Memory in low-grade glioma patients treated with radiotherapy or Temozolomide. A correlative analysis of EORTC study 22033-26033

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**Conflict of interest**

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**

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.
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 radiotherapy 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, gender, 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 radiotherapy patients (group by time; $p = 0.011$). Memory functioning was not associated with radiotherapy gross, clinical, or planned target volumes.

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

Key words: low-grade glioma – radiotherapy – chemotherapy – memory functioning
Key Points:

1. In high-risk low-grade glioma patients radiotherapy does not have a deleterious effect on memory function when compared to Temozolomide chemotherapy at one year.

2. When considering the first year after treatment, the choice for either radiotherapy or Temozolomide chemotherapy does not need to be based on their neurotoxic profiles concerning memory functioning.

Importance of the study

This is the first face-to-face study comparing memory effects of radiotherapy vs. Temozolomide 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 radiotherapy effects.
Introduction

Low-grade gliomas (World Health Organisation (WHO) grade II astrocytomas and oligodendrogliomas,) are a heterogeneous group of primary brain tumors commonly occurring in the third and fourth 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 IDH1 or IDH2 gene are commonly seen in low-grade gliomas (LGG). 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 to IDHmt 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 post-operative (adjuvant) RT in LGG is less clearly defined. In a large EORTC study initiated in the 1980’s,\(^3\) 314 LGG patients were randomized to immediate versus deferred RT. Although early RT allowed for delaying the time to tumor progression, there was no OS difference between treatment groups. In a more recent RTOG study,\(^4\) 251 high-risk LGG patients received RT, and were subsequently randomized to receive or not up to 6 cycles of 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 to 69) and 40% (95% CI, 31 to 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 year 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 PFS without excessive neurocognitive decline over RT alone. In EORTC 22033-26033 where high-risk LGG patients were randomized to treatment with either Temozolomide (TMZ) or RT, there was no difference in health-related quality of life (HRQOL) and MMSE between treatment arms during the 36 months’ follow-up.

Considering the low sensitivity of the MMSE to detect changes in specific neurocognitive domains and the finding of a multi-center study where neurocognitive disability in the memory domain was a prominent feature of irradiated LGG patients, 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 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 3 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 x 1.8 Gy/d, 50.4 Gy) versus dose-dense chemotherapy (Temozolomide 75 mg/m$^2$ 21/28 days x 12 cycles [TMZ], Temodal®, MSD/Merck & Co., Kenilworth, NJ). 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 health-related quality of life, overall neurocognitive functioning using the Mini-Mental State Examination [MMSE], comprehensive neurocognitive assessments, and assessment of
seizure frequency if applicable), and complete blood counts and blood chemistry as well. RT treatment volumes were defined based on T2 or fluid-attenuated inversion recovery (FLAIR) MRI.

Health-related quality of life and overall neurocognitive (MMSE) functioning have been reported elsewhere. 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). 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 is visually presented to the patient five times, and then the patient is immediately asked to recall as many as words as he/she remembers. This procedure is repeated for 5 consecutive trials (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 (i.e. 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 vs. 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 pre-specified statistical analysis plan with compliance cut-off 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 analysis of variance (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 (i.e. RT vs. 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 gender. A sample of 470 healthy controls was used in the matching process. Matching was done using fuzzy matching with exact matches for gender 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 using post-hoc analyses using Bonferroni corrections to correct for multiple comparisons. Statistical significance was set as at a p-value of less than 0.05 (two-tailed). Follow-up assessments for this study are ongoing and is registered at EudraCT, number 2004-002714-11, and ClinicalTrials.gov, number 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 Temozolomide 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 Dec 6, 2005, and Dec 21, 2012, 477 of 707 registered patients (67%), were randomly assigned to receive RT (RT, n=240) or TMZ (n=237). Of this group, 98 patients (Table 1) from the 8 centers in 4 countries listed in the acknowledgements 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 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 two 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 $F(2,150) = 4.19, p = 0.017$) independent of treatment arm ($p = 0.172$).

Figure 1B shows the VVLT Total Recall scores by time point for the two 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 ($p = 0.146$) or 12 months follow-up ($p = 0.515$). In the TMZ patient group the VVLT total recall score was significantly lower at baseline compared to 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 to 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 measure analysis showed no effect of treatment over time on VVLT Delayed Recall (see Figure 1D; $F(2,148) = 2.695, p = 0.071$), no main effects of time ($p = 0.057$) or treatment ($p = 0.294$).

-Figure 1-
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 month follow-up (see tables 2 and 3). At baseline there were also no statistically significant associations between gross tumor volume and memory outcomes.

- Table 2 –

- Table 3-

Comparison with healthy controls

To have an additional anchor of memory performance, the treatment groups were compared to healthy controls using one-way ANOVAs at baseline (see Table 4). The number of words recalled at trial one (VVLT Immediate Recall) differed significantly between the three 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 to their matched healthy controls, possibly because of motivational factors. The number of words learned between trial one and five (VVLT Learning Capacity) differed significantly between the three 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 trial one and five. These differences are indicative of relatively mild impairment and unlikely to have a major impact in 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 4-
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. However, over the 12-months observation period we were unable to detect any significant difference in memory functioning between these treatment arms. This is in agreement with other studies that demonstrated cognitive decline might not be present four years after RT, and that it might take at least five years for cognitive decline to manifest itself after RT treatment.  

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 (IADL, e.g. telephone communication, financial management) as has been shown to be the case among HIV-infected adults.  

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 (WBRT) where neurocognitive deterioration may be present as early as 3–4 months post WBRT.\textsuperscript{16,17} Interestingly, in these patients, memory function was preferentially affected as well.\textsuperscript{18,19}

Considering the radiosensitivity of the hippocampus and its hypothesized clinical implications,\textsuperscript{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.\textsuperscript{21} Based on a study among adult patients with benign or low-grade brain tumours,\textsuperscript{22} Gondi suggested that sparing of the hippocampus or rather the hippocampal neural stem-cell compartment, via highly conformal RT techniques 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.\textsuperscript{9} However, when a subsample was again tested at a mean of 12 years after first diagnosis,\textsuperscript{23} we found a progressive decline in attentional, but not in memory functioning in irradiated patients. This lack of a memory decline in our opinion 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{26} Our earlier\textsuperscript{23}
findings that LGG patients who received RT in the long-run have deficits in several higher-order domains of neurocognitive functioning (i.e. 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 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 radiotherapy.

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, although elderly patients potentially run higher risks of developing neurocognitive deficits during the concomitant course of the Stupp regimen.

Our study is the first prospective randomized, multicenter, head-to-head comparison of the effect of these two 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 Temozolomide chemotherapy or radiotherapy on memory functioning did not differ in patients with high-risk low-grade glioma.
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Figure captions:

**Figure 1.** Scoring profiles for the two 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 trial 1-5; C: learning, the number of additional items learned between trial 1 and 5; D: delayed recall, the number of items recalled after a 20-minute delay.
|                      | Radiotherapy (n=52) | Temozolomide (n=46) | P*  |
|----------------------|---------------------|---------------------|-----|
| **Age (years)**      | 43 (sd = 10)        | 44 (sd = 11)        | 0.664|
| <40                  | 22 (42.3%)          | 18 (39.1%)          | 0.749|
| ≥40                  | 30 (57.7%)          | 28 (60.9%)          |     |
| **Gender**           |                     |                     | 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** |                   |                     | 0.603|
| Tumor involving midline |                   |                     |     |
| 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 | Multifocal | Other |
|------------|----------|------------|-------|
|            | 13 (25%) | 16 (31%)   | 3 (6%) |

**WHO grade II Histology**

| Tumour Type        | Temporal | Multifocal | Other |
|--------------------|----------|------------|-------|
| Astrocytoma        | 20 (39%) | 17 (37%)   |       |
| Oligoastrocytoma** | 13 (25%) | 11 (24%)   |       |
| Oligodendroastrocytoma | 19 (37%) | 18 (39%)   |       |

**Molecular markers**

| IDH1 or IDH2 mutation status | Temporal | Multifocal | Other |
|------------------------------|----------|------------|-------|
| IDH1 or IDH2 mutated         | 41 (79%) | 34 (74%)   |       |
| IDH wt                       | 7 (14%)  | 4 (9%)     |       |
| Undetermined                 | 4 (8%)   | 8 (17%)    |       |

| 1p/19q status                | Temporal | Multifocal | Other |
|------------------------------|----------|------------|-------|
| 1p/19q co-deleted            | 14 (27%) | 11 (24%)   |       |
| 1p/19q non-co-deleted        | 25 (48%) | 25 (54%)   |       |
| Undetermined                 | 11 (21%) | 8 (17%)    |       |
| Missing                      | 2 (4%)   | 2 (4%)     |       |

**Medication use**

| Medication         | Temporal | Multifocal | Other |
|--------------------|----------|------------|-------|
| Corticosteroids    | 6 (12%)  | 0 (0%)     |       |
| Antiepileptics     | 47 (90%) | 45 (98%)   |       |

**Table 1:** patient characteristics. *Chi-Square Tests cannot be calculated due cells with less than the expected count of 5 cases. sd=standard deviation. **Oligoastrocytomas have not been reclassified according to the 2016 guidelines.*
|                      | Gross Tumour 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 2: Spearman’s Rho correlation coefficients at 6 months follow-up*
|                  | Gross Tumour 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 3: Spearman’s Rho correlation coefficients at 12 months follow-up*
|                         | 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 (trial 5-1) | 4.8 (0.3)    | 5.0 (0.3)    | 6.4 (0.2)        | < 0.001 |
| VVLT Delayed Recall      | 9.1 (0.5)    | 9.2 (0.4)    | 9.9 (0.3)        | 0.190 |

*Table 4: Baseline comparison between treatment groups and healthy controls*
