Neuro-Oncology

23(5), 803–811, 2021 | doi:10.1093/neuonc/noaa252 | Advance Access date 1 November 2020

Memory in low-grade glioma patients treated with radiotherapy or temozolomide: a correlative analysis of EORTC study 22033-26033

Martin Klein, A. Josephine Drijver, Martin J. van den Bent, Jacolien C. Bromberg, Khê Hoang-Xuan, Martin J. B. Taphoorn, Jaap C. Reijneveld, Mohamed Ben Hassel, Elodie Vauleon, Daniëlle B. P. Eekers, Tzahala Tzuk-Shina, Anna Lucas, Salvador Villà Freixa, Vasilis Golfinopoulos, Thierry Gorlia, Andreas F. Hottinger, Roger Stupp, and Brigitta G. Baumert, on behalf of the EORTC Brain Tumor and Radiation Oncology Groups

Brain Tumor Center Amsterdam at Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (M.K., A.J.D., J.C.R.); Brain Tumor Center at Erasmus Medical Center Cancer Institute, Rotterdam, the Netherlands (M.J.v.d.B., J.C.B.); Department of Neuro-Oncology, La Pitié Salpêtrière University Hospitals, Sorbonne University, Paris, France (K.H-X.); Department of Neurology, Haaglanden Medical Center, The Hague, Netherlands (M.J.B.T.); Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands (M.J.B.T.); Foundation for Epilepsy Institutions in the Netherlands (SEIN), Heemstede, the Netherlands (J.C.R.); Department of Radiation Therapy, Eugène Marquis Center, Rennes, France (M.B.H., E.V.); Department of Radiation Oncology (MAASTRO), GROW–School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands (D.B.P.E., B.G.B.); Proton Therapy Center South-East Netherlands (ZON-PTC), Maastricht, the Netherlands (D.B.P.E.); Oncology Institute, Rambam Health Care Campus, Haifa, Israel (T.T.S.); Catalan Institute of Oncology, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Barcelona, Spain (A.L., S.V.F.); European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium (V.G., T.G.); Departments of Oncology and Clinical Neurosciences, Vaudois University Hospital Center and University of Lausanne, Lausanne, Switzerland (A.F.H., R.S.); Malnati Brain Tumor Institute of the Lurie Comprehensive Cancer Center, Departments of Neurological Surgery and Neurology, Northwestern Medicine and Northwestern University, Chicago, Illinois, USA (R.S.); Department of Radiation Oncology, Cantonal Hospital of Graubünden, Chur, Switzerland (B.G.B.)

Corresponding Author: Prof. Dr. M. Klein, Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medical Psychology, De Boelelaan 1118 - PK 1Y 176, 1081 HZ Amsterdam, The Netherlands. T: +31 20 4448432 (m.klein@amsterdamumc.nl).

Abstract

Background. EORTC study 22033–26033 showed no difference in progression-free survival between high-risk low-grade glioma receiving either radiotherapy (RT) or temozolomide (TMZ) chemotherapy alone as primary treatment. Considering the potential long-term deleterious impact of RT on memory functioning, this study aims to determine whether TMZ is associated with less impaired memory functioning.

Methods. Using the Visual Verbal Learning Test (VVLT), memory functioning was evaluated at baseline and subsequently every 6 months. Minimal compliance for statistical analyses was set at 60%. Conventional indices of memory performance (VVLT Immediate Recall, Total Recall, Learning Capacity, and Delayed Recall) were used as outcome measures. Using a mixed linear model, memory functioning was compared between treatment arms and over time.

Results. Neuropsychological assessment was performed in 98 patients (53 RT, 46 TMZ). At 12 months, compliance had dropped to 66%, restricting analyses to baseline, 6 months, and 12 months. At baseline, patients in either treatment arm did not differ in memory functioning, sex, age, or educational level. Over time, patients in both arms showed improvement in Immediate Recall ($P = 0.017$) and total number of words recalled (Total Recall; $P < 0.001$, albeit with delayed improvement in RT patients (group by time; $P = 0.011$). Memory functioning was not associated with RT gross, clinical, or planned target volumes.

© The Author(s) 2020. Published by Oxford University Press on behalf of the Society for Neuro-Oncology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Conclusion. In patients with high-risk low-grade glioma there is no indication that in the first year after treatment, RT has a deleterious effect on memory function compared with TMZ chemotherapy.

Key Points

1. In high-risk low-grade glioma patients, RT does not have a deleterious effect on memory function compared with TMZ chemotherapy at one year.
2. When considering the first year after treatment, the choice for either RT or TMZ chemotherapy does not need to be based on its neurotoxic profile concerning memory function.

Importance of the Study

This is the first face-to-face study comparing memory effects of RT versus TMZ chemotherapy in high-risk low-grade glioma patients. This study showed improvement over a 12-month period with no difference between treatment arms. Radiotherapy patients, however, had a delayed recovery in memory functioning, probably associated with early RT effects.

Low-grade gliomas (LGGs) (World Health Organization [WHO] grade II astrocytomas and oligodendrogliomas) are a heterogeneous group of primary brain tumors commonly occurring in the third and 4th decade of life. Known clinical negative prognostic factors include older age, astrocytic histology, a tumor diameter of 6 cm or more, tumors crossing the midline, and persistence of neurologic symptoms already present prior to surgery. Mutations in the isocitrate dehydrogenase 1 (*IDH1*) or *IDH2* gene are commonly seen in LGGs. If accompanied by codeletion of chromosomal arms 1p and 19q, this is diagnostic for oligodendroglioma that has a more protracted natural history and better response to both chemotherapy and irradiation compared with IDH mutant astrocytoma.[1]

Surgery, radiotherapy (RT), and chemotherapy all have a role in the management of LGG; however, the sequence and optimal timing remain a matter of debate. The highly variable natural course and often initially indolent history warrant special consideration of potential late treatment-related toxicities.

Immediate surgery is generally required for patients presenting with a large mass or extensive neurologic symptoms. Retrospective studies suggest a survival advantage for early and radical tumor resection.[2] However, the role for immediate postoperative (adjuvant) RT in LGG is less clearly defined. In a large 1980s-initiated EORTC study,[3] 314 LGG patients were randomized to immediate versus deferred RT. Although early RT allowed for delaying the time to tumor progression, there was no overall survival (OS) difference between treatment groups. In a more recent Radiation Therapy Oncology Group study,[4] 251 high-risk LGG patients received RT and were subsequently randomized to receive or not to receive up to 6 cycles of procarbazine/lomustine/vincristine (PCV). With long-term follow-up of over a decade, prolonged OS was observed in patients who received adjuvant PCV.[5] The benefit appears to be confined to the subgroup of patients with IDH mutation. At 10 years, OS was 60% (95% CI: 51–69) and 40% (95% CI: 31–49) in the RT + PCV group and RT only group, respectively. Neurocognitive functioning using the Mini-Mental State Examination (MMSE) was assessed at baseline and at 1, 2, 3, and 5 years follow-up. Since most patients in both arms experienced a gain in MMSE scores over time, with no difference between arms, the authors conclude that the addition of PCV to RT improves progression-free survival without excessive neurocognitive decline over RT alone.[6] In EORTC 22033-26033, where high-risk LGG patients were randomized to treatment with either temozolomide (TMZ) or RT,[7] there was no difference in health-related quality of life (HRQoL) and MMSE between treatment arms during the 36 months of follow-up.[8]

Considering the low sensitivity of the MMSE to detect changes in specific neurocognitive domains and the finding of a multicenter study where neurocognitive disability in the memory domain was a prominent feature of irradiated LGG patients,[9] EORTC 22033-26033 incorporated comprehensive neurocognitive testing with a special focus on memory functioning in dedicated centers. Because of the extensive literature suggesting that brain RT is associated with white matter changes, neurocognitive deficits, and radiation necrosis,[9–11] we hypothesized that TMZ chemotherapy would be associated with a more favorable memory outcome over time. To discern whether RT affected memory outcome, we calculated the associations between RT brain target volumes and memory functioning at follow-up in the RT patient group.

Materials and Methods

Study Design and Participants

The EORTC–National Cancer Institute of Canada—Canadian Cancer Trials Group (NCIC CTG)–Trans Tasman

Radiation Oncology Group (TROG)–Medical Research Council (MRC)–Clinical Trial Unit (CTU) intergroup study, EORTC 22033-26033, was a prospective, randomized, open-label, phase III study among patients with histologically verified high-risk supratentorial diffuse (WHO grade II) LGG (astrocytoma and oligodendroglioma). The protocol compared primary postoperative treatment modalities, standard RT (28 × 1.8 Gy/d, 50.4 Gy) versus dose-dense chemotherapy (TMZ 75 mg/m^2 21/28 days × 12 cycles, Temodal, MSD/Merck & Co). A total of 78 medical centers and hospitals in 19 countries participated in the trial, which has been reported in detail previously.[7]

In the 8 participating centers listed in the acknowledgments, additional comprehensive prospective neurocognitive evaluation was performed. These investigations are the basis of the current report.

The study was approved by the institutional review boards and ethics committees of all participating centers and the respective authorities. The trial was completed according to the Declaration of Helsinki. All patients provided written informed consent.

In addition to LGG patients, normative data from a cohort of healthy controls were included in this study.

Procedures

Baseline evaluation (within 6 weeks before randomization and before the start of treatment) included contrast-enhanced MRI, a neurological evaluation (including HRQoL, overall neurocognitive functioning using the MMSE, comprehensive neurocognitive assessments, and assessment of seizure frequency if applicable), and complete blood counts and blood chemistry as well. RT volumes were defined based on T2 or fluid-attenuated inversion recovery MRI.

Health-related quality of life and overall neurocognitive (MMSE) functioning have been reported elsewhere.[8] Comprehensive neurocognitive assessments were performed in selected European centers with specific interest in this outcome measure of treatment efficacy. To ensure optimal compliance and to ensure standardization of testing by all personnel, guidelines and training for neurocognitive assessments were provided to participating centers.

Memory functioning was assessed using the Visual Verbal Learning Test (VVLT).[12] This version of the Rey Auditory Verbal Learning Test is a neuropsychological tool that is used for assessing episodic memory by providing scores for evaluating different aspects of memory. Briefly, the VVLT consists of a list of 15 words, which are visually presented to the patient 5 times, and then the patient is immediately asked to recall as many words as he/she remembers. This procedure is repeated for consecutive trials 1 to 5. After 20 minutes of interpolated testing, the patient is again asked to recall the words (delayed recall). Different indices of learning and memory capacity are derived from raw VVLT scores. These include VVLT Immediate Recall (the number of words recalled on trial 1), which reflects immediate word span under memory overload conditions; VVLT Total Recall (the total number of words recalled by trial 5 [ie, trial 1 + trial 2 + trial 3 + trial 4 + trial 5]), reflecting efficiency of the memory encoding process; VVLT Learning Capacity (the score of trial 5 recall minus the score of trial 1 recall); and VVLT Delayed Recall (the total number of words recalled after 20 minutes), reflecting efficiency of the memory consolidation process. After baseline, follow-up assessments were performed every 12 weeks using alternative forms to control for test–retest effects.

Per protocol, data collection was continued until progression, death, loss to follow-up, or if the patient refused further participation. Since inclusion of patients with progression would complicate interpretation of RT versus TMZ effects on memory function, only patients who did not progress during the observation period were selected for this analysis. Time windows for eligible follow-up assessment were set at 6 weeks before and 6 weeks after the scheduled follow-up assessment. Forms completed outside the eligible time windows or duplicates within a window were removed from the analysis.

Statistical Analyses

All statistical analyses were done by AJD with SPSS version 22.0 for Windows according to a prespecified statistical analysis plan with compliance cutoff set at 60%. Descriptive statistics were used to characterize the study sample. Student's *t*-tests for independent samples and chi-square tests were done to test for differences in sociodemographic and clinical characteristics between the patients who had RT and those who had TMZ. Memory performance at baseline in the patients who had RT compared with those who had TMZ was assessed with one-way ANOVA. A mixed model analysis was used to assess differences in memory performance over time between the patients who had RT and those who had TMZ. The mixed model included time point, treatment (ie, RT versus TMZ), and their interaction as fixed variables and participants as a random variable. Significant interactions were interpreted by performing post-hoc analyses using Bonferroni corrections for multiple comparisons. Within the RT patient group, bivariate correlations (Spearman's rho) for each combination of memory measures and gross target volume, clinical target volume, and planned target volume were calculated at successive follow-up time points.

To determine how LGG patients' memory differed from the healthy population, patients were individually matched to healthy controls based on age, level of education, and sex. A sample of 470 healthy controls was used in the matching process. Matching was done using fuzzy matching with exact matches for sex and educational level and 5-year variability for age. One-way ANOVA was executed for baseline and follow-up measurements using treatment arm as the predictor and the raw scores on the VVLT as the dependent variable. Significant differences between the groups were assessed with post-hoc analyses using Bonferroni corrections to correct for multiple comparisons. Statistical significance was set as at a *P*-value of <0.05 (two-tailed). Follow-up assessments for this study are ongoing and are registered at EudraCT (European Union Drug Regulating Authorities Clinical Trials Database), #2004-002714-11, and at ClinicalTrials.gov, #NCT00182819.

Role of the Funding Source

EORTC was the study sponsor and was responsible for overseeing the conduct and statistical analyses. The study was conducted as an intergroup study in collaboration with NCIC, CTG, TROG, MRC, and CTU. MSD/Merck & Co (formerly Schering-Plough) supported this study with an unrestricted educational grant to EORTC and by providing free TMZ for the study. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (MK), JD, TG, RS, and BGB had full access to all the data and had the final responsibility to submit for publication.

Results

Between December 6, 2005 and December 21, 2012, 4 hundred seventy-seven of 707 registered patients (67%) were randomly assigned to receive RT ($n = 240$) or TMZ ($n = 237$). Of this group, 98 patients (Table 1) from the 8 centers in 4 countries listed in the Acknowledgments underwent neuropsychological testing. No significant differences were found between the RT and TMZ groups in tumor, clinical, and sociodemographic characteristics. Before start of treatment at baseline, 52 patients scheduled for RT and 46 patients scheduled for TMZ were included. At 6 months follow-up, the compliance had dropped to 38 patients for TMZ and 40 patients for RT. At 12 months follow-up the compliance had dropped to 34 patients for TMZ and 35 patients for RT. At 18 months follow-up, the participation rate had dropped to only 54% of the original sample. For this reason, all analyses were performed up to 12 months follow-up. The primary study endpoints and quality of life analyses have previously been reported.[7,8]

Memory Performance at Baseline

At baseline, patients did not differ significantly between treatment arms on the major indices of memory functioning (VVLT Immediate Recall [$P = 0.532$], VVLT Total Recall [$P = 0.504$], VVLT Learning Capacity [$P = 0.728$], and VVLT Delayed Recall [$P = 0.900$]).

Memory Performance Over Time

Figure 1A shows the VVLT Immediate Recall scores at the various time points for the 2 patient groups. Mixed linear model analysis showed no statistically significant interaction effect of treatment over time at the group level on VVLT Immediate Recall, $F(2,150) = 2.82$, $P = 0.063$, indicating that immediate word span under memory overload conditions was not disproportionally affected by treatment with either RT or TMZ. Over time, there was a significant improvement in memory function—main effect of time on VVLT Immediate Recall $F(2,150) = 4.19$, $P = 0.017$—independently of treatment arm ($P = 0.172$).

Figure 1B shows the VVLT Total Recall scores by time point for the 2 treatment groups. Similar to the performance on trial 1 of the VVLT, analyses also showed a statistically significant main effect of time for the VVLT Total Recall scores $F(2,144) = 10.5$, $P < 0.001$, indicating that patients were able to recall increasingly more items over the 5 trials during the 12 months follow-up period. There was no main effect of treatment ($P = 0.583$). There was a statistically significant group by time interaction effect, $F(2,144) = 4.68$, $P = 0.011$. Post-hoc analyses using Bonferroni corrections to control for multiple comparisons detected no statistically significant differences between treatment groups at baseline ($P = 0.506$), at 6 months ($P = 0.146$) or at 12 months follow-up ($P = 0.515$). In the TMZ patient group the VVLT Total Recall score was significantly lower at baseline compared with 6 months ($P = 0.018$) or to 12 months ($P < 0.001$). No significant improvement in VVLT Total Recall score between 6 and 12 months ($P = 0.311$) was seen. VVLT Total Recall score in the RT group at baseline did not significantly differ from that at 6 months ($P = 0.436$) or at 12 months ($P = 0.188$). At 12 months the VVLT Total Recall score in the RT group was significantly higher when compared with 6 months ($P = 0.005$). Repeated measures analysis showed no effect of treatment over time on learning capacity, $F(2,148) = 1.278$, $P = 0.282$ (Figure 1C). There were no main effects of time ($P = 0.367$) or treatment ($P = 0.887$).

In line with the findings for learning capacity, repeated measures analysis showed no effect of treatment over time on VVLT Delayed Recall, $F(2,148) = 2.695$, $P = 0.071$ (Figure 1D), no main effects of time ($P = 0.057$) or treatment ($P = 0.294$).

In the irradiated patients there was no statistically significant association between RT gross target volume, clinical target volume, and planned target volume and memory outcome at 6 and 12 months follow-up (Tables 2 and 3). At baseline there were also no statistically significant associations between gross tumor volume and memory outcomes.

Comparison with Healthy Controls

To have an additional anchor of memory performance, the treatment groups were compared with healthy controls using one-way ANOVAs at baseline (see Table 4). The number of words recalled at trial 1 (VVLT Immediate Recall) differed significantly between the 3 groups ($P < 0.001$). Bonferroni post-hoc tests discerned that both the TMZ group ($P = 0.008$) and the RT group ($P = 0.003$) significantly differed from the control group at baseline; patients recalled *more* words at baseline compared with their matched healthy controls, possibly because of motivational factors. The number of words learned between trials 1 and 5 (VVLT Learning Capacity) differed significantly between the 3 groups ($P < 0.001$). Bonferroni post-hoc tests showed that both the TMZ group ($P < 0.001$) and the RT group ($P < 0.001$) significantly differed from the control group of healthy subjects at baseline, specifically, patients learned less words between trials 1 and 5. These differences are indicative of relatively mild impairment and are unlikely to have a major impact in the everyday life of patients. There was, however, no significant difference between the groups in the total number of words recalled from trial 1 through 5 (VVLT Total Recall) and recall of the items assessed 20 minutes after trial 5 (VVLT Delayed Recall).

Table 1. Patient characteristics

	Radiotherapy ($n = 52$)	Temozolomide ($n = 46$)	P*
Age, y	43 ($sd = 10$)	44 ($sd = 11$)	0.664
<40	22 (42.3%)	18 (39.1%)	0.749
≥40	30 (57.7%)	28 (60.9%)	
Sex			0.484
Male	19 (36.5%)	20 (43.5%)	
Female	33 (63.5%)	26 (56.5%)	
Years of education	13 ($sd = 4$)	14 ($sd = 4$)	0.172
WHO performance status			0.549
0	37 (71.2%)	31 (67.4%)	
I	14 (26.9%)	15 (32.6%)	
II	1 (1.9%)	0 (0%)	
Initial resection status (by investigator)			0.492
Biopsy	25 (48%)	22 (48%)	
Partial removal	20 (39%)	14 (30%)	
Total removal	7 (14%)	10 (22%)	
Tumor characteristics			
Tumor involving midline			0.603
No	39 (75%)	35 (76%)	
Midline shift	6 (12%)	6 (13%)	
Midline infiltration	5 (10%)	5 (11%)	
Both	2 (4%)	0 (0%)	
Hemisphere			0.269
Left	29 (56%)	21 (46%)	
Right	20 (38%)	18 (39%)	
Both	3 (6%)	7 (15%)	
Lobe			0.364
Frontal	17 (33%)	23 (50%)	
Occipital	1 (2%)	0 (0%)	
Parietal	2 (4%)	2 (4%)	
Temporal	13 (25%)	5 (11%)	
Multifocal	16 (31%)	14 (30%)	
Other	3 (6%)	2 (4%)	
WHO grade II histology			0.966
Astrocytoma	20 (39%)	17 (37%)	
Oligoastrocytoma**	13 (25%)	11 (24%)	
Oligodendroastrocytoma	19 (37%)	18 (39%)	
Molecular markers			
IDH1 or IDH2 mutation status			0.294
IDH1 or IDH2 mutated	41 (79%)	34 (74%)	
IDH wt	7 (14%)	4 (9%)	
Undetermined	4 (8%)	8 (17%)	
1p/19q status			0.926
1p/19q codeleted	14 (27%)	11 (24%)	
1p/19q non-codeleted	25 (48%)	25 (54%)	
Undetermined	11 (21%)	8 (17%)	
Missing	2 (4%)	2 (4%)	
Medication use			
Corticosteroids	6 (12%)	0 (0%)	*
Anti-epileptics	47 (90%)	45 (98%)	*

sd = standard deviation. *Chi-square tests cannot be calculated due to cells with less than the expected count of 5 cases. **Oligoastrocytomas have not been reclassified according to the 2016 guidelines.

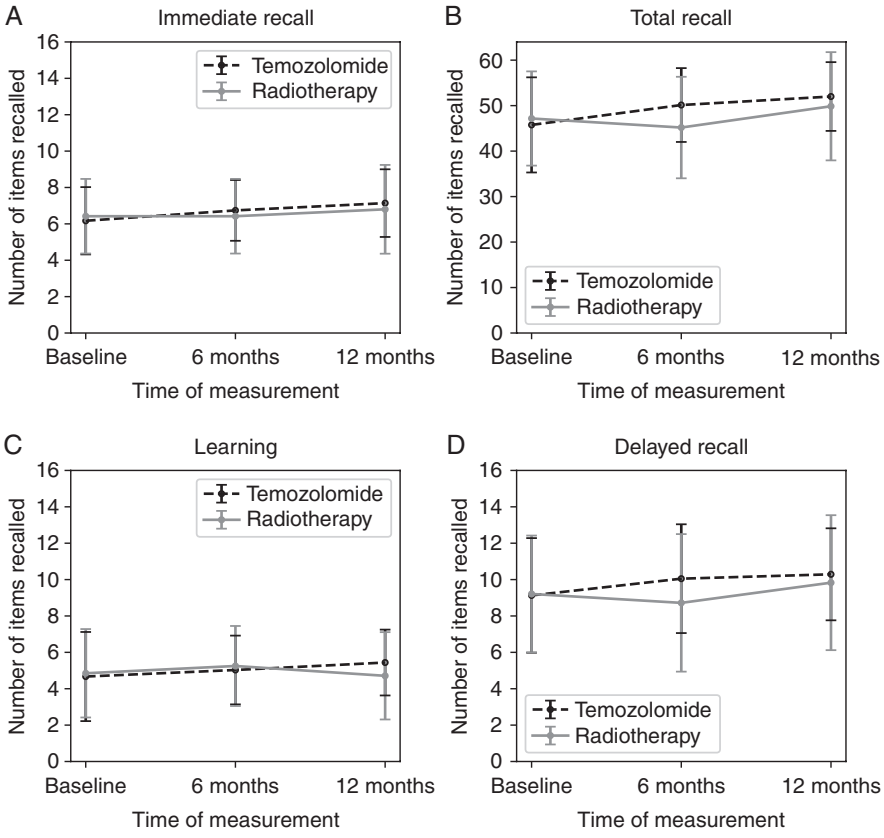

Fig. 1 Scoring profiles for the 2 treatment arms on the Visual Verbal Learning Test over time. (A) Immediate recall, the number of items recalled in trial 1. (B) Total recall, the total number of items recalled over trials 1–5. (C) Learning, the number of additional items learned between trials 1 and 5. (D) Delayed recall, the number of items recalled after a 20-minute delay.

Discussion

This study aimed at determining whether there is a difference in treatment-associated memory functioning between RT and TMZ. Based on our prior observations, our hypothesis was that irradiation may negatively affect memory functioning, while chemotherapy would be devoid of a detrimental neurological effect.[9] However, over the 12-month observation period we were unable to detect any significant difference in memory functioning between these treatment arms. This is in agreement with other studies demonstrating that cognitive decline might not be present 4 years after RT, and that it might take at least 5 years for cognitive decline to manifest itself after RT.[13,14]

Over time, patients in both arms showed improvement in immediate recall and the total number of words patients recalled by trial 5. Yet it remains unclear whether in LGG patients these gains in memory encoding efficiency also translate to improvements in instrumental activities of daily living (eg, telephone communication, financial management), as has been shown to be the case among HIV-infected adults.[15]

Concerning the total number of words patients recalled, it is interesting to note that irradiated patients needed more time to benefit from repeated presentation of information than patients using TMZ. This suggests an early but transient side effect of RT on memory: detailed analyses demonstrated that this effect results from delayed improvement in memory performance in RT patients between the baseline and 6 month evaluation in comparison to patients treated with TMZ. This finding is in line with studies among patients receiving whole-brain RT, where neurocognitive deterioration may be present as early as 3–4 months posttreatment.[16,17] Interestingly, in these patients, memory function was preferentially affected as well.[18,19]

Considering the radiosensitivity of the hippocampus and its hypothesized clinical implications,[20] it would be tempting to postulate that the delayed memory effect in the RT patients would be due to reduced neurogenesis in the subgranular zone of the hippocampus and the subventricular zone of the lateral ventricles.[21] Based on a study among adult patients with benign or low-grade brain tumors,[22] Gondi suggested that sparing of the hippocampus or rather the hippocampal neural stem-cell compartment, via highly conformal RT techniques

Table 2. Spearman's rho correlation coefficients at 6 months follow-up

		Gross Tumor Volume	Clinical Target Volume	Planning Target Volume
Immediate Recall	Spearman's rho	0.185	0.141	0.079
	sig. (2-tailed)	0.287	0.399	0.633
	N	35	38	39
Total Recall	Spearman's rho	–0.019	–0.007	–0.067
	sig. (2-tailed)	0.912	0.967	0.685
	N	35	38	39
Learning	Spearman's rho	–0.208	–0.254	–0.284
	sig. (2-tailed)	0.230	0.123	0.079
	N	35	38	39
Delayed Recall	Spearman's rho	–0.073	–0.103	–0.190
	sig. (2-tailed)	0.680	0.546	0.254
	N	34	37	38

Table 3. Spearman's rho correlation coefficients at 12 months follow-up

		Gross Tumor Volume	Clinical Target Volume	Planning Target Volume
Immediate Recall	Spearman's rho	–0.018	–0.013	–0.007
	sig. (2-tailed)	0.926	0.943	0.968
	N	30	33	34
Total Recall	Spearman's rho	–0.188	–0.113	–0.168
	sig. (2-tailed)	0.320	0.530	0.342
	N	30	33	34
Learning	Spearman's rho	0.036	–0.038	–0.095
	sig. (2-tailed)	0.850	0.834	0.591
	N	30	33	34
Delayed Recall	Spearman's rho	–0.194	–0.165	–0.249
	sig. (2-tailed)	0.305	0.358	0.155
	N	30	33	34

Table 4. Baseline comparison between treatment groups and healthy controls

	TMZ	RT	Healthy Controls	*P*
VVLT Immediate Recall (trial 1)	6.2 (0.3)	6.3 (0.3)	5.2 (0.2)	<0.001
VVLT total recall (trial 1 to 5)	46.5 (1.5)	46.9 (1.3)	45.7 (1.0)	0.754
VVLT Learning Capacity (trials 5-1)	4.8 (0.3)	5.0 (0.3)	6.4 (0.2)	<0.001
VVLT Delayed Recall	9.1 (0.5)	92 (0.4)	9.9 (0.3)	0.190

might prevent long-term memory impairment. In a previous study we found effects of conventional, non-hippocampal-sparing RT specifically on memory functioning 6 years after initial diagnosis.[9] However, when a subsample was again tested at a mean of 12 years after first diagnosis,[23] we found a progressive decline in attentional, but not in memory, functioning in irradiated patients. In our opinion, this lack of a memory decline suggests that other mechanisms, like time-dependent reorganization of the neuronal circuitry underlying long-term memory storage, might also play a role in the long-term outcome.[24,25]

A number of dosimetry studies recently evaluated the radiosensitivity of cortical regions important for higher-order cognition, like memory, executive function, and attention,[26] and found entorhinal (memory) and inferior

parietal (attention/memory) areas of the cerebral cortex to be most vulnerable to radiation-related atrophy. Cortical thinning increased with the total dose, but interestingly varied depending on the cortical location.[26] Our earlier[23] findings that LGG patients who received RT in the long run have deficits in several higher-order domains of neurocognitive functioning (ie, attentional, executive, and information processing) support the notion that the effects of RT likely are not limited to the hippocampus and the memory domain. In this light, a cortex-sparing approach based on the finding that RT doses above 28.6 Gy resulted in a greater than 20% probability of cortical atrophy[27] is promising but needs to be confirmed by assessing their survival and clinical benefit in large numbers of patients. Evidently, several other factors may explain long-term neurocognitive impairment observed following brain RT.[23]

Despite the large number of papers addressing the effects of RT, the psychometric quality of most papers is limited. Unequivocally interpretable information on the potential effects of TMZ on neurocognitive functioning in LGG patients is lacking. Toxicity of TMZ is in general acceptable at commonly used doses,[28] although elderly patients potentially run higher risks of developing neurocognitive deficits during the concomitant course of the Stupp regimen.[29]

Our study is the first prospective randomized, multicenter, head-to-head comparison of the effect of these 2 treatment modalities in LGG patients. Although only a subgroup of patients in selected centers could undergo repeat detailed neurocognitive assessments, our dataset is on a homogeneous group of patients with histologically verified and centrally reviewed diffuse LGG. Other strengths were the prospective study design with prespecified time points for measurements of neurocognitive functioning. However, our study is also subject to the limitations of brain tumor trials incorporating assessments of neurocognitive functioning, the most important being missing data due to insufficient compliance. Common reasons for missing data usually are administrative failure, patient refusal, and poor health status of the patient. Another limitation is that only memory functioning has been studied. Although the strongest impact of RT was expected on memory functioning because of hippocampal damage, it would be interesting to investigate the effect of treatment type on other cognitive domains such as executive functioning and attention.

In conclusion, in the first year, the effect of TMZ chemotherapy or RT on memory functioning did not differ in patients with high-risk LGG.

Keywords

chemotherapy | low-grade glioma | memory functioning | radiotherapy

Funding

EORTC trial 22033–26033 was supported in part by MSD/Merck & Co (formerly Schering-Plough), the Canadian Cancer Society, the Swiss Cancer League, the UK National Institutes of Health Research, the Australian National Health and Medical Research Council, the US National Cancer Institute, and the European Organization for Research and Treatment of Cancer Research Fund.

Acknowledgments

Patients for this side study were recruited from Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; Erasmus MC Cancer Institute, Rotterdam, the Netherlands; APHP Hôpitaux Universitaires La Pitié Salpêtrière; Sorbonne Université; Paris, France; Haaglanden Medical Centre, The Hague, the Netherlands; Centre Eugène Marquis, Rennes, France; Maastricht University Medical Centre, Maastricht, the Netherlands; Rambam Health Care Campus, Oncology Institute, Haifa, Israel; Hospital Duran i Reynals, L'Hospitalet de Llobregat, Barcelona, Spain. This trial was partly supported by an unrestricted educational grant and free supply of Temozolomide drug by MSD/Merck & Co (formerly Schering-Plough). We would like to thank the Canadian Cancer Society, the Swiss Cancer League, the UK National Institutes of Health Research, the Australian National Health and Medical Research Council, the US National Cancer Institute, and the EORTC for their support. We like to thank all colleagues involved in neurocognitive testing, specifically G. Costa, M. Eland, D. Coule, and I. van der Heuvel.

Conflict of interest statement. MK reports personal fees from Hoffmann La Roche, outside the submitted work. BGB reports personal fees from Merck Sharp & Dohme (MSD), outside the submitted work. MJvdB reports grants from Roche and Abbvie, and personal fees from Roche, Abbvie, Merck AG, Novocure, Cavion, Bristol-Myers Squibb, Novartis, and Actelion, outside the submitted work. MJBT reports personal fees from Hoffmann La Roche, outside the submitted work. AJD, JCB, KH-X, JCR, MBH, EV, DBPE, TT-S, AL, VF, VG, TG, and AFH declare no competing interests.

Authorship statement. Design of trial concept and protocol: BGB, RS. Design concept and protocol neurocognitive testing: MK. Principal investigators for trial coordination: BGB, RS. Statistical analysis: AJD. Data collection and interpretation: all authors. Manuscript writing, reviewing and approval final version of the manuscript: all authors.

References

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131(6):803–820.
2. Sanai N, Berger MS. Surgical oncology for gliomas: the state of the art. *Nat Rev Clin Oncol.* 2018;15(2):112–125.
3. van den Bent MJ, Afra D, de Witte O, et al; EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet.* 2005;366(9490):985–990.
4. Shaw EG, Wang M, Coons SW, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. *J Clin Oncol.* 2012;30(25):3065–3070.
5. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med.* 2016;374(14):1344–1355.
6. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol.* 2014;32(6):535–541.
7. Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1521–1532.
8. Reijneveld JC, Taphoorn MJB, Coens C, et al. Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1533–1542.
9. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet.* 2002;360(9343):1361–1368.
10. Surma-aho O, Niemelä M, Vilkki J, et al. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. *Neurology.* 2001;56(10):1285–1290.
11. Olson JD, Riedel E, DeAngelis LM. Long-term outcome of low-grade oligodendroglioma and mixed glioma. *Neurology.* 2000;54(7):1442–1448.
12. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment.* New York, NY: Oxford University Press; 2004.
13. Armstrong CL, Hunter JV, Ledakis GE, et al. Late cognitive and radiographic changes related to radiotherapy: initial prospective findings. *Neurology.* 2002;59(1):40–48.
14. Vigliani MC, Sichez N, Poisson M, Delattre JY. A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults: 4-year results. *Int J Radiat Oncol Biol Phys.* 1996;35(3):527–533.
15. Fazeli PL, Doyle KL, Scott JC, et al; HIV Neurobehavioral Research Program (HNRP) Group. Shallow encoding and forgetting are associated with dependence in instrumental activities of daily living among older adults living with HIV infection. *Arch Clin Neuropsychol.* 2014;29(3):278–288.
16. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA.* 2016;316(4):401–409.
17. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037–1044.
18. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol.* 2004;22(1):157–165.
19. Laack NN, Brown PD. Cognitive sequelae of brain radiation in adults. *Semin Oncol.* 2004;31(5):702–713.
20. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. *Lancet.* 2009;374(9701):1639–1651.
21. Gibson E, Monje M. Effect of cancer therapy on neural stem cells: implications for cognitive function. *Curr Opin Oncol.* 2012;24(6):672–678.
22. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys.* 2013;85(2):348–354.
23. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8(9):810–818.
24. Bontempi B, Laurent-Demir C, Destrade C, Jaffard R. Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature.* 1999;400(6745):671–675.
25. Lisman J, Morris RG. Memory. Why is the cortex a slow learner? *Nature.* 2001;411(6835):248–249.
26. Karunamuni R, Bartsch H, White NS, et al. Dose-dependent cortical thinning after partial brain irradiation in high-grade glioma. *Int J Radiat Oncol Biol Phys.* 2016;94(2):297–304.
27. Karunamuni RA, Moore KL, Seibert TM, et al. Radiation sparing of cerebral cortex in brain tumor patients using quantitative neuroimaging. *Radiother Oncol.* 2016;118(1):29–34.
28. Pouratian N, Gasco J, Sherman JH, Shaffrey ME, Schiff D. Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas. *J Neurooncol.* 2007;82(3):281–288.
29. Saito K, Mukasa A, Narita Y, et al. Toxicity and outcome of radiotherapy with concomitant and adjuvant temozolomide in elderly patients with glioblastoma: a retrospective study. *Neurol Med Chir (Tokyo).* 2014;54(4):272–279.