Long-term outcome of patients with WHO Grade III and IV gliomas treated by fractionated intracavitary radioimmunotherapy

*Hans-Juergen Reulen, MD,¹ Gabriele Poepperl, MD,² Claudia Goetz, MD,¹ Franz Joseph Gildehaus, PhD,² Michael Schmidt, MD,³ Klaus Tatsch, MD,² Torsten Pietsch, MD,⁵ Theo Kraus, MD,⁴ and Walter Rachinger, MD¹

Departments of ¹Neurosurgery, ²Nuclear Medicine; ³Munich Cancer Registry, Institute of Medical Informatics, Biometry, and Epidemiology; and ⁴Department of Neuropathology, Ludwig Maximilian University Munich, Klinikum Grosshadern, Munich; and ⁵Department of Neuropathology, University of Bonn, Germany

OBJECT The aim in this study was to present long-term results regarding overall survival (OS), adverse effects, and toxicity following fractionated intracavitary radioimmunotherapy (RIT) with iodine-131- or yttrium-90-labeled anti-tenascin monoclonal antibody (¹³¹I-mAB or ⁹⁰Y-mAB) for the treatment of patients with malignant glioma.

METHODS In 55 patients (15 patients with WHO Grade III anaplastic astrocytoma [AA] and 40 patients with WHO Grade IV glioblastoma multiforme [GBM]) following tumor resection and conventional radiotherapy, radioimmunoconjugate was introduced into the postoperative resection cavity. Patients received 5 cycles of ⁹⁰Y-mAB (Group A, average dose 18 mCi/cycle), 5 cycles of ¹³¹I-mAB (Group B, average dose 30 mCi/cycle), or 3 cycles of ¹³¹I-mAB (Group C, 50, 40, and 30 mCi).

RESULTS Median OS of patients with AA was 77.2 months (95% CI 30.8 to > 120). Five AA patients (33%) are currently alive, with a median observation time of 162.2 months. Median OS of all 40 patients with GBM was 18.9 months (95% CI 15.8–25.3), and median OS was 25.3 months (95% CI 18–30) for those patients treated with the ¹³¹I-mAB. Three GBM patients are currently alive. One-, 2-, and 3-year survival probabilities were 100%, 93.3%, and 66.7%, respectively, for AA patients and 82.5%, 42.5%, and 15.9%, respectively, for GBM patients. Restratification of GBM patients by recursive partitioning analysis (RPA) Classes III, IV, and V produced median OSs of 31.1, 18.9, and 14.5 months, respectively ($p = 0.004$), which was higher than expected. Multivariate analysis confirmed the role of RPA class, age, and treatment in predicting survival. No Grade 3 or 4 hematological, nephrologic, or hepatic toxic effects were observed; 4 patients developed Grade 3 neurological deficits. Radiological signs of radionecrosis were observed in 6 patients, who were all responding well to steroids.

CONCLUSIONS Median OS of GBM and AA patients treated with ¹³¹I-mABs reached 25.3 and 77.2 months, respectively, thus markedly exceeding that of historical controls. Adverse events remained well controllable with the fractionated dosage regimen.

<http://thejns.org/doi/abs/10.3171/2014.12.JNS142168>

KEY WORDS radioimmunotherapy; glioblastoma; anaplastic astrocytoma; I-131-labeled anti-tenascin mAB; radioimmunoconjugate; oncology

MALIGNANT gliomas are invasive tumors associated with a poor prognosis for the patient despite improvements in surgery, radiotherapy, and chemotherapy.^{33,34} Most of these tumors recur at or adjacent to the site of origin, indicating that failure to eradicate local

tumor growth is a major factor contributing to poor outcome.¹⁰ Therefore, locoregional intracavitary therapies have been in clinical testing at a few centers since the middle of the 1990s.^{15,29,30,39} Direct application of a drug into the postoperative resection cavity (RC) bypasses the

ABBREVIATIONS AA = anaplastic astrocytoma; ALA = 5-aminolevulinic acid; CTC = Common Toxicity Criteria; GBM = glioblastoma multiforme; HR = hazard ratio; IDH1 = isocitrate dehydrogenase; KPS = Karnofsky Performance Scale; mAB = monoclonal antibody; MGMT = O⁶-methylguanine-DNA methyltransferase; OS = overall survival; RC = resection cavity; RIT = radioimmunotherapy; RPA = recursive partitioning analysis; RTOG = Radiation Therapy Oncology Group.

SUBMITTED September 16, 2014. **ACCEPTED** December 12, 2014.

INCLUDE WHEN CITING Published online July 3, 2015; DOI: 10.3171/2014.12.JNS142168.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. This work was supported by grants from the German research foundation DFG (GO998/1-1), the Deutsche Krebshilfe (10-1782-GO2), and a fund of the MMW Foundation (Verein zur Förderung von Wissenschaft und Forschung an der Medizinischen Fakultät der LMU München e.V.).

* Drs. Reulen and Poepperl contributed equally to this work.

blood-brain barrier, ensures higher concentrations of the drug at its destination, and reduces the risks of systemic therapy.

Glioma cells are known to express specific receptors or glycoproteins that can be used as biological targets for treatment. A well-examined target is tenascin-C, an extracellular matrix glycoprotein ubiquitously expressed by malignant gliomas, but only minimally expressed in normal brain tissue.^{13,37} Studies with anti-tenascin monoclonal antibodies (mABs) labeled with iodine-131 or yttrium-90 and applied in the postoperative RC via an Ommaya reservoir have demonstrated very promising results regarding prolonged survival in patients with malignant gliomas.^{3,4,12,25–27,29–31} It is assumed that the radioimmunoconjugate travels through the tissue, binds to tumor cells, and exerts its effect by radiation-mediated DNA damage.^{9,15,31,39} With the recent availability of new mABs,^{7,9,17,36} smaller compounds such as peptides, and tailored antibody fragments,^{9,14} there is resurging interest in this promising approach.

Intracavitary application of radiolabeled mABs has been performed either as a fixed single high dose^{3,4,25–27} or as fractionated lower doses.^{12,29–31} However, follow-up for these studies was only between 1 and 3 years. In this report, we present the results of a 55-patient cohort prospectively treated with fractionated radioimmunotherapy (RIT) and followed over time to allow for long-term analysis (> 10 years) of survival, adverse events, and treatment toxicity. Initial results describing the feasibility of and experiences with this technique in a first group of patients have been reported previously.¹² One aspect of the present study was to evaluate the effects of different fractionation regimens on long-term outcomes.

Methods

Patients and Selection Criteria

Fifty-five patients suffering from malignant glioma were treated with RIT in a prospective observational study between 1996 and 2003. The first patients were treated in cooperation with the Department of Nuclear Medicine in Cesena, Italy; all other patients were treated at the University Hospital in Munich. The study protocol was approved by the ethical review board of the Ludwig Maximilian University Munich. Patients had to understand and sign written informed consent before participating in the study. Eligible patients were between 18 and 70 years old, had a histologically confirmed supratentorial World Health Organization (WHO) Grade III (n = 15) or IV (n = 40) tumor with positive immunoreactivity for tenascin, and a Karnofsky Performance Scale (KPS) score of at least 70% at study entry. Total or near-total resection, according to early postoperative MRI (within 72 hours, residual tumor volume 0–3.0 cm³), was an essential entry criterion. Standard fractionated radiotherapy (60 Gy) should have been completed prior to study entry. Exclusion criteria were multifocal glioma manifestations, massive tumor progression during radiotherapy, other malignancies (apart from basaloidomas), pregnancy, or severe medical comorbidity with reduced life expectancy. If a test dose of technetium-99m human serum albumin

(^{99m}Tc HSA), injected into the cavity, showed leakage into CSF spaces or ventricles on scintigraphy, patients were excluded from treatment.

Study Design and Follow-Up

Surgeons operated on patients using 5-aminolevulinic acid (ALA) fluorescence-guided resection.³³ If a ventricle was opened during surgery, the opening was sealed with a collagen or a gelatin sponge saturated with fibrin glue. Standard fractionated radiotherapy consisted of irradiation of the tumor bed and a 2- to 3-cm peritumoral margin at a dose of 2 Gy per fraction; patients were given 5 doses per week for a total radiation dose of 60 Gy. An Ommaya reservoir was implanted with its catheter reaching into the RC. Prior to each treatment cycle, MRI (MPRAGE sequence) was performed to document treatment effects or tumor progression and to determine the volume of the tumor cavity by segmentation. Also prior to each treatment cycle, the KPS and neurological status were recorded, and laboratory tests for blood count, liver, and kidney functions were performed. Concomitant medications were started 1 day before each RIT cycle and consisted of dexamethasone (12 mg for 3 days, tapered thereafter), antiepileptic medication (phenytoin), and a mild analgetic medication. Patients receiving ¹³¹I-mAB (iodine-131-labeled anti-tenascin monoclonal antibody) were given potassium iodine (0.3 g/day until Day 10 after treatment) for protecting the thyroid from radiation. Since progression-free survival (PFS) was not a prespecified endpoint, the follow-up MRIs were not performed with the necessary technical accuracy to allow retrospectively a precise and meaningful volumetric progression analysis.

For injection of the ¹³¹I-mAB or yttrium-90-labeled anti-tenascin monoclonal antibody (⁹⁰Y-mAB), respectively, the Ommaya reservoir was accessed with a 20-gauge port access needle using sterile technique. The mAB was dissolved in a volume of 1–3.5 ml saline (depending on the volume of the RC) and injected into the reservoir. Patients were isolated in a shielded room until whole body retention, as measured by the local radiation dose rate, reached the level required by national regulations. Patients treated with ¹³¹I could usually be dismissed after 5–7 days. To document stability of the radioimmunoconjugate in some patients, small liquid probes were removed from the RC 5 days after treatment.

Three treatment regimens were tested in the course of this study. Initially, a comparison was planned using ⁹⁰Y-mAB (Group A, dose = 18 mCi/666 MBq per cycle) and ¹³¹I-mAB (Group B, dose = 30 mCi/1110 MBq per cycle) for 5 treatment cycles each with a 6-week interval between the cycles. The doses used in our study were recommended by Riva et al.^{30,31} Groups of 2–3 eligible patients alternatively received either ¹³¹I-mAB or ⁹⁰Y-mAB. In the course of the study, clinical practice showed that because of local recurrence, shrinking of the cavity volume, and obstruction of the catheter, the administration of all 5 intended cycles was often not feasible. Therefore, the administration protocol was amended, and patients received only 3 cycles of ¹³¹I-mAB (Group C) but with higher initial doses (50, 40, 30 mCi/1850, 1480, 1110 MBq). A typical time course and dose plan is shown in Fig. 1. The term “dose”

or “cumulative dose” in this context indicates the administered amount of radioactivity and not the absorbed dose of the treated tissue.

After the completion of RIT, MRI was repeated every 3 months in the 1st year and every 6 months thereafter. In all patients [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) was performed. In the event of significant contrast enhancement on MRI where radionecrosis was suspected, a *O*-(2-[18F]fluoroethyl)-L-tyrosine PET (FET-PET) was performed to differentiate recurrence from radionecrosis.²⁴ A lack of amino acid uptake in the FET-PET supports the diagnosis of radionecrosis and vice versa. All adverse events and complications related to therapy were documented, including laboratory values, neurology, skin necrosis, or radionecrosis.

In the case of tumor progression, systemic chemotherapy or repeat surgery was allowed following RIT. Since both are regarded as a possible source of bias with effects on survival, additional therapies were analyzed according to their frequency.

Antibodies and Radiolabeling

The murine IgG₁ antibodies BC-4 and BC-24 used for this study were directed against tenascin. BC-4 and BC-24 recognize an epitope within the epidermal growth factor–like sequence that is present in all tenascin isoforms.⁵ BC-4 and/or BC-24 labeling with ¹³¹I (1.1–1.85 GBq/patient) by a simplified and modified iodogen method, and radioimmunoconjugate stability and residence time in the RC were described previously.^{23,30,38}

Adverse Events and Toxicity

Adverse events were classified according to the grading system of the US National Cancer Institute Common Toxicity Criteria (CTC), version 2.0. Grades 0, 1, and 2 correspond to no, mild, or moderate symptoms (medical intervention not indicated); and Grades 3 and 4 correspond to severe and life-threatening symptoms, respectively (medical intervention indicated). The precise etiology of neurological deficits following RIT application was often difficult to reliably distinguish from the effects of recurrent tumor growth. The toxic effects of radiation (radionecrosis) were recorded using FDG-PET in combination with MRI (in selected cases, FET-PET was also used).

Histology

Histology was reviewed by 2 independent neuropathologists (local neuropathologist and Brain Tumor Reference Center of the DGNN [German Society for Neuropathology and Neuroanatomy] located at the Department of Neuropathology, University of Bonn). Tenascin expression was investigated in either fresh or paraffin-embedded tissue according to standard immunohistochemical methods using a murine tenascin antibody (BC4). *MGMT* promoter methylation status (methylation-specific polymerase chain reaction [PCR]) and *IDH1* mutation status were analyzed retrospectively in a subset of patients from the retrospective analysis for whom sufficient tumor material was available at the time of follow-up (Table 1).^{16,20}

FIG. 1. Time course and characteristic dose plan of Groups A, B, and C. Op = operation; RT = radiotherapy; (%) = percentage of patients who actually received this RIT cycle.

End Points and Statistical Analysis

In this prospective observational study, efficacy and safety of RIT were assessed. According to a recent Cochrane report, observational studies report results comparable to similarly conducted randomized controlled trials.² The primary end point was overall survival (OS), and the secondary end points were adverse events and toxicity. Since the study was not randomized, it was assumed that there were imbalances or selection effects within or between the groups. Therefore, factors leading to bias and asymmetry that possibly affected survival were carefully analyzed, and statistical measures were taken to adjust for such bias.

The mean, standard deviation, median, range, and 95% confidence interval were calculated using conventional methods. Differences in sex, age, and between groups were computed using the Mann-Whitney U-test and Kruskal-Wallis test. All statistical tests were 2-sided, and the level of significance was set at $p = 0.05$. Pearson's chi-square tests or Fisher's exact tests were applied for testing primary efficacy parameters. The method of Kaplan and Meier was used to estimate survival distributions measured from operation to death or last contact. Group comparisons in survival were made using log-rank tests and Z-tests. The Cox proportional-hazards model was used to investigate various covariates, including age (< 50 vs ≥ 50 years), KPS score (< 90 vs ≥ 90), RC volume (≤ 15 vs > 15 cm³), location, and side, separately for WHO Grade III and IV tumors. Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc.).

To allow comparison with “historical” data,^{8,17} patients were classified using the Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) Classes I–V based on age, KPS score, neurological condition, and mental status.^{8,17}

Results

Patient Characteristics and Survival

Forty patients in the study had a WHO Grade IV tumor, and 15 patients had a Grade III tumor. One glioblastoma multiforme (GBM) patient with a Grade IV oligo-

TABLE 1. Demographic characteristics and distribution of preoperative covariates*

Parameter	Grade III	Grade IV	p Value	Grade IV		
				Group A	Group B	Group C
All patients	15 (27)	40 (73)		13 (32)	16 (40)	11 (28)
Sex						
M	6 (40)	22 (55)	NS	7 (54)	6 (38)	9 (82)
F	9 (60)	18 (45)		6 (46)	10 (62)	2 (18)
Age in yrs						
Median (range)	38 (25–65)	49 (22–68)	0.001	49 (41–68)	48 (26–65)	54 (22–68)
<50 yrs	14 (93)	22 (55)	0.008	8 (62)	11 (69)	3 (27)
≥50 yrs	1 (7)	18 (45)		5 (38)	5 (31)	8 (73)
KPS score						
<90	1 (7)†	11 (28)	NS	2 (15)	6 (38)	3 (27)
≥90	13 (93)†	29 (72)		11 (85)	10 (62)	8 (73)
RPA class						
III	1 (7)	16 (40)		6 (46)	7 (44)	3 (27)
IV	0	17 (42)		5 (38)	6 (38)	6 (54)
V	0	7 (18)		2 (15)	3 (19)	2 (18)
Hemisphere						
Rt	10 (67)	18 (45)	NS	4 (31)	8 (50)	6 (54)
Lt	5 (33)	22 (55)		9 (69)	8 (50)	5 (45)
Localization						
frontal	8 (53)	11 (28)	‡	5 (38)	4 (25)	2 (18)
parietal	3 (20)	7 (18)		1 (8)	4 (25)	3 (27)
occipital	1 (7)	7 (18)		2 (15)	1 (6)	2 (18)
temporal	3 (20)	15 (38)		5 (38)	7 (44)	4 (36)
Cavity vol						
≤15 cm ³	10 (71)†	16 (43)§	NS	4 (33)	7 (47)	5 (50)
>15 cm ³	4 (29)†	21 (57)§		8 (67)	8 (53)	5 (50)
Number of RITs						
1	15 (100)	40 (100)		13 (100)	16 (100)	11 (100)
2	12 (80)	26 (65)		10 (77)	12 (75)	8 (73)
3	9 (60)	21 (52)		7 (54)	9 (56)	5 (45)
4	6 (40)	8 (20)		3 (23)	5 (31)	0
5	4 (27)	3 (8)		1 (8)	2 (12)	0
6	0	2 (5)		0	2 (12)	0
MGMT status¶						
methyated	3 (30)	12 (52)	NS	3 (50)	6 (60)	3 (43)
not methyated	7 (70)	11 (48)		3 (50)	4 (40)	4 (57)
IDH1 status¶						
mutation	7 (54)	6 (22)	0.072	2 (25)	2 (17)	2 (29)
no mutation	6 (46)	21 (78)		6 (75)	10 (83)	5 (71)

NS = not significant.

* Values expressed as the number (%), unless indicated otherwise.

† Data missing in 1 patient.

‡ Not computed due to small numbers of patients in subgroups. All differences between the 3 therapy groups were not significant and not computed due to small numbers.

§ Data missing in 3 patients.

¶ Comparison made with retrospective subset.

dendrogloma and 1 patient with Grade III oligoastrocytoma were also included (Table 1). Patients with Grade III tumors were younger, more frequently female, and had a higher KPS score than patients with Grade IV tumors.

Two patients, both with Grade III tumors, refused standard radiotherapy. Four patients had recurrent tumors: 2 of them initially had a Grade II astrocytoma that later progressed to Grade III, and 2 patients initially had a

FIG. 2. Kaplan-Meier plots of OS for patients with AA and GBM. The GBM patients are stratified by treatment group ($n = 40$). Group A = ^{90}Y -mAB (5 cycles), Group B = ^{131}I -mAB (5 cycles), Group C = ^{131}I -mAB (3 cycles). Comparison of Group A versus B+C has a $p = 0.073$ (log-rank test). Comparison of AAs versus all GBMs, $p < 0.001$.

Grade III anaplastic astrocytoma (AA) that later became Grade IV.

Median OS for the 15 patients with WHO Grade III tumors was 77.2 months (95% CI 30.8 to > 120 ; Fig. 2), and 5 patients (33%) are currently alive, with a median observation time of 162.2 months (range 134.9–202.5; Table 2). Of the 40 patients with Grade IV tumors, the median OS was 18.9 months (95% CI 15.8–25.3); 3 patients (7.5%) are alive, and 1 patient was censored due to an unknown date of death (observation time 23.5 months). The 1-, 2-, and

3-year survival probabilities were 100%, 93.3% (95% CI 80.7–100.0), and 66.7% (95% CI 42.8–90.5), respectively, for Grade III tumors, and 82.5% (95% CI 70.7–94.3), 42.5% (95% CI 27.2–57.8), and 15.9% (95% CI 4.3–27.5), respectively, for Grade IV GBMs.

The demographic characteristics of patients with Grade IV tumors in the 3 therapy Groups A, B, and C are listed in Table 1. Group C patients tended to be older than Group A or B patients. The cumulative dose of the applied radioactivity was comparable between Groups B and C (Table 2). Survival analysis revealed a strong tendency toward increased median OS and 12- and 24-month survival rates for Group B and particularly Group C, as compared with Group A (Fig. 2). If Groups B and C (treated with the ^{131}I -mAB) are pooled and compared with Group A (treated with the ^{90}Y -mAB), there is a survival benefit of 25.3 versus 14.5 months (log-rank test, $p = 0.073$).

When all 40 GBM patients were stratified into RPA Classes III, IV, and V (Fig. 3), they showed median survival times of 31.6 (95% CI 15.8–59.4), 18.9 (95% CI 11.7–27.8), and 14.5 months (95% CI 11.0–16.7), respectively (log-rank test, $p = 0.004$; Table 3). These values were associated with 24-month survival rates of 70.6% (95% CI 48.9–92.2), 35.3% (95% CI 12.6–58.0), and 0%, and thus were higher than expected.

Cox proportional-hazard analysis was performed with all 40 GBM patients; variables were included only if they were significant on univariate analysis (Table 4). Sex, age, histology, therapy groups, and RTOG-RPA class were significantly prognostic for survival on univariate analysis, whereas KPS score, volume of RC, and MGMT methylation status were not. However, the computed coefficients of these factors clearly indicated an impact on prognosis.

Despite the small number of cases, the multivariate Cox model confirmed the role of RPA class (including age) and

TABLE 2. Overall survival and cumulative radioactive dose*

Category	Grade III	Grade IV	p Value	Grade IV			p Value
				Group A	Group B	Group C	
No. of patients	15	40		13	16	11	
Median OS (mos)	77.2 (31 to >120)	18.9 (16–25)	$<0.001^\dagger$	14.5 (11–19)	19.2 (14–33)	25.3 (18–30)	0.073 †
OS (%)							
At 12 mos	100.0	82.5 (71–94)	0.004 ‡	69 (44–94)	88 (71–100)	91 (74–100)	NS ‡
At 24 mos	93.3 (81–100)	42.5 (27–58)	$<0.001^\ddagger$	23 (0–46)	44 (19–68)	64 (35–92)	0.057 ‡
At 36 mos	66.7 (43–91)	15.9 (4–28)	$<0.001^\ddagger$	8 (0–22)	25 (4–46)	11 (0–30)	NS ‡
Dose: cumulative MBq							
Median	2435	2145	NS §	1442	3002	3020	0.004 ¶
25th–75th percentile	1777–5738	1353–3632		533–1746	1353–4721	1850–4090	
Dose: cumulative mCi							
Median	65.8	58.0		38.9	81.1	81.6	
25th–75th percentile	48–155	37–98		14–47	37–128	50–111	

* Values expressed with 95% confidence intervals in parentheses. Dose is presented as MBq and mCi (median, 25th–75th percentile).

† Log-rank test for Grade III versus Grade IV and for therapy Group A versus Groups B and C, respectively.

‡ Z-tests for Grade III versus Grade IV and for therapy Group A versus Groups B and C, respectively.

§ Mann-Whitney U-test.

¶ Kruskal-Wallis test.

FIG. 3. Kaplan-Meier plots of OS for GBM patients by RPA Classes III, IV, and V (n = 40).

treatment in predicting survival. In the adjusted model, patients in RPA Class IV have a 2.8-fold increased risk of dying as compared with patients in RPA Class III, and the risk was more than 6-fold higher in RPA Class V patients. The hazard ratio (HR) for the therapy Groups B+C was 0.384 (95% CI 0.180–0.822, $p = 0.014$) as compared with Group A, which corresponds to a 61.6% reduction in the probability of death.

Fluid samples, taken from the RC in some patients, showed a stable radioimmunoconjugate for at least 5 days. In therapy Groups A and B, 5 RIT cycles were planned; in therapy Group C, only 3 cycles were planned. The percentage of patients who actually received each of the RIT cycles is presented in Fig. 1 and Table 1. In most cases, the reason for applying less than the planned number of cycles was local recurrence together with deterioration of the patient, occlusion of the catheter, or shrinking of the RC.

Additional Therapies

Twenty percent of patients with Grade III tumors and 25% of those with Grade IV tumors received 1 or more cycles of chemotherapy (nitrosourea-based or temozolomide) before the first cycle of RIT. If tumor progression occurred, systemic chemotherapy was administered following RIT; this applied to 60% of patients with Grade III tumors and 56.4% of those with Grade IV tumors (procarbazine, lomustine, vincristine [PCV], $n = 17$; temozolomide, $n = 14$). Thirty-three percent of AA patients and 33% of GBM patients had a local recurrence removed during or after RIT; 4 patients had a stereotactic ^{125}I seed implantation. Although there were small differences in the frequency of reinterventions and chemotherapies between the 3 therapy groups, they were not significant. A univariate Cox model in the GBM subgroup excluded any significant influence of repeat surgery and chemotherapy on observed median OS. The biopsies obtained during the surgical reinterventions in 15 patients were examined histologically, and the results were divided into 3 categories: tumor, radionecrosis, and mixed tumor and radionecrosis.²⁷ Four of the 15 patients predominantly revealed tumor, 5 patients showed different degrees of radionecrosis, and 6 patients displayed mixed tumor and radionecrosis.

Adverse Events and/or Toxicity

During RIT and follow-up, no Grade 3 or 4 hematological, nephrologic, or hepatic toxic effects were observed with the administration of ^{90}Y -mAB or ^{131}I -mAB. Sixteen patients developed mild and 4 patients developed moderate (Grade 1 or 2) leukopenia, thrombocytopenia, and/or erythropenia, and these resolved without further treatment (Table 5). A mild ($n = 8$) or moderate ($n = 2$) increase in creatinine, uric acid, and/or urea; and a mild ($n = 18$) or moderate ($n = 7$) change in prothrombin time, aspartate aminotransferase, total bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, and/or creatine kinase were observed; none needed further treatment. Since some patients received chemotherapy, the precise etiology of such changes was difficult to distinguish. Additional significant adverse events included thrombosis

TABLE 3. RTOG-RPA classes, median survival time, and survival rates

RPA Class	No. of Patients	Median Survival (mos)	95% CI	12-Mo Survival (%)	95% CI	24-Mo Survival (%)	95% CI	36-Mo Survival (%)	95% CI
All Patients									
I	12	76.0	25.5 to >120	100.0	*	91.7	76.0–100.0	66.7	40.0–93.3
II	2†								
III	17	31.6	15.8–59.4	94.1	82.9–100.0	70.6	48.9–92.2	38.5	14.6–62.4
IV	17	18.9	11.7–27.8	76.5	56.3–96.6	35.3	12.6–58.0	5.9	0.0–17.1
V	7	14.5	11.0–16.7	71.4	38.0–100.0	no patient left			
Grade IV									
III	16	31.1	15.8–59.4	93.8	81.9–100.0	68.8	46.0–91.5	34.4	10.2–58.5
IV	17	18.9	11.7–27.8	76.5	56.3–96.6	35.3	12.6–58.0	5.9	0.0–17.1
V	7	14.5	11.0–16.7	71.4	38.0–100.0	no patient left			

* 95% confidence interval for 12-month survival rate not computed since all patients lived.

† One patient died at 31.7 months; 1 was censored at 202.5 months.

TABLE 4. Cox proportional-hazard analysis for WHO Grade IV subgroup

Parameter	No. of Patients	Coefficient	p Value	HR (95% CI)
Univariate analysis				
Female sex	40	-0.797	0.033	0.451 (0.216–0.939)
Age ≥50 yrs	40	0.738	0.039	2.091 (1.038–4.211)
Grade IV*	55	1.170	0.001	3.222 (1.570–6.614)
Therapy Groups B+C	40	-0.633	0.078	0.531 (0.263–1.074)
KPS ≥90	40	-0.476	NS	0.621 (0.304–1.268)
Tumor vol >15 ml	37	0.277	NS	1.319 (0.665–2.618)
MGMT methylated	23	-0.708	NS	0.493 (0.201–1.208)
RPA class	40		0.007	
IV vs III		0.779	0.043	2.178 (1.025–4.629)
V vs III		1.676	0.002	5.346 (1.860–15.369)
Multivariate analysis				
RPA	40		0.002	
IV vs III		1.047	0.011	2.848 (1.273–6.370)
V vs III		1.859	0.001	6.416 (2.176–18.925)
Therapy Groups B+C		-0.956	0.014	0.384 (0.180–0.822)

* (n = 40) versus WHO Grade III (n = 15).

(n = 1), pneumonia (n = 1), and skin necrosis over the subgaleal reservoir (n = 4), with 2 of the 4 instances requiring plastic surgery. In 5 cases the reservoir with the catheter had to be removed because of a seroma (n = 1), an abscess in the tumor cavity (n = 2), and/or skin necrosis (n = 3). An exchange of the reservoir was necessary in 1 case.

During RIT, 9 patients developed seizures rated as Grade 2 on the CTC scale (all self-limited); 2 developed

dysphasias (Grade 2); 2 developed aphasias with hemiparesis (Grade 3); 1 developed severe hemiparesis (Grade 3); and 1 developed hydrocephalus (Grade 3). Headache was reported by some patients immediately following injection of the radioactive complex into the RC. Except for the hydrocephalus, these events resolved either spontaneously or with corticosteroids; in patients with seizures, antiseizure medication was administered.

TABLE 5. Adverse effects and toxicity*

Category	CTC Grade†	WHO Grade III	WHO Grade IV	Total No.	WHO Grade IV		
					Therapy Group A	Therapy Group B	Therapy Group C
Blood	0	5 (38)	25 (68)	30 (60)	10 (77)	8 (53)	7 (78)
	1	7 (54)	9 (24)	16 (32)	2 (15)	6 (40)	1 (11)
	2	1 (8)	3 (8)	4 (8)	1 (8)	1 (7)	1 (11)
	3	0	0	0	0	0	0
Kidney	0	10 (77)	30 (81)	40 (80)	11 (85)	12 (80)	7 (78)
	1	3 (23)	5 (14)	8 (16)	2 (15)	2 (13)	1 (11)
	2	0	2 (5)	2 (4)	0	1 (7)	1 (11)
	3	0	0	0	0	0	0
Liver	0	7 (54)	18 (49)	25 (50)	8 (62)	5 (33)	5 (56)
	1	4 (31)	14 (38)	18 (36)	5 (38)	6 (40)	3 (33)
	2	2 (15)	5 (14)	7 (14)	0	4 (27)	1 (11)
	3	0	0	0	0	0	0
CNS	0	8 (53)	30 (75)	38 (69)	10 (77)	12 (75)	8 (73)
	1	0	1 (3)	1 (2)	0	0	1 (9)
	2	6 (40)	5 (13)	11 (20)	2 (15)	2 (12)	1 (9)
	3	1 (7)	4 (10)	5 (9)	1 (8)	2 (12)	1 (9)
Radionecrosis		2 (13)	4 (10)	6 (11)	0	2	2

* Values expressed as number (%).

† Grade 0 = no toxicity, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening toxicity.

In the course of treatment, MRI studies were suspicious for radionecrosis in 6 patients (10.9%); 2 of these patients were treated with ^{90}Y -mAB and 4 patients with ^{131}I -mAB. These findings were supported by either FDG- or FET-PET and were confirmed by the later course. Time from the first RIT cycle to radiological signs of radionecrosis (positive MRI enhancement and negative FET-PET) ranged between 3.6 and 31 months with a median of 10.8 months. Median OS of these patients was 135.8 months. No radionecrosis was observed below a cumulative dose of 82 mCi/3000 MBq in 33 patients. However, radionecrosis was observed in 4 (27%) of 15 patients at a cumulative dose between 82 and 135 mCi/3000–5000 MBq and in 2 (28%) of 7 patients at doses between 135 and 240 mCi/5000–9000 MBq. All patients with radiological signs of radionecrosis responded well to steroids, and no one required reoperation. All other neurological events were attributable to tumor progression.

MGMT promoter methylation and *IDH1* mutation status, analyzed retrospectively in a subset of patients, showed promoter methylation in 30% of Grade III tumors and in 52% of Grade IV tumors (Table 1). No significant difference existed in the frequency of methylation status between the 3 therapy groups. In the Cox regression model, methylation status had a coefficient of -0.708 and a HR of 0.493 but did not reach significance, most likely due to the small numbers. *IDH1* mutations were found in 54% of Grade III tumors and in 22% of Grade IV tumors. The latter figure is higher than expected, probably since 1 GBM had an oligodendroglioma component and 2 others were initially designated Grade III. There was no significant difference in the mutation rate between the 3 therapy groups. All mutations were found in the group with an age < 50 years (Fisher's exact test, $p = 0.001$).

Discussion

Intracavitary radioimmunotherapy depends on sufficient exposure of infiltrating tumor cells to the therapeutic agent. Thus, for an optimal effect the antibody conjugate should be able to reach infiltrating cells, located some distance from the resection margin. Migration of the antibody into the adjacent parenchyma occurs predominantly by diffusion, and its velocity is dependent on the diffusion gradient, the diffusion coefficient, and the width and tortuosity of the extracellular space.^{1,28} Diffusion may account for a migration of 0.15–0.6 mm/hour of linear distance in edematous tissue.^{1,11,15,21,28} If the values are extrapolated, the transition time through a 20-mm tissue depth is theoretically between 40 and 160 hours.

Our study investigates the effects of repeated intracavitary radioimmunotherapy and demonstrates this concept to be feasible and efficacious. Fractionated treatment with radiolabeled anti-tenascin mAB markedly prolongs median OS in patients with GBM or AA, but particularly those with AA. Median OS in the small group with AA was 77.2 months, and 5 (33%) of the 15 patients survived 11 years and longer. All 5 of the surviving patients at the last MRI follow-up were without recurrence and able to work. To overcome heterogeneities in known prognostic factors, we restratified patient data according to the prognostic classes

constructed by Curran et al.⁸ These prognostic classes have been used to provide reliable “historical” controls, to which results of nonrandomized studies can be compared.^{8,18} Survival in our cohort of AA patients was markedly longer than what would be expected from appropriate RTOG-RPA Classes I–III,^{8,18} and the high percentage of long-term survivors (33%) with a KPS between 90 and 100 is particularly impressive.

Median OS in all 40 patients with GBM was 18.9 months, and it was 25.3 months in those treated with the ^{131}I -mAB. The corresponding 2-year survival rates were 42.5% and 52%, respectively, and 3 (7.5%) of the 40 patients are currently alive with observation times of 112, 156, and 193 months. Median OS in the RPA Classes III–V, even when analyzed conservatively with all 40 GBM patients, was markedly higher than expected given historical controls. The greatest treatment effect for GBM was seen in RPA Class III and IV with a gain in survival of 13 and 7.5 months, respectively, as compared with the RTOG data. Even in RPA Class V, the worst prognostic category, there was a survival gain of about 7 months. The survival gain and the 2-year survival probability were also superior to results obtained in the complete resection arm of the ALA trial as well as those obtained in the RT and temozolomide arm of the Stupp study.^{19,22} These positive effects become even more pronounced when only patients treated with ^{131}I -mAB (Groups B+C) are regarded.

When interpreting the results of Groups A (treated with ^{90}Y -mAB) and Groups B and C (treated with ^{131}I -mAB), the differences in the physical properties of the 2 radionuclides have to be taken into account. ^{90}Y has a shorter half-life (64 hours) than ^{131}I (192.5 hours) but emits a much higher energy of β -particles, with maximal energy of 2.28 MeV. This allows for deeper particle penetration (median/maximum tissue penetration range: 3.6/11 mm) compared with ^{131}I , resulting in higher radiation doses at the target area. The maximal energy of ^{131}I is relatively low (0.61 MeV), and the median/maximum tissue penetration range is 0.5/2.1 mm. Potential advantages of ^{131}I for RIT include availability, easy chemistry, longer half-life, and an emission spectrum that allows for dosimetric studies. The administered doses of ^{90}Y , as compared with ^{131}I , are generally lower to avoid radiation-induced toxicity. Given a previous dose-escalation study in which the maximum tolerated dose to the brain was 25 mCi (925 MBq),³⁰ we applied an average dose of 18 mCi (666 MBq) per cycle in Group A in the present study. Although prognostic factors and the number of applied cycles were similar in Groups A and B (Table 1), survival parameters in Group A were less favorable than in Group B and particularly Group C. In Group A there were fewer hematological adverse events, no radiological signs of radionecrosis, but nearly the same rate of neurological adverse events. Median survival was more favorable for Group B (5 cycles of 30 mCi each) and most favorable for Group C (3 cycles of 50, 40, and 30 mCi). This observation is important, since in this rapidly progressing disease 3 cycles are easier to administer than a higher number of cycles. Based on our experience, the third and/or succeeding cycles were often not feasible, and an interval shorter than 6 weeks between the cycles seems appropriate. It also appeared that the higher initial dose

of radiation given in Group C had the greatest benefit for survival, but the optimal combination of the initial and subsequent doses has yet to be determined.

The Cox proportional-hazards multivariate analysis of all 40 GBM patients showed RPA status (including age) to be the strongest significant prognostic factor for patient survival. The adjusted model accounts for a survival benefit for therapy Groups B and C compared with Group A with a HR of 0.384, corresponding to a 61.6% reduction in the probability of death. Importantly *IDH1*, *MGMT* methylation status, and frequency of additional therapies were balanced between GBM therapy groups and did not skew results. No significant influence was found in the univariate Cox model for both additional therapies—repeat surgery or chemotherapy—after radiological progression.

Favorable effects of intracavitary RIT with ^{131}I -mABs have been described.^{25–27,29–31} Two different treatment concepts were applied. Riva et al. found a median survival of 19.0 months using repeated doses of 30–55 mCi (1110–2035 MBq)/cycle ^{131}I -labeled anti-tenascin murine BC-2 and BC-4 in patients with primary and recurrent GBM.^{29–31} Reardon et al. reported a median survival time of 19.9 months in GBM patients following a single dose of 120 mCi (4400 MBq) ^{131}I -labeled murine 81C6 mABs in primary AA ($n = 6$) and GBM ($n = 27$).^{25,27} In a recent pilot study in which the single dose of ^{131}I -mAB was adapted to the volume of the RC to achieve a 44-Gy boost to the RC margin, the median OS in GBM patients was 22.6 months.²⁶ A study using 3 intravenous injections of ^{125}I -labeled anti-epidermal growth factor receptor antibody reported a median OS of 14.5 months in patients with RIT alone and 20.4 months in patients treated with RIT and temozolamide.¹⁷

Adverse Events and Toxicity

There appears to be an association between cumulative administered radioactivity and hematological and neurological adverse events. No Grade 3 or 4 hematological or neurological toxicity was observed with a single or repeated intracavitary dose at or below 80 mCi/2960 MBq using ^{131}I -conjugated antibodies.^{4,25,29,31} However, with a higher single dose of 100 mCi/3700 MBq into the RC, reversible hematological Grade 3 or 4 toxicity was reported in 23% of patients, and Grade 3 neurotoxicity occurred in 12% of patients, all of whom were responsive to steroids and none of whom required reoperation for radionecrosis.^{3,27} In 2 previous studies using a still higher single dose of 120 mCi (4400 MBq), 27% and 39% of the patients, respectively, had Grade 4 reversible hematological toxicities, and 15% and 39% of the patients, respectively, experienced treatment-related Grade 3 and 4 neurological toxicity, including radionecrosis requiring reoperation.^{3,25} Conversely, with fractionated application and 6-week intervals between cycles, we observed no Grade 3 or 4 hematological, nephrologic, or hepatic toxicity; a low percentage of patients experiencing Grade 3 neurological toxicity (9%); no Grade 4 neurological toxicity; and radiological signs of radionecrosis in 10.9% patients, who responded well to steroids. It must be noted, however, that many of the patients in the cited studies simultaneously received adjuvant chemotherapy, which itself has some type of Grade 3 and 4 hematological toxic effects.³⁴

In all cases with Grade 3 neurological deficits (hemiparesis, aphasia), the RC was in immediate proximity to the motor or language cortex, suggesting that the local radiation dose was adversely affecting adjacent tissue. This finding is in line with observations made by Akabani et al.³ Since patients received external beam radiation therapy at 60 Gy prior to RIT, the total cumulative dose has to be considered. Akabani et al., after a single injection of 120 mCi ^{131}I -mAB into the RC, estimated the average absorbed doses to regions of interest 1 and 2 cm from the margins of the cavity interface to be 71 (range 26–136 Gy) and 40 Gy (range 16–68 Gy) and approximately 8 Gy for normal brain tissue.^{3,4} The wide range of the absorbed doses may be explained by the varying size of the RC volume. If the estimated doses are added to the absorbed dose from external fractionated radiotherapy, this may exceed the dose tolerance of brain tissue in some patients. In a recent survey on re-irradiation of recurrent glioma, radiation-induced necrosis occurred with conventional fractionation beyond a cumulative EQD2 of around 100 Gy (EQD2 = equivalent total dose when applied in 2-Gy fractions, estimated using the linear quadratic model).³² The radiation dose that can be tolerated increases with higher conformality (fractionated stereotactic radiotherapy) and smaller treatment volumes (linear accelerator [LINAC]-based stereotactic radiosurgery).^{6,32} In summary, repeated injections at similar or even higher cumulative doses appear to be associated with less hematological and neurological adverse events than a single high-dose application. This underlines the importance of biological repair mechanisms of brain tissue between the cycles. Unfortunately, data are lacking for the repair half-time of brain tissue radiation damage.³²

Study Limitations

This study is limited by several factors. It is a single-institution nonrandomized trial with a small sample size and most likely contains imbalances and bias. There is also a certain selection effect, as only patients with small residual tumor volumes were eligible for study inclusion. We made our best attempt to carefully analyze all differences and took statistical measures to adjust for such bias. We must emphasize that despite the small number of cases, the multivariate Cox model clearly confirmed the role of RPA class (including age) and treatment in predicting survival. In particular, restratification of the data according to RTOG-RPA Classes I–V, as part of the initial study design, showed a promising survival benefit compared with historical controls. Since retrospective analysis of *MGMT* and *IDH1* was not possible in all tumors, these incomplete data are used mainly to exclude major differences among the subgroups.

Conclusions

In this study with a limited case number and selected patient group, the median survival of AA and GBM patients treated with intracavitary fractionated applications of radiolabeled anti-tenascin mABs favorably exceeds that of historical controls (RTOG-RPA)^{8,18} treated with conventional radiotherapy and chemotherapy, as well as other recently published approaches,^{33–35} even after adjusting for

established prognostic parameters. The results need to be validated by a larger or randomized trial. With the doses used in our study, adverse events remained well controlled. Several factors can be further optimized: adjusting the activity of the labeled mAb to the cavity volume, reducing the time between cycles, using a higher initial dose of radiation, and adding the administration of temozolomide. Currently, a randomized trial is in preparation to further assess this promising approach.

Acknowledgments

We are indebted to Prof. P. Riva (Department of Nuclear Medicine, M. Bufalini Hospital, Cesena, Italy) for supplying support during the introduction of RIT. We thank the patients and their families for agreeing to participate in this study. W. Stummer's and J. C. Tonn's critical and helpful comments are appreciated.

References

1. Aaslid R, Gröger U, Patlak CS, Fenstermacher JD, Huber P, Reulen HJ: Fluid flow rates in human peritumoural oedema. *Acta Neurochir Suppl (Wien)* **51**:152–154, 1990
2. Anglemeyer A, Horvath HT, Bero L: Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev* **4**:MR000034, 2014
3. Akabani G, Reardon DA, Coleman RE, Wong TZ, Metzler SD, Bowsher JE, et al: Dosimetry and radiographic analysis of ¹³¹I-labeled anti-tenascin 81C6 murine monoclonal antibody in newly diagnosed patients with malignant gliomas: a phase II study. *J Nucl Med* **46**:1042–1051, 2005
4. Akabani G, Reist CJ, Cokgor I, Friedman AH, Friedman HS, Coleman RE, et al: Dosimetry of ¹³¹I-labeled 81C6 monoclonal antibody administered into surgically created resection cavities in patients with malignant brain tumors. *J Nucl Med* **40**:631–638, 1999
5. Balza E, Siri A, Ponassi M, Caocci F, Linnala A, Virtanen I, et al: Production and characterization of monoclonal antibodies specific for different epitopes of human tenascin. *FEBS Lett* **332**:39–43, 1993
6. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC: Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* **77**:996–1001, 2010
7. Casacó A, López G, García I, Rodríguez JA, Fernández R, Figueredo J, et al: Phase I single-dose study of intracavitary-administered Nimotuzumab labeled with ¹⁸⁸Re in adult recurrent high-grade glioma. *Cancer Biol Ther* **7**:333–339, 2008
8. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* **85**:704–710, 1993
9. De Bonis P, Lofrese G, Anile C, Pompucci A, Vigo V, Mangiola A: Radioimmunotherapy for high-grade glioma. *Immunotherapy* **5**:647–659, 2013
10. Gaspar LE, Fisher BJ, Macdonald DR, LeBer DV, Halperin EC, Schold SC Jr, et al: Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int J Radiat Oncol Biol Phys* **24**:55–57, 1992
11. Gildehaus FJ, Rächinger W, Decker M, Stocker S, Goetz C, Poepperl G, et al: Migration properties of a radiolabeled intact antibody and Fab-fragment after locoregional application in C6 glioma of the rat. *J Nucl Med* **44 Suppl**:36P, 2003 (Abstract)
12. Goetz C, Riva P, Poepperl G, Gildehaus FJ, Hischa A, Tatsch K, et al: Locoregional radioimmunotherapy in selected patients with malignant glioma: experiences, side effects and survival times. *J Neurooncol* **62**:321–328, 2003
13. Herold-Mende C, Mueller MM, Bonsanto MM, Schmitt HP, Kunze S, Steiner HH: Clinical impact and functional aspects of tenascin-C expression during glioma progression. *Int J Cancer* **98**:362–369, 2002
14. Hdeib A, Sloan A: Targeted radioimmunotherapy: the role of ¹²⁵I-chTNT-1/B mAb (Cotara) for treatment of high-grade gliomas. *Future Oncol* **8**:659–669, 2012
15. Hopkins K, Chandler C, Bullimore J, Sandeman D, Coakham H, Kemshead JT: A pilot study of the treatment of patients with recurrent malignant gliomas with intratumoral yttrium-90 radioimmunoconjugates. *Radiother Oncol* **34**:121–131, 1995
16. Kraus TF, Globisch D, Wagner M, Eigenbrod S, Widmann D, Münzel M, et al: Low values of 5-hydroxymethylcytosine (5hmC), the “sixth base,” are associated with anaplasia in human brain tumors. *Int J Cancer* **131**:1577–1590, 2012
17. Li J, Wang M, Won M, Shaw EG, Coughlin C, Curran WJ Jr, et al: Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. *Int J Radiat Oncol Biol Phys* **81**:623–630, 2011
18. Li L, Quang TS, Gracely EJ, Kim JH, Emrich JG, Yaeger TE, et al: A Phase II study of anti-epidermal growth factor receptor radioimmunotherapy in the treatment of glioblastoma multiforme. *J Neurosurg* **113**:192–198, 2010
19. Mirmanoff RO, Gorlia T, Mason W, Van den Bent MJ, Kortmann RD, Fisher B, et al: Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol* **24**:2563–2569, 2006
20. Möllemann M, Wolter M, Felsberg J, Collins VP, Reifenberger G: Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendroglial tumors. *Int J Cancer* **113**:379–385, 2005
21. Nakagawa H, Groothuis DR, Owens ES, Fenstermacher JD, Patlak CS, Blasberg RG: Dexamethasone effects on [¹²⁵I] albumin distribution in experimental RG-2 gliomas and adjacent brain. *J Cereb Blood Flow Metab* **7**:687–701, 1987
22. Pichlmeier U, Bink A, Schackert G, Stummer W: Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. *Neuro Oncol* **10**:1025–1034, 2008
23. Pöpperl G, Götz C, Gildehaus FJ, Yousry TA, Reulen HJ, Hahn K, et al: [Initial experiences with adjuvant locoregional radioimmunotherapy using ¹³¹I-labeled monoclonal antibodies against tenascin (BC-4) for treatment of glioma (WHO III and IV).] *Nuklearmedizin* **41**:120–128, 2002 (Ger)
24. Pöpperl G, Götz C, Rächinger W, Schnell O, Gildehaus FJ, Tonn JC, et al: Serial O-(2-[(¹⁸F]fluoroethyl)-L-tyrosine PET for monitoring the effects of intracavitary radioimmunotherapy in patients with malignant glioma. *Eur J Nucl Med Mol Imaging* **33**:792–800, 2006
25. Reardon DA, Akabani G, Coleman RE, Friedman AH, Friedman HS, Herndon JE II, et al: Phase II trial of murine (¹³¹I)-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. *J Clin Oncol* **20**:1389–1397, 2002
26. Reardon DA, Zalutsky MR, Akabani G, Coleman RE, Friedman AH, Herndon JE II, et al: A pilot study: ¹³¹I-antitenascin monoclonal antibody 81c6 to deliver a 44-Gy resection cavity boost. *Neuro Oncol* **10**:182–189, 2008
27. Reardon DA, Zalutsky MR, Bigner DD: Antitenascin-C monoclonal antibody radioimmunotherapy for malignant glioma patients. *Expert Rev Anticancer Ther* **7**:675–687, 2007

28. Reulen HJ, Graham R, Spatz M, Klatzo I: Role of pressure gradients and bulk flow in dynamics of vasogenic brain edema. **J Neurosurg** 46:24–35, 1977
29. Riva P, Arista A, Tison V, Sturiale C, Franceschi G, Spinelli A, et al: Intralesional radioimmunotherapy of malignant gliomas. An effective treatment in recurrent tumors. **Cancer** 73 (3 Suppl):1076–1082, 1994
30. Riva P, Franceschi G, Frattarelli M, Lazzari S, Riva N, Giuliani G, et al: Loco-regional radioimmunotherapy of high-grade malignant gliomas using specific monoclonal antibodies labeled with ⁹⁰Y: a phase I study. **Clin Cancer Res** 5 (10 Suppl):3275s–3280s, 1999
31. Riva P, Franceschi G, Frattarelli M, Riva N, Guiducci G, Cremonini AM, et al: ¹³¹I radioconjugated antibodies for the locoregional radioimmunotherapy of high-grade malignant glioma—phase I and II study. **Acta Oncol** 38:351–359, 1999
32. Sminia P, Mayer R: External beam radiotherapy of recurrent glioma: radiation tolerance of the human brain. **Cancers (Basel)** 4:379–399, 2012
33. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. **Lancet Oncol** 7:392–401, 2006
34. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. **Lancet Oncol** 10:459–466, 2009
35. Thomas AA, Omuro A: Current role of anti-angiogenic strategies for glioblastoma. **Curr Treat Options Oncol** 15:551–566, 2014
36. Veeravagu A, Liu Z, Niu G, Chen K, Jia B, Cai W, et al: Integrin $\alpha_v\beta_3$ -targeted radioimmunotherapy of glioblastoma multiforme. **Clin Cancer Res** 14:7330–7339, 2008
37. Ventimiglia JB, Wikstrand CJ, Ostrowski LE, Bourdon MA, Lightner VA, Bigner DD: Tenascin expression in human glioma cell lines and normal tissues. **J Neuroimmunol** 36:41–55, 1992
38. Weadock KS, Sharkey RM, Varga DC, Goldenberg DM: Evaluation of a remote radioiodination system for radioimmunotherapy. **J Nucl Med** 31:508–511, 1990
39. Zalutsky MR, Bigner DD: Radioimmunotherapy with alpha-particle emitting radioimmunoconjugates. **Acta Oncol** 35:373–379, 1996

Author Contributions

Conception and design: Reulen, Poepperl, Goetz. Acquisition of data: Reulen, Poepperl, Goetz, Gildehaus, Tatsch, Pietsch, Kraus, Rachinger. Analysis and interpretation of data: all authors. Drafting the article: Reulen, Poepperl. Critically revising the article: Reulen, Poepperl, Goetz, Schmidt, Tatsch, Pietsch, Kraus, Rachinger. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Reulen. Statistical analysis: Schmidt. Administrative/technical/material support: Reulen. Study supervision: Reulen. Radiochemical preparation and dose calculations: Gildehaus. Central neuropathology: Pietsch.

Correspondence

Hans-J. Reulen, Department of Neurosurgery, Hospital of the University of Munich, Campus Grosshadern, Marchioninstr. 15, Munich 81377, Germany. email: hjreulen@gmx.de.