# Could upfront temozolomide chemotherapy postpone the intervene of radiotherapy in young patients with high-risk low-grade gliomas?

**Zeyang Li**
Fudan University Huashan Hospital Department of Neurosurgery
**Shiwen Yuan**
Butler Hospital
**Hong Chen**
Huashan Hospital Fudan University
**Dongxiao Zhuang**
Fudan University Huashan Hospital Department of Neurosurgery
**Junfeng Lu**
Fudan University Huashan Hospital Department of Neurosurgery
**Fangyuan Gong**
Fudan University Huashan Hospital Department of Neurosurgery
**Abudumijit Aibaidula**
Fudan University Huashan Hospital Department of Neurosurgery
**Zhifeng Shi**
Fudan University Huashan Hospital Department of Neurosurgery
**Shuai Wu**
Fudan University Huashan Hospital Department of Neurosurgery
**Qihao Guo**
Shanghai 6th Peoples Hospital Affiliated to Shanghai Jiaotong University School of Medicine
**Yanyan Song** ( syyssmu@126.com )
Shanghai Jiao Tong University School of Medicine
**Jinsong Wu** ( wjsongc@126.com )
Fudan University Huashan Hospital Department of Neurosurgery

**Research article**

**Keywords:** Low grade gliomas, Temozolomide, Chemotherapy, Cognition

**Posted Date:** December 31st, 2019

**DOI:** https://doi.org/10.21203/rs.2.19773/v1

# Abstract

### Background

Low-grade gliomas that involves eloquent areas are difficult to be removed totally. Standard strategies for these young patients are radiotherapy and chemotherapy after maximum safe resection. Radiotherapy always brings cognitive impairments. We wonder whether temozolomide chemotherapy can postpone the intervene of radiotherapy to protect cognitive function.

### Methods

Patients underwent temozolomide chemotherapy (75mg/$m^2$/day for 21 days per 28-day for 6 cycles) and were followed up by MRI and cognitive function evaluation. Primary endpoints are objective response rate (ORR), and secondary endpoints are intensity of response (IOR), duration of response (DOR), cognitive function results and the safety of chemotherapy.

### Results

65 patients were recruited with a median follow-up of 39.6 months, and ORR was 37/65(56.92%). IDH mutant patients had better ORR than IDH wildtype patients (64.29% vs 11.11%, p=0.004), and IOR of IDH mutant tumors was more obvious (p=0.023). IDH-mutant group had longer DOR than IDH-wildtype group (median DOR, 52.4 vs 25.8 months; log-rank p=0.0007; HR, 4.269; 95%CI, 3.411 - 47.35), and 1p/19q codeletion group had a longer DOR than 1p/19q retain group (median DOR, 52.4 vs 37.5 months; log-rank p=0.049; HR, 2.369; 95%CI, 1.012 - 5.397). Cognitive function results showed improvement in cognitive function at early stage compared with radiotherapy.

### Conclusion

IDH mutation was a predictive factor for better temozolomide response. Cognitive function evaluation proved that temozolomide chemotherapy could avoid cognitive impairments at early stage. We propose that young patients with IDH mutation can use upfront chemotherapy to postpone radiotherapy until progression to avoid potential cognitive impairments.


# Background

Gliomas can be classified into 3 categories according to treatment strategy and prognosis.[1] The first category is tumors with early recurrence and poor prognosis after operation such as glioblastoma, and early radiotherapy and chemotherapy are needed after operation. The second category is tumors with good prognosis, 10-year survival rate, such as pilocytic astrocytoma and pleomorphic xanthoastrocytoma. Only regular follow-up is needed after operation. The last category is advanced recurrent tumors such as low-grade gliomas. National Comprehensive Cancer Network (NCCN) points out that for LGGs patients in high-risk group patients (below 40 years old and subtotal resection), standard strategies are maximum safe resection with radiotherapy and adjuvant chemotherapy, but didn't address the question of whether patients need adjuvant therapy immediately after diagnosis because of RTOG 9802[2].

EORTC 22845 has shown that compared with delayed radiotherapy, early radiotherapy prolongs PFS, but does not prolong OS significantly[3]. Worse still, Radiotherapy brings significant treatment-related side effects as cognitive dysfunction in the meantime of its controlling tumor recurrence according to a 12-year follow-up for patients below 40 years old[4]. A 10-year follow-up suggested that greater dose of radiotherapy was associated with a greater cognitive decline[5].

Temozolomide (TMZ) is one of the first line regimens for LGGs chemotherapy[6], but whether temozolomide has neurotoxicity still remains unknown. The results of the EORTC 22033-26033 has shown that compared with temozolomide chemotherapy, radiotherapy didn't prolong PFS in LGGs patients significantly, and OS outcomes still remains unknown[7]. EORTC 22033-26033 also has not figured out the intervention time of radiotherapy and the sequence of intervention for radiotherapy and chemotherapy. For residual tumors that can't be totally removed, if upfront chemotherapy can decrease the burden of the tumor, it will contribute to improving curative effect of radiotherapy theoretically.

Because young patients need to avoid cognitive impairment, the intervention of postoperative radiotherapy immediately is questionable. We wonder that chemotherapy can be used to postpone the intervention of radiotherapy to avoid cognitive impairment at early stage. And IDH mutation is considered to be a prognostic indicator identifying a subgroup of gliomas with an improved survival, but whether a predictive factor related to a better temozolomide response is questionable[8, 9].

Our study focused on LGGs patients under 40 years old with non-totally resected tumors in the eloquent areas, and tested temozolomide response. We focused on three questions: 1) which groups/biomarkers favor LGGs patients to higher temozolomide chemotherapy sensitivity and longer survival; 2) how does neurocognitive function change with temozolomide chemotherapy; 3) does chemotherapy better protects cognitive function than radiotherapy and can we use temozolomide to postpone the intervene of radiation to prolong survival and delay cognitive impairments.

We therefore initiated an interventional study (NCT02209428) to validate whether young patients with non-totally resected LGGs in eloquent areas could be controlled by upfront temozolomide, and whether radiotherapy could be postponed until progression to avoid potential cognitive impairments. We anticipate our results can enhance and further facilitate the decision-making process in creating an individualized therapeutic approach for these young LGGs patients to ensure the high-quality survival and the healthy social life.

# Methods

### Study design and participants

NCT02209428 was initiated in 2014, as a prospective, one arm, open-label study in a single tertiary specialized center (Glioma Surgery Division, Neurological Surgery Department of Huashan Hospital, Fudan University) in Shanghai, China. The selection criteria were: 1) 18 years < age ≤ 40 years, both genders. 2) No neurologic cognitive deficits (MMSE ≥ 27), no psychiatric abnormalities before surgery, pre-operative KPS ≥ 80. 3) Tumor located in eloquent areas or deeply located nuclei, rendering radiological complete resection inapplicable. [10] 4) Post-operative histological pathology confirms LGGs (astrocytomas, oligodendrogliomas, or oligoastrocytomas, 2007 WHO classification Grade II). 5) No contraindications to temozolomide chemotherapy. 6) Informed consent to temozolomide chemotherapy. They were informed and provided proof of their written agreement to participate to the present study. The study was approved by the Huashan Hospital's institutional review board.

### Chemotherapy

Chemotherapy was started within 2 weeks to 3 months after surgery and continued for 6 cycles. Metronomic temozolomide regimen[11] was administrated from day 1 to 21 at a dose of 75 mg/m2/day, repeated every 28 days. (**Additional file 1**) Toxicity and adverse effects were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC v4.0).

### Follow up

All patients were evaluated by an independent neurosurgeon and a neuropsychologist, before and after operation, every 2 months during the course of chemotherapy, every 3 months during the half year after chemotherapy and later on every 6 months until progression.

The baseline evaluation and follow-up evaluation included 2 parts: 1) MRI for tumor volume.. Real-time calculation of dynamic tumor volume (Osirix) on T2/FLAIR sequence was performed and objective response was assessed according to RANO standard[12]. 2) Neuropsychological evaluation. Neuropsychological evaluation was performed using comprehensive neurocognitive battery in Huashan hospital, including Learning Test-Revised (HVLT-R), Trail Making Test time A and B (TMT time A and B), Mini-Mental State Examination (MMSE), Multilingual aphasia examination controlled oral word association (COWAT).

### Surgical procedure

All patients underwent multi-modality navigated tumor resection: "Maximum Safely Resection" realized with awake craniotomy and electrophysiological mapping[13, 14].

### Pathological and molecular diagnosis

Pathological diagnosis of tumor tissue from surgery confirms LGGs. In August 2017, we centrally reviewed all enrolled tumor pathology information and renewal them as 2016 WHO classification of tumors of the central nervous system according to the test of IDH1/2[15, 16], 1p/19q co-deletion, TP53 and ATRX[17].

### Endpoints

The primary endpoint is objective response rate (ORR), which is defined as response and no response. According to RANO standard[12], response includes complete response (CR), partial response (PR) and minor response (MR), while no response includes stable disease (SD) and disease progression (PD). Secondary endpoints are as follows: 1) Intensity of response (IOR) is defined as the ratio of

maximum volume reduction to residual volume after operation. 2) Duration of response (DOR) is used instead of progression-free survival and defined as the time between the date of operation and the date of treatment escape or relapse.[18] 3) Malignant progression-free survival (MPFS), cognitive function results and the safety of chemotherapy.

### Statistical analysis

We enrolled 11 patients as the pilot study, and the response rate of IDH mutant group and IDH wildtype group is 61% and 17% respectively. IDH mutant accounts for 80% of low-grade gliomas, and we estimated 54 patients were sufficient to provide 80% power and a significance level of 5% to detect difference in ORR between IDH mutant group and IDH wild-type group. Dynamic assessment of sample size was sufficient to reflect the trial efficacy, and thus adjusted the sample size. In our study, no patients were lost for a specially-assigned person reminding them of regular follow-ups in our hospital. Because patients who met the admission criteria and were willing to receive temozolomide chemotherapy alone were rare, especially for IDH wild-type LGGs patients, and in order to better explore the efficiency of chemotherapy, we finally enrolled 54 patients and had analysis of 65 patients including 11 patients in pilot study (**Fig 1**). Comparisons for ORR were performed using the Fisher's exact test, which was defined as response and no response. Unpaired nonparametric test (Wilcoxon-Mann-Whitney U test) was performed for comparison of IOR between groups, and logistic regression for correlation between tumors residual volume and ORR. Kaplan-Meier method are used for DOR. Repeated mixed model was used for comparison among cognitive test scores, which could handle missing values. And unpaired t test with Welch's correction was used for comparing our cognitive test data with that in historical literature. For all analyses, a P value of less than 0.05 was regarded as significant. Statistical analysis was done with SPSS version 19.0 (SPSS Inc. at IBM Company) and charted with GraphPad Prism version 6.0 (GraphPad Software).

This study is registered at ClinicalTrials.gov, number NCT02209428.

## Results

Up to December 30th 2019, 65 patients receiving adjuvant temozolomide only were recruited with a median follow-up of 39.6 months (**Fig 1**), and 50 patients had long-term evaluation with extensive serial neuropsychological batteries. The patients' basic characteristics were shown on Table 1.

Overall ORR was 37/65(56.92%), including 22/65 (33.85%) PR and 15/65 (23.07%) MR. No response rate was 28/65 (43.08%), including 2/65 (3.08%) SD and 26/65(40.00%) PD. No complete responses occurred. IDH mutant patients had a more obvious ORR compared with IDH wildtype patients (64.29%vs 11.11%, Fisher's exact p=0.004). There was no evidence to prove correlation between ORR and other biomarkers such as 1p/19q codeletion, MGMT promoter methylation, ATRX loss and TERT mutation (p=0.112, 0.291, 0.732 and 0.245 respectively). IOR of IDH mutant patients was more obvious than that of IDH wildtype patients (Mann-Whitney U test p=0.023), and IOR of 1p/19q codeletion patients was more obvious than that of 1p/19q retain patients (Mann-Whitney U test p=0.002). There was no statistically difference in IOR for MGMT promoter methylation, ATRX loss and TERT mutation (p=0.188, 0.464 and 0.577 respectively). Yet there is no significant correlation between residual volume percentage and ORR (p=0.594).

According to 2016 WHO Classification, diffuse astrocytoma, IDH-mutant and oligodendroglioma, IDH-mutant and 1p/19q-codeleted can be classified as IDH-mutant group, and diffuse astrocytoma, IDH-wildtype is IDH-wildtype group. We found that IDH-mutant group had longer DOR than IDH-wildtype group (median DOR, 52.4 vs 25.8 months; log-rank p=0.0007; HR, 4.269; 95%CI, 3.411 - 47.35). And 1p/19q codeletion group also had a longer duration of response than 1p/19q retain group (median DOR, 52.4 vs 37.5 months; log-rank p=0.049; HR, 2.369; 95%CI, 1.012 - 5.397). As for histological features, both diffuse astrocytoma, IDH-mutant and oligodendroglioma, IDH-mutant and 1p/19q-codeleted had a longer duration of response than diffuse astrocytoma, IDH-wildtype ( median DOR, log rank p, HR, 95%CI: 44.5 vs 25.8 months, 0.004, 3.421; 1.807 – 19.38; 52.4 vs 25.8 months, 0.0003, 5.449; 3.128 – 43.67 ). (**Fig 2**)

Malignant progression rate for IDH-mutant was 6/34(17.65%), and that for diffuse astrocytoma, IDH-wildtype was 44.44%. Malignant progression rate for oligodendroglioma, IDH-mutant and 1p/19q-codeleted patients was 2/22(9.09%). Oligodendroglioma, IDH-mutant and 1p/19q-codeleted also had a longer MPFS than diffuse astrocytoma, IDH-wildtype (median MPFS, unreached vs 43.7 months; log-rank p=0.025; HR, 5.573; 95%CI, 1.299 - 48.96). And MPFS for diffuse astrocytoma, IDH-mutant was unreached (**Fig 2**). Follow-up information of 4 patients were arranged as illustrated cases. (**Additional file 2**)

50 of 65 patients who only received temozolomide chemotherapy had long-term evaluation with extensive serial neuropsychological batteries. (**Fig 3**) We analyzed the cognitive data at 5 time points: before chemotherapy, after chemotherapy, 1 year after surgery, 2 years after surgery and 3 years after surgery, and results are as follows.(**Table 2**) Mean HVLT-R score for each group is 14.5, 17.6, 20.5, 22.4,

23.9, and scores of 2 and 3 years after surgery were statistically higher than those of 1 year after surgery and before. Although the mean HVLT-R score of 3 years after surgery is higher than that of 2 years after surgery, there was no statistically difference. There was no statistical difference in HVLT-R percentage of retention among every group, which means there is no learning effect affects validity. For TMT time A, mean time consuming for each group is 54.4s, 37.8s, 37.0s, 31.8s and 31.5s. For TMT time B, mean time consuming for each group is 180.7s, 107.2s, 92.0s, 94.1s and 80.1s. Both TMT time A and B showed during follow-up, the time to complete tests decreased gradually, and the patients completed tests in much shorter time comparing to their performance before chemotherapy. For COWAT, the mean number of animal naming for each group is 13.5, 16.3, 17.8, 18.4 and 19.1, and that for furniture naming is 12.7, 14.9, 16.4, 16.8 and 17.5. At the same time, the mean number for switch naming is 12.3, 15.6, 17.1, 17.4 and 18.4. COWAT showed during follow-up, the number of naming had statistically increased as compared to that before chemotherapy. Mean MMSE score for each group is 26.8, 28.2, 28.9, 28.7, 29.1, and scores of 1, 2 and 3 years after surgery were statistically higher than those of before and after chemotherapy. Although the mean MMSE score of 1, 2 and 3 years after operation increased gradually, there was no statistically difference among these 3 groups. And we compared our patients with patients undergoing early radiotherapy (NCCTG protocol 86-72-51) [19], the cognitive dysfunction was significantly lessened after chemotherapy. (MMSE [difference between groups, 95%CI, p value], -1.3, -2.388 to -0.212, 0.0200; AVLT/HVLT-R total [difference between groups, 95%CI, p value], -8.5, -13.64 to -3.350, 0.0023, TMT time Part A [difference between groups, 95%CI, p value], 21.0, 12.81 to 29.19, <0.0001; TMT time Part B [difference between groups, 95%CI, p value], 87.4, 50.23 to 124.6, <0.0001;). At the same time, we compared cognitive results of patients receiving chemotherapy alone with that of 11 patients receiving postoperative radiotherapy with or without adjuvant chemotherapy for patients' choice or other pathologies. The results showed an obvious improvement in MMSE score, AVLT/HVLT-R total and TMT time Part B tests (MMSE [difference between groups, 95%CI, p value], -2.5, -4.624 to -0.3755, 0.0242; AVLT/HVLT-R total [difference between groups, 95%CI, p value], -8.8, -13.82 to -3.780, 0.0022; TMT time Part B [difference between groups, 95%CI, p value], 63.2, 16.78 to 116.4, 0.0108;) (**Table 3**).

The temozolomide chemotherapy was well tolerated by all recruited patients, and all adverse effects could be relieved by expectant treatment. Adverse effects were shown on Table 1. Leucogen, peanut coat or recombinant granulocyte colony stimulating factor were used for hematologic adverse reactions, and Bicyclol or other hepatic protectants were used for elevated live enzymes. And no discontinuation of chemotherapy occurred among all patients except one patient for Grade 3 thrombocytopenia.

## Discussion

For LGGs, IDH mutation and 1p/19q codeletion are tightly associated with characteristics of gliomas at better biological behavior and clinical prognosis[20]. In our study, IDH mutant group had a better ORR than IDH wild-type group. It suggested that IDH mutation was a predictive factor for better temozolomide response, and 64.29% of LGG patients with IDH mutation can achieve partial or minor response after temozolomide chemotherapy.

IDH mutant group had a longer DOR than IDH wild-type group, and 1p/19q codeletion group also had a longer DOR than 1p/19q retain group. This suggested that both IDH mutation and 1p/19q codeletion were meaningful prognostic markers, which helped us to decide whether the patient needed to receive chemotherapy alone at early stage to delay radiotherapy. The median DOR for the diffuse astrocytoma, IDH-mutant subgroup was 44.5 months, and that for oligodendroglioma, IDH-mutant and 1p/19q-codeleted was 52.4 months. This suggests that for the majority of IDH mutant patients, temozolomide chemotherapy alone can control tumor progression for 4 years or longer. We recommend that providers should engage close follow-up for patients on upfront temozolomide chemotherapy after surgery, and cautiously decide whether the radiotherapy should intervene based on their response. As for IDH wild-type group, IOR and DOR showed poor response and prognosis. This group of tumors biologically and clinically resembles the behavior of glioblastomas, and these patients might need to receive concurrent chemo and radiotherapy at early stage.

Compared with EORTC 22033-26033[7], our study focused on young patients below 40 years old, who needed to protect their cognitive function. The age of temozolomide alone group in EORTC 22033-26033 ranged from 37-53, and 64% patients were above 40. EORTC 22033-26033 didn't figure out whether patients need to receive chemotherapy immediately after operation, and some of them received chemotherapy 30 months after diagnosis. As for extension of resection, the EORTC 22033-26033 contained biopsy, partial resection and total resection, while all patients in our study receive subtotal resection.

Temozolomide treatment of LGGs might induce driver mutations in the RB and AKT-mTOR pathways, which may drive malignant progression to secondary GBM[21]. Some chemotherapy-induced metabolic stress in IDH1 mutant gliomas might lead to poor chemotherapy response[22]. In our study, malignant progression occurred in 17.65% of diffuse astrocytoma, IDH-mutant and in 9.09% of oligodendroglioma, IDH-mutant and 1p/19q-codeleted. Temozolomide treatment was safe for most of gliomas with IDH mutation,

especially for oligodendroglioma, IDH-mutant and 1p/19q-codeleted. Our next step is to explore the mechanism in IDH mutated tumors with poor temozolomide response and prognosis.

EORTC 22033-26033[23] showed that the effect of temozolomide chemotherapy or radiotherapy on health-related quality of life (HRQOL) or MMSE scores did not differ in patients with LGG, and it wasn't consistent with a prior report of 12-year follow-up[4]. In our study, TMT time A and B and COWAT showed that executive function, visual spatial perception ability, language proficiency and plasticity of patients improved at the end of chemotherapy. MMSE showed cognitive function was still statistically improved even 1 year after surgery, and HVLT-R showed memory and attentional function was still statistically improved even 2 years after surgery. This suggests that temozolomide chemotherapy might has no obvious neurotoxicity, which leads to cognitive impairment. Cognitive function can be improved compared to that before chemotherapy. Meanwhile, the comparison between our results to the prospective study with the similar group of patients undergoing radiotherapy (NCCTG protocol 86-72-51)[19] suggested that chemotherapy might protect neurocognitive function better than radiotherapy. This answers our previous questions –– it is worth considering upfront adjuvant temozolomide chemotherapy in biologically favorable groups early after tumor resection to control tumor progression and delay radiotherapy intervention to prevent early cognition decline in young high-functioning patients.

This is an ongoing study with continuous long-term follow-up for cognitive function and survival data. Limitations of the study lie in the inter-study comparison of neurocognitive evaluation results between chemo and radiation therapy. The demographics, diagnostic and treatment protocols might not be completely comparable between the studies. This could affect the validity of the comparison as well as the generalization of the results. Future prospective phase III studies should involve randomization between the two adjuvant therapies in the same demographic group of patients.

## Conclusion

Temozolomide is the first line for LGGs chemotherapy, and generally well tolerated. We infer that 1) IDH mutation is a predictive factor for better temozolomide response, and a prognostic factor for longer survival. Upfront temozolomide therapy might be more appropriate for IDH mutant LGGs to postpone radiation; 2) Compared with early radiotherapy, patients undergoing adjuvant chemotherapy would have a better cognitive rehabilitation at an early stage. Therefore, IDH mutant young patients could choose upfront chemotherapy to postpone the intervene of radiation and delay potential cognitive impairments.

## Abbreviations

**LGG** Low-grade gliomas

**ORR** objective response rate

**IOR** intensity of response

**DOR** duration of response

**MPFS** malignant progression free survival

## Declarations

**Ethics approval and consent to participate.** This study was approved by the Huashan Hospital's institutional review board. Informed consent obtained from all individual participants included in the study was written.

**Consent for publication.** All subjects participating in the image acquisition signed the consent form.

**Availability of data and materials.** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests.** None declared.

**Funding**

This work was supported by Chinese Society of Clinical Oncology (CSNO-2015-MSD06), and Shiwen Yuan's effort was supported by National Institute of Mental Health (R25MH101076). Sponsors had no influence on study design, in the collection, analysis, and

interpretation of data, in the writing of the report, and in the decision to submit the paper for publication. The corresponding Author had full access to all the data in the study and had full responsibility for decision to submit for publication.

**Author contributions.**

Experimental design: SWY

Follow-up: ZYL, SWY, DXZ, JFL, FYG and SW

Pathology Review: HC, AA and ZFS

Statistical analysis: YYS

Writing – original draft: ZYL;

Writing- review & editing: JSW

All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Acknowledgements.** we thank all investigators in the centers who did a tremendous job to collect data, especially for Zhong Yang performing Magnetic Resonance Imaging and Yan Zhou performing cognitive tests.

**Authors' information.** Jinsong Wu, M.D., Ph.D. Professor, Glioma Surgery Division, Neurological Surgery Department of Huashan Hospital, Shanghai Medical College, Fudan University, Mid Wulumuqi Road 12, Jing'an District, Shanghai, China.

## References

1. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Butowski N, Fenstermaker RA, Forsyth P, Hattangadi-Gluth J, Holdhoff M: **NCCN Guidelines Insights: Central Nervous System Cancers, Version 1.2017.** *J Natl Compr Canc Netw* 2017, **15:**1331-1345.
2. Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, Barger GR, Brown PD, Gilbert MR, Mehta MP: **Randomized Trial of Radiation Therapy Plus Procarbazine, Lomustine, and Vincristine Chemotherapy for Supratentorial Adult Low-Grade Glioma: Initial Results of RTOG 9802.** *Journal of Clinical Oncology Official Journal of the American Society of Clinical Oncology* 2012, **30:**3065.
3. Mj VDB, Afra D, De WO, Ben HM, Schraub S, Hoang-Xuan K, Malmström PO, Collette L, Piérart M, Mirimanoff R: **Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial.** *Digest of the World Core Medical Journals* 2006, **366:**985-990.
4. Douw L, Klein M, Fagel SS, Van dHJ, Taphoorn MJ, Aaronson NK, Postma TJ, Vandertop WP, Mooij JJ, Boerman RH: **Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up.** *Lancet Neurology* 2009, **8:**810.
5. Acharya S, Wu S, Ashford JM, Tinkle CL, Lucas JT, Qaddoumi I, Gajjar A, Krasin MJ, Conklin HM, Merchant TE: **Association between hippocampal dose and memory in survivors of childhood or adolescent low-grade glioma: a 10-year neurocognitive longitudinal study.** *Neuro-Oncology* 2019.
6. Viaccoz A, Lekoubou A, Ducray F: **Chemotherapy in low-grade gliomas.** *Current Opinion in Oncology* 2012, **24:**694-701.
7. Baumert BG, Hegi ME, Mj VDB, Von DA, Gorlia T, Hoangxuan K, Brandes AA, Kantor G, Taphoorn MJ, Hassel MB: **Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study.** *Lancet Oncology* 2016, **17:**1521.
8. Dubbink HJ, Taal W, van Marion R, Kros JM, van Heuvel I, Bromberg JE, Zonnenberg BA, Zonnenberg CBL, Postma TJ, Gijtenbeek JMM, et al: **IDH1 mutations in low-grade astrocytomas predict survival but not response to temozolomide.** *Neurology* 2009, **73:**1792-1795.
9. Houillier C, ., Wang X, ., Kaloshi G, ., Mokhtari K, ., Guillevin R, ., Laffaire J, ., Paris S, ., Boisselier B, ., Idbaih A, ., Laigle-Donadey F, . **IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas.** *Neurology* 2010, **75:**1560-1566.
10. Vogelbaum MA, Sarah J, Aghi MK, Heimberger AB, Sampson JH, Wen PY, Macdonald DR, Bent MJ, Van Den, Chang SM: **Application of novel response/progression measures for surgically delivered therapies for gliomas: Response Assessment in Neuro-Oncology (RANO) Working Group.** *Neurosurgery* 2012, **70:**234-243.
11. Lashkari HP, Saso S, Moreno L, Athanasiou T, Zacharoulis S: **Using different schedules of Temozolomide to treat low grade gliomas: systematic review of their efficacy and toxicity.** *Journal of Neuro-Oncology* 2011, **105:**135-147.

12. Bent MVD, Wefel JS, Schiff D, Taphoorn M, Jaeckle K, Junck L, Armstrong T, Choucair A, Waldman AD, Gorlia T: **Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas.** *Lancet Oncology* 2011, **12:**583.
13. Lu JF, Zhang H, Wu JS, Yao CJ, Zhuang DX, Qiu TM, Jia WB, Mao Y, Zhou LF: **"Awake" intraoperative functional MRI (ai-fMRI) for mapping the eloquent cortex: Is it possible in awake craniotomy?** *Neuroimage Clinical* 2013, **2:**132-142.
14. Lu J, Wu J, Yao C, Zhuang D, Qiu T, Hu X, Zhang J, Gong X, Liang W, Mao Y: **Awake language mapping and 3-Tesla intraoperative MRI-guided volumetric resection for gliomas in language areas.** *Journal of Clinical Neuroscience* 2013, **20:**1280-1287.
15. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, Deimling AV: **Analysis of the IDH1 codon 132 mutation in brain tumors.** *Acta Neuropathologica* 2008, **116:**597-602.
16. Sonoda Y, Kumabe T, Nakamura T, Saito R, Kanamori M, Yamashita Y, Suzuki H, Tominaga T: **Analysis of IDH1 and IDH2 mutations in Japanese glioma patients.** *Cancer Science* 2009, **100:**1996-1998.
17. Wang K, Zhang S, Shi L, Wang X, Lin AI, Dai JP: **The 2016 World Health Organization classification of tumors of the central nervous system:A summary.** *Acta Neuropathologica* 2016, **131:**803-820.
18. Mandonnet E, Bauchet L, Taillandier L, Duffau H: *Toward the Definition of New Endpoints.* 2013.
19. Laack NN, Brown PD, Ivnik RJ, Furth AF, Ballman KV, Hammack JE, Arusell RM, Shaw EG, Buckner JC: **Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study.** *International Journal of Radiation Oncology Biology Physics* 2005, **63:**1175.
20. Appin CL: **Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas.** *New England Journal of Medicine* 2015, **372:**2481-2498.
21. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, Mclean CY, Fouse SD, Yamamoto S, Ueda H, Tatsuno K: **Mutational Analysis Reveals the Origin and Therapy-driven Evolution of Recurrent Glioma.** *Neurosurgery* 2014, **343:**N9.
22. Tateishi K, Wakimoto H, Higuchi F, Miller J, Koerner MVA, Lelic N, Shankar G, Tanaka S, Curry WT, Fisher DE, et al: **CHEMOTHERAPY-INDUCED METABOLIC STRESS IN IDH1 MUTANT GLIOMAS.** *Neuro-Oncology* 2016, **18:**vi67-vi67.
23. Reijneveld JC, Taphoorn MJ, Coens C, Bromberg JE, Mason WP, Hoang-Xuan K, Ryan G, Hassel MB, Enting RH, Brandes AA: **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 Oncology* 2016, **17:**1533-1542.

## Tables

Table 1 Baseline patient characteristics

| Characteristic | |
|---|---|
| **Clinical features at diagnosis** | |
| Sex (Male / Female) (N) | 36/29 |
| Median Age (year) (Mean, SD) | 32.3 (6.0) |
| Median KPS (Median, range) | 90 (80-100) |
| **Symptom at diagnosis** | N (%) |
| Seizure | 41 (63.08%) |
| Focal signs | 7 (10.76%) |
| Headache | 15 (23.08%) |
| Incidental on exam | 4 (6.15%) |
| Diplopia | 1 (1.53%) |
| **Tumor side/site (Left/Right)** | N |
| Frontal | 46 (28/18) |
| Non-frontal | 19 (9/10) |
| **Histology (WHO 2016)** | N (%) |
| Diffuse Astrocytoma, IDH-mutant | 34 (52.31%) |
| Diffuse Astrocytoma, IDH-wildtype | 9 (13.84%) |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeletion | 22 (33.85%) |
| **Molecular Pathology** | N/Total (%) |
| IDH (Mutation) | 56/65 (86.15%) |
| MGMT (Promoter Methylation) | 32/51 (62.75%) |
| TERT (Mutation) | 18/42 (42.86%) |
| 1p/19q (Co-deletion) | 24/55 (43.64%) |
| ATRX Loss (IHC negative) | 19/47 (40.43%) |
| **Objective Response** | N/Total (%) |
| Complete Response | 0 |
| Partial Response | 23 (33.85%) |
| Minor Response | 15 (23.07%) |
| Stable Disease | 2 (3.08%) |
| Progression | 26 (40.00%) |
| **Extension of Resection (Median; range; quartiles)** | 66.82%; 13.93% - 94.73%; 55.68% - 78.55% |
| **Adverse effects (NCI-CTC v4.0)** | |
| **Non-hematological effect** | N/Total (%) |
| nausea/vomiting | 21/54 (40.38%) |
| pruritus | 23/54 (42.59%) |
| alopecia | 14/54 (25.92%) |
| Grade 1 elevated live enzymes | 7/54 (12.96%) |
| Grade 1 elevated uric acid | 2/54 (3.70%) |
| Grade 2 elevated uric acid | 1/54 (1.85%) |
| **Hematologic adverse** | N/Total (%) |
| Grade 1 lymphopenia | 7/54 (12.96%) |

| | |
|---|---|
| Grade 2 lymphopenia | 3/54 (5.56%) |
| Grade 3 lymphopenia | 2/54 (3.70%) |
| Grade 1 neutropenia | 2/54 (3.70%) |
| Grade 2 neutropenia | 1/54 (1.85%) |
| Grade 3 neutropenia | 1/54 (1.85%) |
| Grade 1 thrombocytopenia | 1/54 (1.85%) |
| Grade 3 thrombocytopenia | 1/54 (1.85%) |

Table 2. Cognitive test

| | Follow-up time point (mean) | | | | | P value | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) | (1)(2) | (1)(3) | (1)(4) | (1)(5) | (2)(3) | (2)(4) | (2)(5) | (3)(4) | (3)(5) | (4)(5) |
| HVLT-R | | | | | | | | | | | | | | | |
| Score | 14.5 | 17.6 | 20.5 | 22.4 | 23.9 | 0.0004 | <0.0001 | <0.0001 | <0.0001 | 0.0016 | <0.0001 | <0.0001 | 0.0492 | <0.0001 | 0.1999 |
| POR* | 0.41 | 0.17 | 0.11 | 0.12 | 0.11 | 0.8970 | 0.2979 | 0.3969 | 0.2291 | 0.6708 | 0.8893 | 0.6364 | 0.9949 | 0.9889 | 0.9230 |
| TMT test | | | | | | | | | | | | | | | |
| TMT A | 54.4 | 37.8 | 37.0 | 31.8 | 31.5 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | 1.0000 | 0.4741 | 0.0014 | 0.2871 | 0.0172 | 0.8346 |
| TMT B | 180.7 | 107.2 | 92.0 | 94.1 | 80.1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.1892 | 0.7349 | 0.3929 | 0.7938 | 0.9991 | 0.7854 |
| COWAT | | | | | | | | | | | | | | | |
| Animal | 13.5 | 16.3 | 17.8 | 18.4 | 19.1 | 0.0005 | <0.0001 | <0.0001 | <0.0001 | 0.2525 | 0.0769 | 0.0522 | 0.9067 | 0.6494 | 0.9435 |
| Furniture | 12.7 | 14.9 | 16.4 | 16.8 | 17.5 | 0.0185 | <0.0001 | <0.0001 | <0.0001 | 0.3202 | 0.2475 | 0.0959 | 0.9979 | 0.7239 | 0.8863 |
| Switch | 12.3 | 15.6 | 17.1 | 17.4 | 18.0 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.2589 | 0.4120 | 0.1073 | 1.0000 | 0.8527 | 0.6244 |
| MMSE | 26.8 | 28.2 | 28.9 | 28.7 | 29.1 | 0.0047 | 0.0001 | 0.0002 | <0.0001 | 0.0053 | 0.0488 | 0.0144 | 0.9455 | 1.0000 | 0.9419 |

Follow-up time point: (1) Before chemotherapy, (2) After chemotherapy, (3) 1 year after surgery, (4) 2 years after surgery, (5) 3 years after surgery

POR: percentage of retention

P value*: Mixed model

Table 3. Cognitive function compared with NCCTG protocol 86-72-51

| | NCCTG(1) (N=20, median interval 18mon, range 5-35mon) | | Our study TMZ(2) (N=50 median interval 30mon, range 3-52mon) | | Our study RT(3) (N=11 median interval 18mon, range 10-25mon) | | P value | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1 2 | 2 3 | 1 3 |
| **Sex** | | | | | | | 0.4901* | 0.3226* | |
| Male | 14 | | 28 | | 4 | | | | |
| Female | 6 | | 22 | | 7 | | | | |
| **Age (year)** | | | | | | | *<0.0001** | 1.000* | |
| 18-40 | 9/20 | | 47/50 | | 11/11 | | | | |
| **Tumour location** | | | | | | | 0.1514* | 0.0702* | |
| Left | 7 | | 26 | | 9 | | | | |
| Right | 12 | | 24 | | 2 | | | | |
| Both | 1 | | 0 | | 0 | | | | |
| | Median (Range) | Mean (SD) (95%CI) | Median (Range) | Mean (SD) (95%CI) | Median (Range) | Mean (SD) (95%CI) | | | |
| **MMSE score** | 0.0 (-2.0, 6.0) | 0.6(1.6) (-0.1, 1.3) | 1.0 (-4.0,11.0) | 1.9(2.9) (1.0,2.7) | -1.0 (-4,-5) | -0.6(3.0) (-2.7.,1.4) | *0.0200* ** | 0.0242 ** | 0.2388 ** |
| **AVLT/HVLT-R total** | 2.0 (-18, 23) | 1.9 (10.5) (-2.7, 6.5) | 10.5 (-2.0,23.0) | 10.4(5.9) (8.7,12.1) | 1.0 (-10,15) | 1.6(7.2) (-3.2,6.5) | *0.0023* ** | *0.0022* ** | 0.9259 ** |
| **TMT time** | | | | | | | | | |
| PartA | 0.5 (-16, 20) | 0.2 (9.1) (-3.8, 4.2) | -14.0 (-93,39) | -20.8 (25.2) (-27.9, -13.6) | -5.0 (-82,15) | -13.6(27.2) (-31.9,4.7) | *<0.0001* ** | 0.4341 ** | 0.1286 ** |
| PartB | 2.0 (-103, 97) | 3.6 (48.0) (-17.4,26.4) | -72.0 (-438, 207) | -83.8 (107.6) (-114.7, -52.9) | -3.0 (-128,85) | -17.2(62.4) (-59.1,24.7) | *<0.0001* ** | *0.0108* ** | 0.3507 ** |

* Fisher's exact test

** unpaired t test with Welch's correction

Our study TMZ. 50 of 65 patients who only received temozolomide chemotherapy had long-term evaluation with extensive serial neuropsychological batteries.

Our study RT. 11 patients received postoperative radiotherapy with or without adjuvant chemotherapy for patients' choice or other pathologies, but we still followed their cognitive function.

# Figures

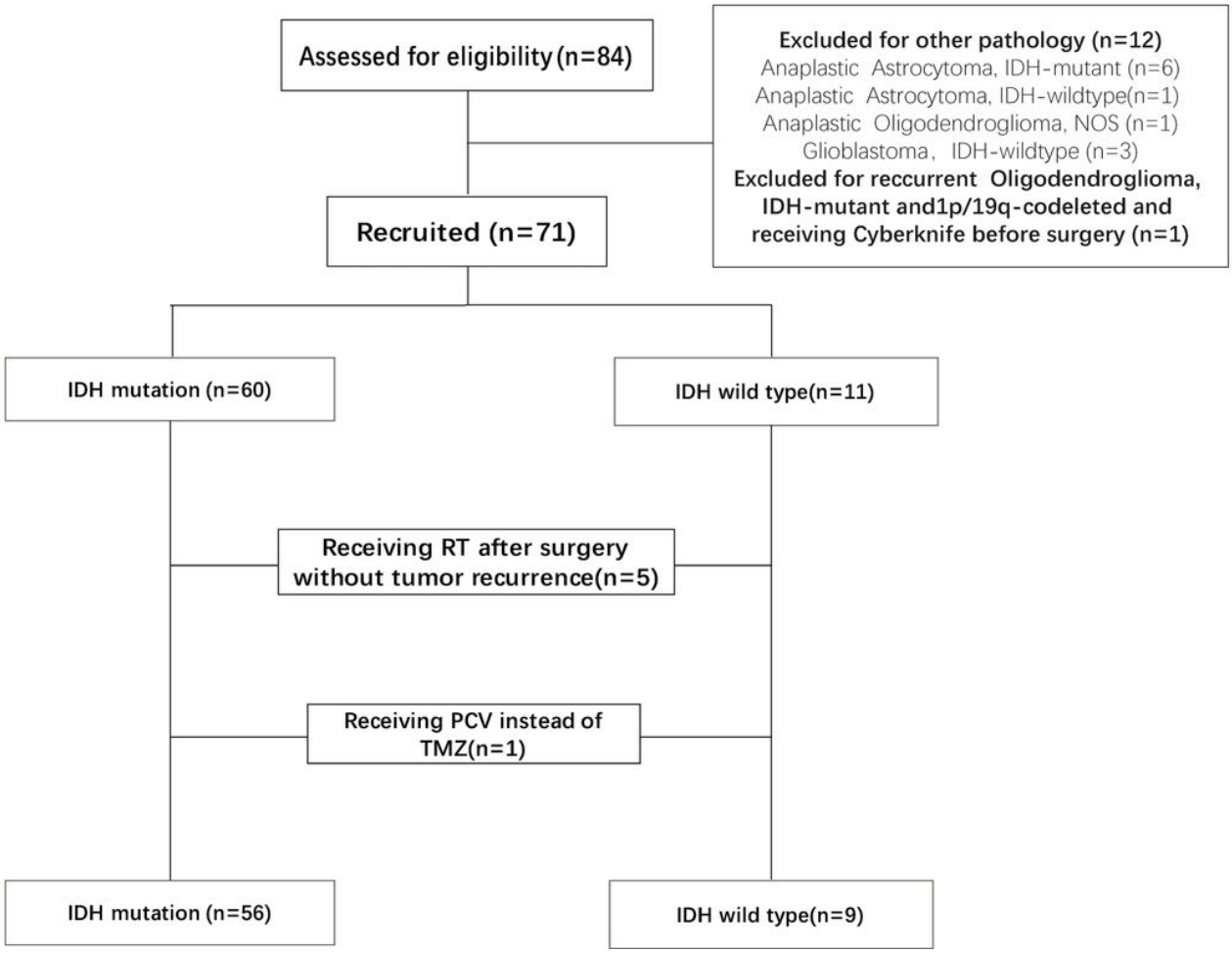
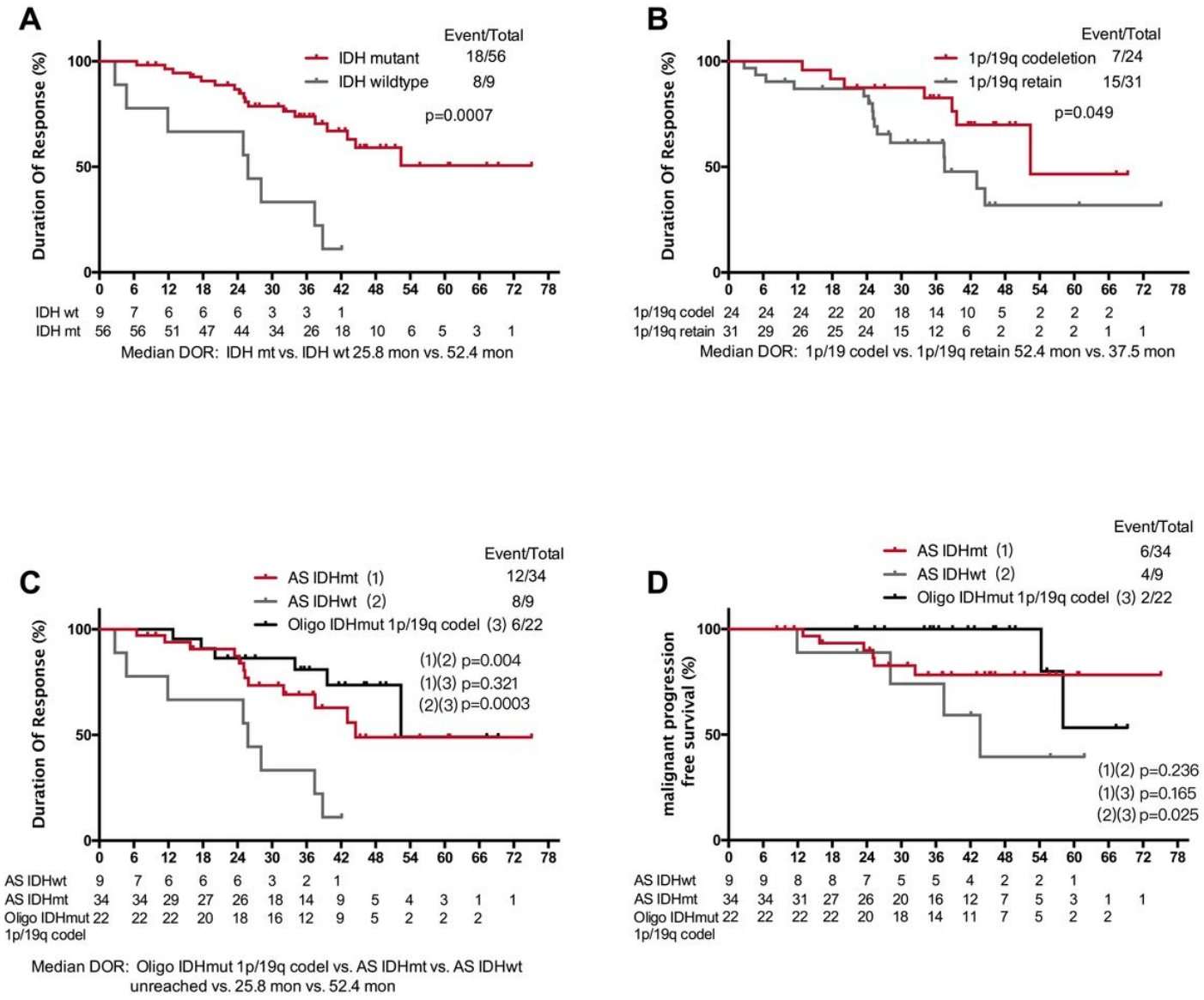



**Figure 1**

Trail profile.




## Figure 2

Kaplan-Meier plots. Duration of response for: (A) IDH-mutant group and IDH-wildtype group; (B) 1p/19q codeletion group and 1p/19q retain group; (C) all pathologies; (D) Malignant progression free survival for all pathologies.

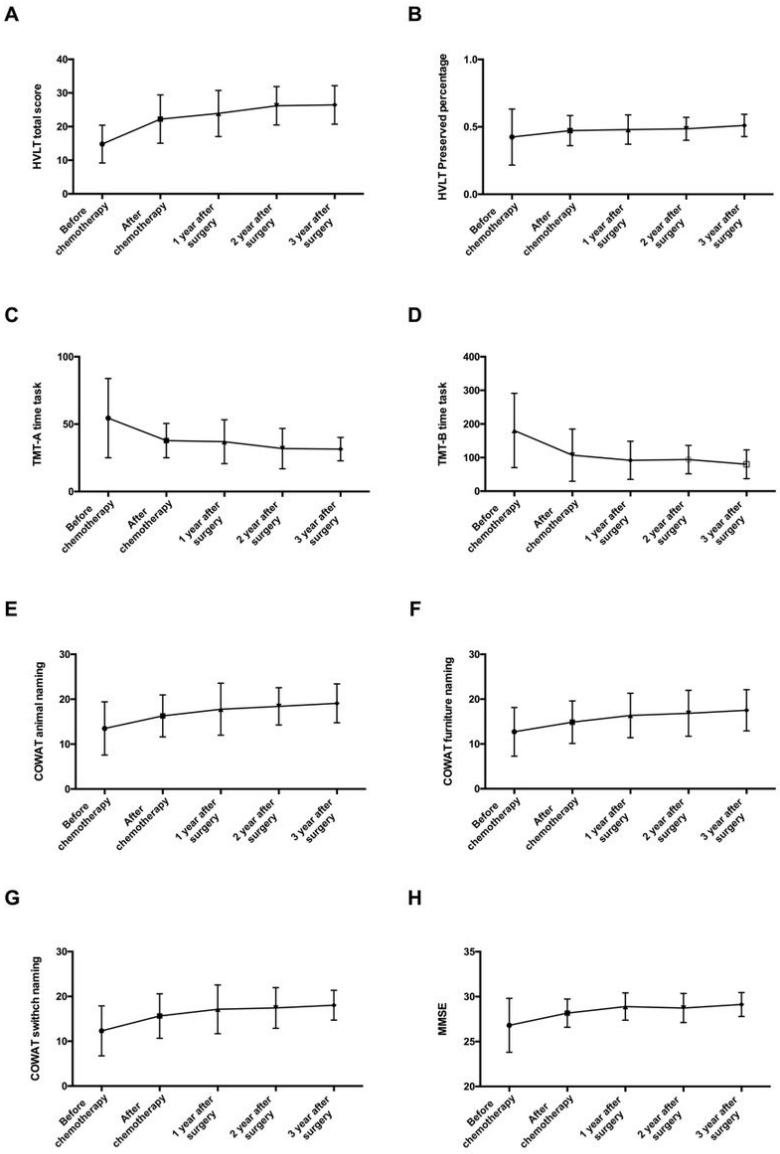



**Figure 3**

Cognitive function tests. Results over time for 6 scales: (A, B) Learning Test-Revised (HVLT-R): improvement in memory and attentional function; (C, D): Trail Making Test time A and B (TMT time A and B): improvement in executive function and the visual perception of space; (E, F, G): Multilingual aphasia examination controlled oral word association (COWAT): improvement in language proficiency and plasticity of cognitive function; (H): Mini-Mental State Examination (MMSE)

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigures.zip