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MRI and thallium-201 SPECT in the prediction of survival in glioma

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Abstract
Introduction This paper aims to study the value of MRI and Thallium 201 (^{201}Tl) single-photon emission computed tomography (SPECT) in the prediction of overall survival (OS) in glioma patients treated with temozolomide (TMZ) and to evaluate timing of radiological follow-up.
Methods We included patients treated with TMZ chemo-radiotherapy for newly diagnosed glioblastoma multiforme (GBM) and with TMZ for recurrent glioma. MRIs and ^{201}Tl SPECTs were obtained at regular intervals. The value of both imaging modalities in predicting OS was examined using Cox regression analyses.
Results Altogether, 138 MRIs and 113 ^{201}Tl SPECTs in 46 patients were performed. Both imaging modalities were strongly related to OS ($P \leq 0.02$). In newly diagnosed GBM patients, the last follow-up MRI (i.e., after six adjuvant TMZ courses) and SPECT (i.e., after three adjuvant TMZ courses) were the strongest predictors of OS ($P=0.01$). In recurrent glioma patients, baseline measurements appeared to be the most predictive of OS ($P<0.01$). The addition of one imaging modality to the other did not contribute to the prediction of OS.
Conclusions Both MRI and ^{201}Tl SPECT are valuable in the prediction of OS. It is adequate to restrict to one of both modalities in the radiological follow-up during treatment. In the primary GBM setting, MRI after six adjuvant TMZ courses contributes significantly to the prediction of survival. In the recurrent glioma setting, baseline MRI appears to be a powerful predictor of survival, whereas follow-up MRIs during TMZ seem to be of little additional value.

Keywords MRI · Thallium-201 SPECT · Glioma · Temozolomide · Overall survival

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Introduction

In glioma patients, follow-up during and after treatment is usually performed with clinical and imaging assessments, and therapeutic efficacy is evaluated with standard criteria for response and progression. In 1990, Macdonald et al. recommended criteria for response assessment in high-grade glioma, based on two-dimensional measurement of CT or MRI contrast-enhancing tumor area while considering the use of corticosteroids and changes in neurologic functioning [1]. These criteria enabled the comparison of response rates between high-grade glioma clinical trials and have been widely used since their introduction. However, it is increasingly apparent that the Macdonald criteria have a number of limitations, such as difficulties in measuring nonenhancing or multifocal tumors and interobserver variability [2]. Furthermore, contrast enhancement in itself is not tumor specific and may be influenced by changes in corticosteroid doses [3, 4], postsurgical changes, ischemia, and seizure activity. Changes in contrast enhancement can also represent post-radiotherapy abnormalities [5–9], and pseudoprogression or pseudoresponse [10–16]. Recently, a proposal for updated response criteria in high-grade glioma was outlined by the RANO Working Group, including serial MRI evaluation of tumor contrast enhancement as well as the nonenhancing (T2/FLAIR) component [17].

Other brain imaging techniques, like single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are supposed to be more tumor specific than conventional MRI techniques. Thallium 201 (^{201}Tl) SPECT is useful in the differentiation of tumor recurrence and radiation necrosis [18–21] and in the evaluation of glioma treatment response [22–26].

Nonetheless, the relation between radiological abnormalities and patient survival is not always clear, and one might argue what the benefit is of stringent imaging follow-up in glioma patients. For example, recent anti-angiogenic studies with bevacizumab in combination with irinotecan demonstrated an increased tumor response on (conventional) MRI in patients with high tumor vascular endothelial growth factor expression, which was not associated with survival benefit, thus not reflecting true tumor response (pseudoresponse) [13, 14, 16].

The aim of the current analysis was to study the value of MRI and ^{201}Tl SPECT in the prediction of overall survival in glioma patients treated with TMZ. Furthermore, the prognostic value of multiple, sequential imaging assessments was evaluated, in order to optimize timing of radiological follow-up during treatment.

Methods

Patients

Two studies (study A and B) were performed in this prospective trial, which was approved by the local medical ethics committee. Patients were asked to participate by their treating physician and informed consent was obtained.

In *study A*, we included patients treated with radiotherapy in combination with concomitant and six cycles adjuvant TMZ for newly diagnosed GBM. The treatment evaluation of these patients consisted of MRI and ^{201}Tl SPECT postoperatively, i.e., prior to the concomitant phase (baseline), and prior to the adjuvant phase. Thereafter, additional MRI was performed after three and six courses and ^{201}Tl SPECT after three adjuvant TMZ courses (flowchart interventions imaging, see Table 1).

Study B, comprised patients treated with TMZ for recurrent glioma. The treatment evaluation of these patients consisted of MRI and ^{201}Tl SPECT prior to chemotherapy (baseline), and additional MRI after three, six, and nine courses, and ^{201}Tl SPECT after three and nine TMZ courses (Table 1).

The difference in scanning frequency between MRI and ^{201}Tl SPECT was related to the applied ^{201}Tl SPECT radiation dose.

Table 1 Flowchart interventions imaging

		BL	TP2	TP3	TP4
Study A	Time[a]	0	2	5	8
	Timing	Prior to concomitant phase	Prior to adjuvant phase	After 3 adjuvant TMZ courses	After 6 adjuvant TMZ courses
	Imaging	MRI + SPECT	MRI + SPECT	MRI + SPECT	MRI
Study B	Time[a]	0	3	6	9
	Timing	Prior to TMZ	After 3 TMZ courses	After 6 TMZ courses	After 9 TMZ courses
	Imaging	MRI + SPECT	MRI + SPECT	MRI	MRI + SPECT

BL baseline, *TP (2-3-4)* time-point (2-3-4), *TMZ* temozolomide

[a] In months from baseline

Imaging

MRI scans were performed on a 1.5-T MRI scanner (Siemens Sonata, Siemens Medical Systems, Erlangen, Germany). Imaging protocol included axial T2- and T1-weighted spin-echo images before and after gadolinium administration. Tumor size was defined as the product of the two largest perpendicular transverse enhancing tumor diameters measured on a post-contrast T1-weighted image.

SPECT was started 30 min after intravenous injection of 150 MBq ^{201}Tl-chloride, using a dual-head gamma camera (ECAM, Siemens, Chicago, IL). Projection data were acquired with a 64×64 matrix, 60 s per projection. Images were reconstructed with a Hanning filter (cut-off frequency, 0.56 cycles/cm), without attenuation correction. Previously validated maximal tumor intensity was defined as the ratio of the mean tumor counts in the axial slice with the maximal tumor activity and the mean activity in the contralateral supratentorial cerebral hemisphere, and expressed as tumor–nontumor ratio (TNT) (Fig. 1) [25, 27]. Based on this definition, the maximal intensity of normal brain tissue is one, and accordingly, in case no tumor activity is detected by ^{201}Tl SPECT, TNT is one.

Analysis

Both MRIs and ^{201}Tl SPECTs were evaluated prospectively, by one examiner (MJV and OSH, respectively) who was blinded to the alternative method and clinical outcome. In the analyses, absolute tumor measurements (MRI tumor size and ^{201}Tl SPECT maximal tumor intensity) as well as relative changes in tumor measurement were used.

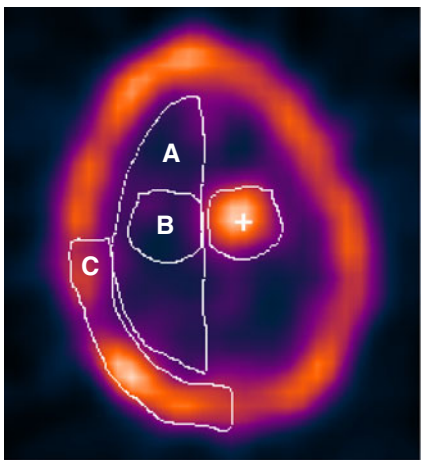

Fig. 1 Manual region of interest (ROI) definition technique: focally enhanced uptake in a left-sided glioma, showing the axial slice with the maximal tumor uptake. Typical manually drawn ROI displayed around the tumor (*plus sign*), the contralateral hemisphere (*A*), its contralateral mirror (*B*) and the scalp (*C*)

Age, tumor histology, and Karnofsky performance score (KPS) were included as clinical variables, of which the latter was obtained repeatedly at the different follow-up time-points. Overall survival (OS) was used as outcome variable, and defined as the interval from baseline imaging to death.

Statistical analysis

The value of MRI and ^{201}Tl SPECT, in combination with clinical variables, in predicting OS was examined by Cox regression analysis with time-dependent covariates. This type of analysis is a variant of the common Cox regression analysis where the value of covariate MRI or ^{201}Tl SPECT is updated when a new imaging result becomes available [28]. The effects of the regression coefficients were evaluated using a Wald test (two-tailed test, $P<0.05$). We examined the effects of MRI tumor size and ^{201}Tl SPECT maximal tumor intensity on OS separately, and in combination with each of the clinical variables. In these analyses, all MRI and ^{201}Tl SPECT scans were used. In case one of both was missing, the preceding scan result was carried forward (analysis I). We also calculated cut-off values for MRI tumor size (in cm^2) and ^{201}Tl SPECT maximal tumor intensity (in TNT) in the prediction of OS by maximizing the log-likelihood of a Cox model with regard to the cut-off value. Ninety-five percent confidence intervals (95% CI) for the cut-off values were obtained by the profile likelihood method.

In subsequent analyses (analysis II), we assessed whether renewing MRIs and ^{201}Tl SPECTs during the course of treatment would contribute significantly to the prediction of OS. We started with a regression model with only the baseline MRI or ^{201}Tl SPECT measurement as a covariate for the whole time window regardless whether the MRI or ^{201}Tl SPECT had been updated during follow-up. We estimated the effect of renewing the scan at the second time-point on OS by extending the regression model with the renewed MRI or ^{201}Tl SPECT measurement as a covariate. The time window of this covariate is from the second time-point onwards. The effects of renewing the scans at the third and fourth time-points were estimated in an analogous way.

The effect of renewing MRI or ^{201}Tl SPECT at a certain time-point on OS is equivalent to the effect of the absolute change in MRI or ^{201}Tl SPECT (when comparing that time-point with the preceding time-point). We repeated analysis II studying the effect of relative change in MRI tumor size or ^{201}Tl SPECT maximal tumor intensity (instead of absolute change) on OS.

The descriptive analyses were performed in SPSS 15.0 (SPSS Inc, Chicago, IL), and the Cox regression analyses

were performed in STATA 10 (StataCorp LP, College Station, TX).

Results

Patient characteristics

From September 2004 to October 2008, 46 patients treated with TMZ in our institution were included: 24 patients for study A and 22 patients for study B. Patient characteristics and outcomes are shown in Table 2.

In *study A*, tumor histology was GBM, except for one patient with an astrocytoma (grade II), who had undergone surgery 1 year before, and started with TMZ chemoradiotherapy under the suspicion of tumor progression and dedifferentiation to a GBM. All GBM patients were operated on recently, and underwent standard focal fractionated radiotherapy (60 Gy) in combination with concomitant TMZ chemotherapy (75 mg/m^2 daily during radiotherapy). After a 4-week interval, adjuvant TMZ treatment was given on a standard schedule (150–200 mg/m^2 daily for 5 days, repeated every 28 days; six courses). All patients were chemonaive. Two patients did not receive adjuvant TMZ as a result of persistent myelosuppression. Eighty-one MRI and 65 ^{201}Tl SPECT scans were performed. The median interval between baseline imaging and start of chemoradiotherapy was 6 days. The median OS was 15 months, and the median (clinical) progression-free survival (PFS) was 9 months. Ten out of 24 patients had not died as of October 2008, two of which had already shown tumor progression. Survival data of these patients were censored at this date.

In *study B*, initial tumor histologies included GBM (n=8), astrocytoma, (n=6), anaplastic astrocytoma (n=3), oligodendroglioma (n=2), anaplastic oligodendroglioma (n=2), and oligoastrocytoma (n=1). Because of the heterogeneity of histology in this relatively small patient group, histology was dichotomised (GBM versus non-GBM). All patients had previously undergone craniotomy and 20 out of 22 irradiation. The median interval between initial glioma therapy and start of TMZ chemotherapy for recurrent disease was 33 (range, 4–187) months. Pathological verification of recurrent disease was obtained in 13 of 22 patients (seven GBMs versus six non-GBMs). TMZ was given on a standard schedule (150–200 mg/m^2 daily for 5 days, repeated every 28 days). Fifty-seven MRIs and 48 ^{201}Tl SPECTs were performed. The median interval between baseline imaging and start of chemotherapy was 7 days. The median OS and PFS were 10 and 5 months, respectively. Six out of 22 patients had neither shown tumor progression nor had died as of October 2008. Survival data of these patients were censored at this date.

Study A: newly diagnosed GBM

Table 3 shows the results of regression analyses in which we examined the effects of MRI and ^{201}Tl SPECT on OS in newly diagnosed GBM patients.

Overall, both MRI tumor size and ^{201}Tl SPECT maximal tumor intensity correlated negatively with OS ($P \leq 0.02$; corresponding hazard ratio (HR), 2.1 and 2.3, respectively; analysis I). The effect of MRI on OS remained significant when age or KPS was added to the model ($P \leq 0.01$; results not tabulated). Cox regression analyses with both MRI and ^{201}Tl SPECT as predictors

Table 2 Patient characteristics

Characteristic	Study A (n=24)	Study B (n=22)
Male/female	18/6	14/8
Median age (years)	54 (18–71)	47 (30–64)
Tumor histology (GBM/non-GBM)	23/1	8/14
Median KPS (at baseline)	90	90
Previous radiotherapy (yes/no)	–	20/2
Mean radiotherapy dose (Gy)	–	48 (30–59)
Previous chemotherapy (yes/no)	0/24	3[a]/19
Surgery (biopsy/resection)[b]	2/22	–
Median number of TMZ courses	6 (0–6)[c]	4.5 (1–18)
Median number of MRIs	4 (0–4)	2 (0–4)
Median number of SPECTs	3 (2–3)	2 (1–3)
Median OS (months)	15 (2–43)	10 (1–31)
Median PFS (months)	9 (2–38)	5 (0–31)
Median MRI tumor size (cm^2)[d]	6.3 (0–44.4)	4.8 (0–60.0)
Median SPECT maximal tumor intensity (TNT)[d]	1.9 (1–4)	2 (1–3.4)

Values in parentheses are ranges

GBM glioblastoma multiforme, *KPS* Karnofsky performance score, *TMZ* temozolomide, *OS* overall survival, *PFS* (clinical) progression-free survival, *TNT* tumor–nontumor ratio

[a] The combination of procarbazine, CCNU and vincristine

[b] Type of surgery at primary diagnosis

[c] Adjuvant courses

[d] All scans

Table 3 Regression analyses in patients with newly diagnosed GBM (study A)

Variable	OS	
	HR (95% CI)[a]	*P*
Analysis I		
MRI	2.1 (1.2–3.6)	0.01
SPECT	2.3 (1.1–4.8)	0.02
KPS	1.0 (.9–1.0)	0.52
Age	1.0 (1.0–1.0)	0.80
Analysis II		
MRI (BL)	1.4 (0.8–2.6)	0.24
TP2	1.0 (0.5–1.8)	0.95
TP3	3.0 (1.0–8.9)	0.04
TP4	4.1 (1.4–12.3)	0.01
SPECT (BL)	1.9 (1.1–3.5)	0.03
TP2	1.0 (0.3–3.1)	0.96
TP3	23.3 (2.3–234.8)	0.01

OS overall survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *KPS* Karnofsky performance score, *BL* baseline, *TP (2-3-4)* time-point (2-3-4)

[a] Increase in the rate of dying per unit increase in imaging modality (MRI tumor size 10 cm^2, SPECT TNT 1)

demonstrated that the addition of one imaging modality to the other did not contribute to the prediction of OS. Cut-off values for MRI and ^{201}Tl SPECT imaging modalities were 16 (95% CI, 10–21) and 2.5 (95% CI, 2.1–2.9), respectively.

Evaluating the effect of renewing MRIs and ^{201}Tl SPECTs during the course of treatment (analysis II), we found that MRI at baseline was not significantly related to OS. Renewing MRI at time-point 3 and 4 contributed significantly to the prediction of OS (P=0.04 and 0.01, respectively), whereas renewing the scan at time-point 2 had no significant effect on OS. In contrast to MRI, ^{201}Tl SPECT at baseline was related to OS (P=0.03). Renewing the ^{201}Tl SPECT scan at time-point 3 also contributed significantly to the prediction of OS (P=0.01). In the analyses with relative change as a covariate, only the change in MRI tumor size from time-point 3 to time-point 4 had a significant effect on OS ($P \leq 0.01$; HR, 2.3). For ^{201}Tl SPECT, the relative change from time-point 2 to time-point 3 had a significant effect on OS ($P \leq 0.01$; HR, 512).

Figure 2 demonstrates SPECT images of two patients with respectively high (TNT 3.1, Fig. 2a) and low (TNT 1.4, Fig. 2b) ^{201}Tl uptake, with corresponding T1-weighted post-gadolinium MR images representing the two largest perpendicular transverse enhancing tumor diameters (in Fig. 2a only the enhancing area with residual tumor postoperatively was calculated).

Study B: recurrent glioma

Table 4 shows the results of regression analyses in which we examined the effects of MRI and ^{201}Tl SPECT on OS of recurrent glioma patients.

Overall, both MRI tumor size and ^{201}Tl SPECT maximal tumor intensity correlated negatively with OS (P<0.01; HR, 1.5 and 2.8, respectively; analysis I). The effect of MRI on OS remained significant when age, KPS or tumor histology were added to the model ($P \leq 0.01$; results not tabulated). Cox regression analyses with both MRI and ^{201}Tl SPECT as predictors demonstrated that the addition of one imaging modality to the other did not contribute to the prediction of OS. Cut-off values for MRI and SPECT imaging modalities were 7 (95% CI, 1–10) and 1.7 (95% CI, 1.0–2.0), respectively.

Evaluating the effect of renewing MRIs and ^{201}Tl SPECTs during the course of treatment (analysis II), results for MRI and ^{201}Tl SPECT were largely comparable, though essentially different from the results of study A. Both for MRI and ^{201}Tl SPECT, tumor measurements at baseline were related to OS (P<0.01; HR, 2.2 and 5.0, respectively), whereas subsequent MRIs and ^{201}Tl SPECTs during the course of treatment (time-points 2–4) did not contribute to the prediction of OS.

In the analyses with relative change as a covariate, the change in MRI tumor size from time-point 1 (baseline) to time-point 2 contributed significantly to the prediction of OS (P<0.01; HR, 1.3). Relative ^{201}Tl SPECT changes did not have a significant effect on OS.

Discussion

In the current study, we found that both MRI and ^{201}Tl SPECT are valuable in the prediction of survival in glioma patients treated with TMZ. Furthermore, we found that the addition of one imaging modality to the other does not contribute to the prediction of survival.

In newly diagnosed GBM patients, the predictive capacity of both modalities appeared to be highest at the last follow-up time-point, i.e., after six adjuvant TMZ courses in case of MRI and after three adjuvant courses in case of ^{201}Tl SPECT. MRI tumor size at baseline and post-concomitantly had no significant prognostic value for survival. We hypothesize that early after chemoradiotherapy the predictive capacity of MRI is influenced by pseudo-progression. In our cohort, 22% of patients met the definition of pseudoprogression, which is in line with data from literature [11, 12, 15]. Our imaging sample was too small to study the value of ^{201}Tl SPECT in this setting.

In recurrent glioma patients, baseline MRI and ^{201}Tl SPECT appeared to be the most predictive of OS, although

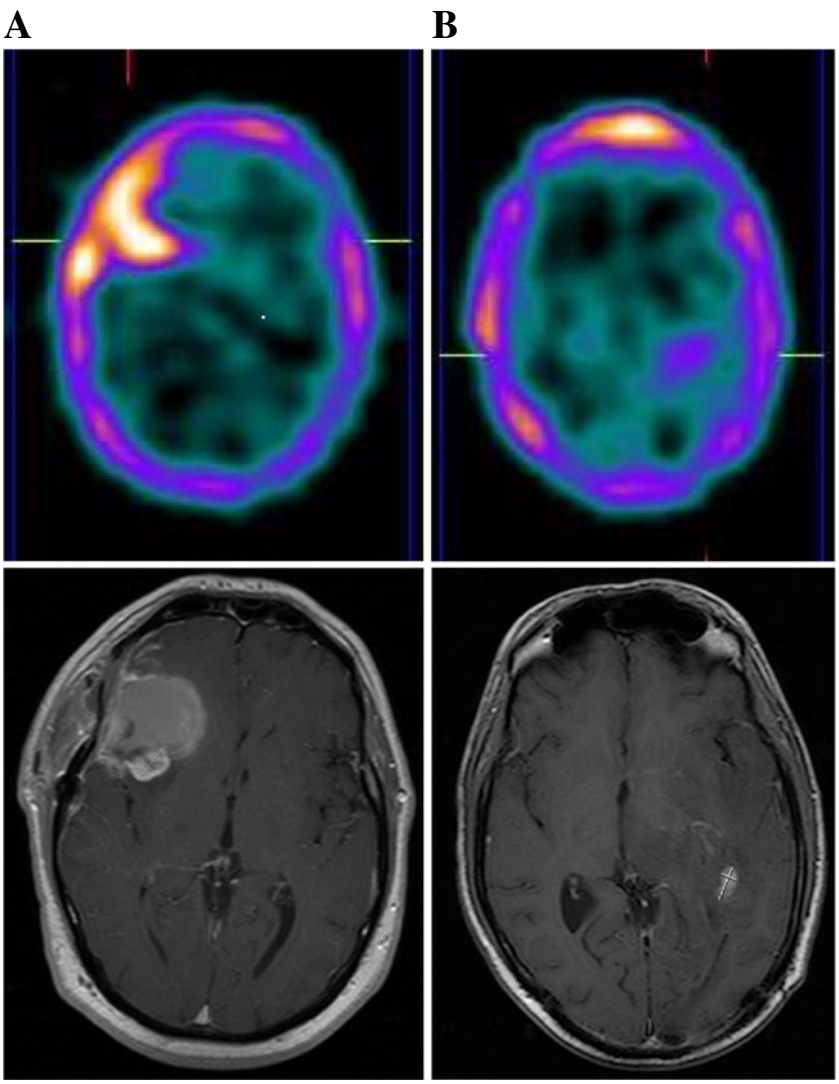

Fig. 2 SPECT images of two patients with respectively high (TNT, 3.1) (**a**) and low (TNT, 1.4) (**b**) ^{201}Tl uptake in right frontal, respectively, left parietotemporal localized tumor, with corresponding T1-weighted post-gadolinium MR images representing the two largest perpendicular transverse enhancing tumor diameters (in (**a**), only the enhancing area with residual tumor postoperatively was calculated)

the relative change in MRI tumor size from baseline to beyond three TMZ courses had a significant effect on OS, which is in line with our previous analyses [25, 26].

Data on the prognostic value of conventional contrast-enhanced MRI in the prediction of survival in glioma patients are somewhat conflicting [25, 26, 29–32]. Baseline MRI tumor size was not significantly related to survival in our newly diagnosed GBM patients. In literature, however, there is some evidence that more extensive surgical resection is associated with longer survival in glioma patients [33]. For ^{201}Tl SPECT, similar data are scarce, yet ^{201}Tl SPECT maximal tumor intensity was found to be a powerful predictor of survival in recurrent glioma patients [25, 26], which is supported by the current results.

To overcome limitations of conventional imaging techniques in the follow-up of glioma patients, the value of several SPECT tracers and other functional brain imaging techniques, such as PET, and advanced MRI techniques, such as perfusion imaging, dynamic contrast-enhanced MRI, diffusion imaging, and magnetic resonance spectroscopy, is being explored. Technetium-99m methoxyisobutylisonitrile SPECT, technetium-99m hexamethylpropylene amine oxime SPECT, and C-11-methionine PET seem to be useful in the differentiation of tumor recurrence and radiation necrosis and in the early detection of response to chemotherapy in glioma patients [18, 34, 35]. Perfusion MRI provides functional information on the regional cerebral blood volume, reflecting the degree of microvascular proliferation in tumor tissue, and has been used for grading, differentiation of tumor recurrence versus treatment-induced changes, and prediction of survival in glioma patients [36–41]. Apparent diffusion coefficient histogram analysis from diffusion-weighted MRI may predict response to anti-angiogenic therapy in patients with recurrent high-grade gliomas, and may be more sensitive than treatment assessment based solely on RANO criteria [42, 43]. Potential advantages of MR spectroscopy in glioma therapy include refinement of preoperative differ-

Table 4 Regression analyses in patients with recurrent glioma (study B)

Variable	OS	
	HR (95% CI)[a]	P
Analysis I		
MRI	1.5 (1.2–1.9)	<0.01
SPECT	2.8 (1.5–5.2)	<0.01
KPS	1.0 (.9–1.0)	<0.01
Histology	5.4 (1.9–15.4)	<0.01
Age	1.1 (1.0–1.1)	0.07
Analysis II		
MRI (BL)	2.2 (1.4–3.6)	<0.01
TP2	1.2 (0.8–1.8)	0.42
TP3	4.4 (0.1–255.6)	0.48
TP4	0.7 (0.0–9.6)	0.77
SPECT (BL)	5.0 (2.1–12.0)	<0.01
TP2	1.5 (0.9–2.4)	0.12
TP4	0.9 (0.3–2.4)	0.78

OS overall survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *KPS* Karnofsky performance score, *BL* baseline, *TP (2-3-4)* time-point (2-3-4)

[a] Increase in the rate of dying per unit increase in imaging modality (MRI tumor size 10 cm^2, SPECT TNT 1)

ential diagnosis, biopsy-site selection and distinction of progressive tumor from treatment effects [41, 44, 45].

Regarding the prognostic value of clinical variables, the results of the current study are largely in accordance with our previous analyses and with other glioma studies [25, 46]. In recurrent glioma patients, both KPS and histology were strongly related to OS. However, in multivariate analyses with MRI and ^{201}Tl SPECT, the effect of the clinical variables on OS decreased, underlining the strength of MRI and ^{201}Tl SPECT in the prediction of outcome. In patients treated with combined chemoradiotherapy for newly diagnosed GBM, the prognostic value of the clinical variables was poor, probably as a result of patient selection bias.

Our prospective study has some limitations. At first, our study sample is relatively small. Second, pathology in our recurrent glioma patients is varied. Therefore, our data should be substantiated in a larger cohort of glioma patients.

Regarding the question how glioma patients should be monitored radiologically during treatment, it seems adequate to restrict to one of both imaging modalities. Since MRI is also useful in the initiation and planning of potential additional treatment modalities (e.g., re-operation/-irradiation in case of tumor progression), in combination with the more invasive character of ^{201}Tl SPECT, it seems logical to prefer MRI.

Regarding the timing of imaging in the course of treatment, a distinction can be made between newly diagnosed GBM and recurrent glioma patients. Our survival analyses indicate that, in patients treated with TMZ chemoradiotherapy for newly diagnosed GBM, MRI after six adjuvant TMZ courses contributes significantly to the prediction of survival. In patients treated with TMZ for recurrent glioma, baseline MRI appears to be a powerful predictor of survival, whereas follow-up MRIs during chemotherapy seem to be of little additional value.

The question as to whether stringent imaging follow-up in glioma patients is superior to follow-up without routine imaging in a clinically stable patient remains to be answered. In every day clinical neuro-oncology practice, the therapeutic dilemma how to deal with an asymptomatic glioma patient with new radiological abnormalities during follow-up appears. This dispute can only be answered in a large, prospective trial in which several modes of follow-up assessment are compared: clinical follow-up versus follow-up with clinical and routine imaging.

Conflict of interest We declare that we have no conflict of interest.

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