TP groups was 31, 10 and 7 months with ^{201}Tl SPECT, and 45, 11 and 5 months with CT-MRI, respectively.

The predicted numbers of patients with TR, SD and TP are presented in Table 2. ^{201}Tl SPECT classified 25% of the patients as TR and 34% as TP, whereas CT-MRI classified the vast majority (82%) of patients as SD, and only 4% and 14% as TR and TP, respectively. Using cross-validation methodology, ^{201}Tl SPECT classified 50% (7/14) of the patients with OS ≥16 months as TR (chance of surviving 10 months ≥67%) , and the remaining 50% (7/14) as SD. From the patients with OS ≤7 months, ^{201}Tl SPECT classified 57% (8/14) as TP (chance of surviving 10 months ≤33%), and the remaining 43% (6/14) as SD. CT-MRI classified only 7% (1/14) of the patients with OS ≥16 months as TR, and only 21% (3/14) of the patients with OS ≤7 months as TP. Moreover, 21% (3/14) of the patients with OS ≥16 months were wrongly classified as TP with CT-MRI.

Discussion

In the current study, we estimated cut-off values that lead to a validated prognostic classification for the end-point OS, both for ^{201}Tl SPECT and for CT-MRI, in a subgroup of patients treated with chemotherapy for recurrent glioma in our hospital. Kaplan-Meier survival curves, constructed by the classification of patients according to the computed cut-off values, indicated that both ^{201}Tl SPECT and CT-MRI were able to distinguish subgroups of patients that differed

Table 2. Predicted number of patients with TR, SD and TP, and corresponding OS

Statistical procedure		Predicted no. of patients (%)					
		^{201} Tl SPECT maximal tumour intensity			CT-MRI tumour size		
		TR	SD	TP	TR	SD	TP
Without cross-validation	OS[a] ≤7	0	6	8	0	9	5
	OS[a] 8–15	2	7	7	0	15	1
	OS[a] ≥16	9	5	0	2	12	0
	Total	11 (25)	18 (41)	15 (34)	2 (4)	36 (82)	6 (14)
With cross-validation[b]	OS[a] ≤7	0	6	8	0	11	3
	OS[a] 8–15	2	6	8	0	14	2
	OS[a] ≥16	7	7	0	1	10	3
	Total	9 (20)	19 (43)	16 (36)	1 (2)	35 (80)	8 (18)

OS overall survival (in months), *TR* tumour regression, *SD* stable disease, *TP* tumour progression

[a] Patients were classified in three tertile groups based on their OS: 33% had an OS of ≤7 months, 33% an OS of 8–15 months and 33% an OS of ≥16 months

[b] Prediction of response was mimicked by removing one patient from the data set, determining cut-off values on the basis of all other patients, and providing a prognosis for the removed patient. Cross-validation was carried out for each patient separately

significantly with regard to OS. With respect to CT-MRI, the current model differentiates the subgroups of patients more strongly with regard to OS than the classification used in our previous study [28]. However, as the vast majority (82%) of patients were now classified as SD, this model appears to be of limited value. The model constructed for ^{201}Tl SPECT, on the other hand, classified a substantial percentage (59%) of patients as TR or TP, and thus appears to be useful in the identification of both good and poor prognosis patients. With respect to patients with a relatively long survival time of at least 16 months, results were even more pronounced after cross-validation. ^{201}Tl SPECT classified 50% of these patients as TR and 50% as SD, whereas CT-MRI classified only 7% of these patients as TR, and 21% wrongly as TP.

A limitation of our study is the small number of patients included. Nevertheless, the sample size was large enough to validate the predictions by cross-validation. A more elaborate approach to validate the current ^{201}Tl SPECT model would be to use an external data set. A source of concern in this respect is the heterogeneity of the ^{201}Tl SPECT literature regarding the quantitative methodology of the various measurement techniques: different methods are being used to define tumour as well as reference tissue activity. In a previous study, however, we provided ^{201}Tl SPECT nomograms, which can be used to convert results of different ^{201}Tl SPECT data sets [34].

In conclusion, we constructed a ^{201}Tl SPECT model that makes it possible to identify patients with a good or a poor prognosis at an early stage during chemotherapeutic treatment for recurrent glioma. With this model, on the basis of two ^{201}Tl SPECT scans, accurate predictions can be made with regard to the expected duration of survival. Such information offers the treating physician the possibility to select responding patients for further treatment, and to avoid ineffective, potentially toxic treatment in non-responding patients. After further refinement of the current ^{201}Tl SPECT model, it would also be interesting to evaluate its utility in the evaluation of response to new brain tumour therapies.

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