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CLINICAL STUDY

Treatment of large low-grade oligodendroglial tumors with upfront procarbazine, lomustine, and vincristine chemotherapy with long follow-up: a retrospective cohort study with growth kinetics

Walter Taal · Carin C. D. van der Rijt · Winand N. M. Dinjens · Peter A. E. Sillevis Smitt · Agnes A. A. C. M. Wertenbroek · Jacoline E. C. Bromberg · Irene van Heuvel · Johan M. Kros · Martin J. van den Bent

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Abstract We treated patients with newly diagnosed and large low-grade oligodendroglial tumors with upfront procarbazine, CCNU and vincristine (PCV) in order to delay radiotherapy. Patients were treated with PCV for a maximum of 6 cycles. The response to treatment was defined according to the RANO criteria; in addition change over time of mean tumor diameters (growth kinetics) was calculated. Thirty-two patients were treated between 1998 and 2006, 18 of which were diagnosed with 1p/19q co-deleted tumors. Median follow-up duration was 8 years (range 0.5–13 years). The median overall survival (mOS) was 120 months and the median progression-free survival (mPFS) was 46 months. Growth kinetics showed an ongoing decrease of the mean tumor diameter after completion of chemotherapy, during a median time of 35 months, but an increase of the mean tumor diameter did not herald progression as detected by RANO criteria. 1p/19q co-deletion was associated with a significant increase in OS (mOS 83 months versus not reached for codeleted tumors; $p = 0.003$)) and PFS (mPFS 35 months versus 67 months for codeleted tumors; $p = 0.024$). Patients with combined 1p/19q loss had a 10 year PFS of 34 % and the radiotherapy in these patients was postponed for a median period of more than 6 years. This long-term follow-up study indicates that upfront PCV chemotherapy is associated with long PFS and OS and delays radiotherapy for a considerable period of time in patients with low-grade oligodendroglial tumors, in particular with combined 1p/19q loss.

Keywords Oligodendroglioma · Oligo-astrocytoma · Low-grade glioma · Chemotherapy · Tumor growth kinetics

W. Taal (✉) · P. A. E. Sillevis Smitt · A. A. A. C. M. Wertenbroek · J. E. C. Bromberg · I. van Heuvel · M. J. van den Bent
Department of Neuro-Oncology/Neurology, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands
e-mail: w.taal@erasmusmc.nl

C. C. D. van der Rijt
Department of Oncology, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

W. N. M. Dinjens · J. M. Kros
Department of Pathology, Josephine Nefkens Institute, Erasmus MC University Medical Center, Dr. Molewaterplein 50, 3015 GE Rotterdam, The Netherlands

Present Address:
A. A. A. C. M. Wertenbroek
Department of Neurology, Ziekenhuis Groep Twente (ZGT), Zilvermeeuw 1, 7609 PP Almelo, The Netherlands

Introduction

Early chemotherapy while withholding radiotherapy (RT) is increasingly used for high-risk low-grade glioma (LGG) [1]. Early reports showed prolonged stable disease or minor responses in a significant subset of patients, both after treatment with temozolomide (TMZ) and with procarbazine, lomustine (CCNU), and vincristine (PCV) combination chemotherapy [2–9]. Not unexpectedly, in particular 1p/19q co-deleted low-grade oligodendroglioma (OD) and low-grade oligo-astrocytoma (OA) showed favorable and longer lasting responses [3, 5]. The major rationale for this approach is the wish to postpone RT, which is associated with delayed cognitive disturbances in LGG patients [10].

This strategy is attractive particularly in patients with chemotherapy responsive tumors and with anticipated long-term survival, because these patients are longer at risk to develop clinically significant cognitive disturbances. Several series have been published on this topic, but all with relatively short follow-up or reporting on anaplastic oligodendroglioma (AO) [4, 5, 11].

Because of the expected chemosensitivity and in order to delay RT, we have been treating patients with newly diagnosed and large OD and OA tumors with upfront PCV chemotherapy since 1998. In 2005, we reported initial results of patients with OD and OA treated with PCV as the first line of treatment or at recurrence [5]. At that time we treated 16 patients with upfront PCV, with a median and maximum follow-up of 2 years and 5.5 years respectively. We now report on the long-term follow-up (median follow-up duration: 8 years, maximum follow-up: 13 years) of 32 patients who received upfront PCV and correlate our findings with the 1p/19q and IDH status.

Patients and methods

Patients

All patients receiving chemotherapy for brain tumors in our hospital are prospectively registered in our institutional glioma chemotherapy database. From this database we selected all RT naïve patients with newly diagnosed OD or mixed OA who started first-line treatment with upfront PCV chemotherapy, and we reviewed their records. Patients who received PCV for a recurrence after RT were not selected for this study. This report describes all patients treated between 1998 and 2006 (in 2006 we joined the EORTC study 22033 which employed TMZ in LGG patients). Patients were selected for treatment with upfront PCV if they had an OD or OA on original histology and had large and/or multi-lobe non-enhancing tumors, for which RT would require large treatment volumes (estimated more than 50 % of the cerebral hemispheres). Adequate hematologic, hepatic, and renal function and a WHO performance status score of 0–2 were required for chemotherapeutic treatment. In case of a favorable response to chemotherapy further treatment was deferred until disease progression occurred. This retrospective study was conducted according to local and national regulations and is approved of by the Institutional Review Board.

Treatment

All patients received the standard PCV schedule, consisting of lomustine 110 mg/m^2 on day 1, procarbazine 60 mg/m^2 on days 8–21, and vincristine 1.4 mg/m^2 (maximum of 2 mg) on days 8 and 29 in cycles of 6 weeks for a maximum of 6 cycles. Toxicity was assessed with the National Cancer Institute Common Toxicity Criteria Version 2.0. Dose reductions were made as described previously [12].

Evaluation

Response was assessed with MRI scans made after every second cycle during chemotherapy and routinely thereafter at least every 6 months. All MRI scans (baseline and follow-up) were made with and without gadolinium contrast. For tumor measurements in these non-enhancing tumors the T2 weighted MRI images were used. The response to treatment and progression was primarily defined using the product of perpendicular diameters on T2-weighted images according to the RANO criteria [13]. In addition, tumor size was calculated by one of the investigators (W.T.) using the three diameters technique ($V = (D_1 \times D_2 \times D_3)/2$) as described elsewhere [14]. With this technique the three tumor diameters ($h \times w \times l$) are converted into a single mean tumor diameter ($MTD = (2 \times V)^{1/3}$). MTD measurements were done before and after the chemotherapy and yearly thereafter, until progression occurred according to RANO criteria. The diameter expansion velocity (DEV; the glioma growth curve) was plotted as a function of MTD over time. A negative DEV indicates a tumor volume decrease. Fast responders were defined as patients with a DEV of less than the median DEV during the PCV chemotherapy. The MTD was not used for the classification of response and/or progression.

Histopathology and molecular diagnostics

All tumor specimens were centrally reviewed by J.M.K., who was kept unaware of the clinical data. From each selected tumor block, multiple consecutive 4 muM sections were prepared for molecular diagnostics. For genotyping, the tissue area composed of the highest percentage neoplastic cells was selected. Either fluorescence in situ hybridization (FISH) analysis or loss of heterozygosity (LOH) was used to determine loss of 1p and 19q as described previously, depending on the year of diagnostics [5, 15].

IDH1 mutational status and MIB-1 labeling was assessed with immunohistochemistry as described earlier [16–18]. Tumors with clear positive cells on IDH immunohistochemistry were considered IDH mutated.

Statistical analysis

The primary objectives of this study were the assessment of overall survival (OS) and progression-free survival (PFS) from the start of chemotherapy. Secondary objectives were

the objective response rate [(ORR); complete response (CR), partial response (PR) or minor response (MR)] and MTD charts were calculated. The Kaplan–Meier method was used to estimate PFS and OS. PFS and OS were measured in months, from the first day of start of PCV chemotherapy to the date of the event, with censoring at the date of last follow-up for survivors. The survival distributions between the subgroups (combined 1p/19q loss, no vs. yes; IDH1 mutational status, mutated vs wild type; and MIB-1 labelling <5 % vs. >=5 %) were compared using the log-rank test. All reported P values are two sided; in this exploratory analysis, no adjustments were made for multiple testing. IBM SPSS statistics 21 software was used for statistics and MS Excel 2010 was used for plotting the MTD charts.

Results

Baseline characteristics

Between July 1998 and November 2006 we treated 32 patients with an OD or OA with upfront PCV chemotherapy. The baseline characteristics are listed in Table 1. From 30 patients tumor material was available for genotyping and in 27 patients immunohistochemistry could be performed (see Table 1). In tumors of 18 patients the 1p/19q co-deletion was found.

Table 1 Baseline characteristics of patients treated with upfront PCV for large low-grade oligodendroglial tumors

Characteristic	N
Gender	
Male	23 (72 %)
Female	9 (28 %)
Median age (range)	46.5 year (28–64 year)
Number of involved brain lobes:	
2 lobes	14 (44 %)
3 lobes	5 (16 %)
4 lobes	9 (28 %)
5 lobes	2 (6 %)
6 lobes	1 (3 %)
7 lobes	1 (3 %)
Initial symptom	
Epilepsy	27 (84 %)
Other	5 (16 %)
Type of surgery	
Biopsy	19 (59 %)
Partial resection	13 (41 %)
WHO performance score	
0–1	28 (88 %)
2	4 (12 %)
Median time from 1st symptom till start chemotherapy (range)	37 months (3–202 months)
Median mean tumor diameter at start chemotherapy (range)	82.5 mm (55–122 mm)
Histology at central review	
Low-grade oligodendroglioma	17 (53 %)
1p/19q loss (no/yes/unknown)	4/12/1
Low-grade oligo-astrocytoma	10 (31 %)
1p/19q loss (no/yes/unknown)	6/4/0
Anaplastic oligodendroglioma	3 (10 %)
1p/19q loss (no/yes/unknown)	1/2/0
Unspecified low-grade glioma	2 (6 %)
1p/19q loss (no/yes/unknown)	1/0/1
Molecular characteristics	
Combined 1p/19q loss	18 out of 30 patients (60 %)
IDH1 positive cells	17 out of 27 patients (63 %)
MIB1 labeling of more than 5 %	2 out of 27 patients (7 %)

PCV Procarbazine, *CCNU* (lomustine) and vincristine chemotherapy, *IDH1* isocitrate dehydrogenase 1

PCV chemotherapy and toxicity

A total number of 159 PCV cycles were administered; the median number of cycles given was 5.5 (range 1–6). Sixteen patients (50 %) completed 6 cycles. Reasons for premature discontinuation of PCV were hematological toxicity in nine patients, non-hematological toxicity in four patients, tumor progression in two patients, and one patient stopped because of an unrelated second malignancy. Grade 3 toxicities were seen in 15 (47 %) and grade 4 toxicities in one (3 %) out of the 32 patients (see Table 2). In four patients in whom PCV was discontinued after 3 cycles because of toxicities (two patients with grade 3 pancytopenia, one patient with grade 3 elevated transaminases and one patient with grade 3 fatigue) chemotherapy was continued with TMZ for a maximum of 12 cycles.

Progression free and overall survival

The median follow-up was 94 months (range 6–154 months). Table 3 shows the median PFS (mPFS), median OS (mOS) and ORR. Both the mPFS ($p = 0.024$; see Fig. 1a) and the mOS ($p = 0.003$; see Fig. 1b) were significantly longer in patients with 1p/19q loss. The ten years PFS in 1p/19q co-deleted tumors was 34 %. The two patients with gliomas in which the MIB-1 labeling index was 10 and 15 % (both with 1p/19q loss) had a lower PFS than the patients with a MIB1 labeling index of 0 % (mPFS 13 months versus 65 months; $p = 0.001$), but OS was similar. Three patients were diagnosed with an AO at central review, OS and PFS in these patients was similar compared to the patients with WHO grade

Table 2 Maximum toxicity (grade 3 and 4) in patients treated with upfront PCV for large low-grade oligodendroglial tumors

Toxicity	Grade 3 (%)	Grade 4 (%)
WBC count	4/32 (13)	
Neutrophils	3/32 (9)	1/32 (3)
Platelets	3/32 (9)	
Any hematological toxicity	5/32 (16)	1/32 (3)
Nausea and vomiting	2/32 (6)	
Allergic skin reaction	4/32 (13)	
Hepatotoxicity	1/32 (3)	
Fatigue	6/32 (19)	
Neuropathy	1/32 (3)	
Any (non)-hematological toxicity	15/32 (47)	1/32 (3)

PCV procarbazine, *CCNU* (lomustine) and vincristine chemotherapy, *WBC* white blood cell

Table 3 Progression free survival, overall survival and objective response rate in patients treated with upfront PCV chemotherapy for large low-grade oligodendroglial tumors

	mPFS (mo)	mOS (mo)	ORR [n (%)]
All patients (n = 32)	46	120	23 (72)
Combined 1p/19q loss (n = 18*)	67	NR (mFU 107 mo)	14 (78)
No 1p/19q loss (n = 12*)	35	83	9 (75)

* Tumor material was available for genotyping in 30 out of 32 patients

PCV procarbazine, *CCNU* (lomustine) and vincristine, mPFS median progression free survival, *mo* months, *mOS* median overall survival, *ORR* objective response rate according to the RANO criteria, including minor response, *NR* not reached, *mFU* median follow-up

2 tumors at central review. IDH1 did not correlate with either PFS or OS. In patients with the largest tumors (MTD higher than the median MTD of 82.5 mm) a trend to a shorter PFS (mPFS 36 versus 63 months; $p = 0.054$) and a significantly shorter OS (mOS 84 months versus not reached; $p = 0.006$) were found in comparison to the rest of the patients. An objective response according to the RANO criteria was seen in 23 patients (18 MR and 5 PR). Eleven of the 12 patients with more than 5-year progression free survival were able to perform daily activities and work at their pre-chemotherapy level until progression. One patient was unable to perform work at baseline because of neurological deficits, but he continued to be able to live independently. In one patient with severe cognitive deficits treatment was discontinued because of lack of clinical improvement after one cycle of PCV.

Volumetric measures

The MTD decreased in all patients during the PCV treatment with a median DEV of −11.7 mm/year (range −1.1 to −55.4 mm/year). After discontinuation of the PCV an ongoing decrease of the MTD was seen for a median duration of 35 months (range 5–136 months) in the 18 patients with combined 1p/19q loss and 15.5 months (range 6–56 months) in the patients without combined 1p/19q loss measured from the start of the treatment. None of the patients developed an increasing MTD during the PCV chemotherapy. The patient in whom treatment was discontinued because of lack of improvement showed a stable MTD. Fast (DEV < -11.7 mm/year during the treatment with PCV) and slow responders (DEV > -11.7 mm/year during the treatment with PCV) did not differ in OS and PFS.

Most patients (15/22; 68 %) progressed with enhancement on the T1 weighted MRI after gadolinium. The progression according to the RANO criteria was heralded by an increase of the MTD (positive DEV) in only 3 of 22 (14 %) progressive patients (patient 5,8 and 9; Fig. 1c, d).

Treatment at progression

Table 4 shows the details on further treatment after progression. Twenty out of the 22 patients who progressed were further treated with RT. The interval between the start of the PCV chemotherapy and initiation of RT was 31 months in the patients with intact 1p/19q and 75 months in the patients with 1p/19q loss.

Discussion

The role of chemotherapy in LGG is gradually being clarified. Initial reports in uncontrolled studies on chemotherapy in LGG showed modest response rates with mostly minor responses but of interesting long duration especially in 1p/19q co-deleted tumors. Data from randomized trials are now becoming available. A first and still early analysis of the European Organization for Research and Treatment of Cancer (EORTC) study 22033 presented at the ASCO meeting in 2013 suggests that PFS does not differ between patients with LGG with 1p loss receiving upfront dose-dense TMZ (75 mg/m^2 daily × 21 days, q28 days, max. 12 cycles) versus patients receiving RT (50.4 Gy/28 fractions). In contrast RT may provide a superior PFS in patients without 1p loss ($p = 0.06$) [19]. The median OS was not yet reached in that study.

Data on long term follow-up on chemotherapy in LGG are however scarce. It therefore remains unclear whether sustained responses are obtained, especially in patients with oligodendroglial tumors and if so of what duration. Although the present study has several limitations (retrospective design, based on a limited number of patients, no serial neurocognitive tests, no data on the outcome of epileptic seizures and molecular data not available in all

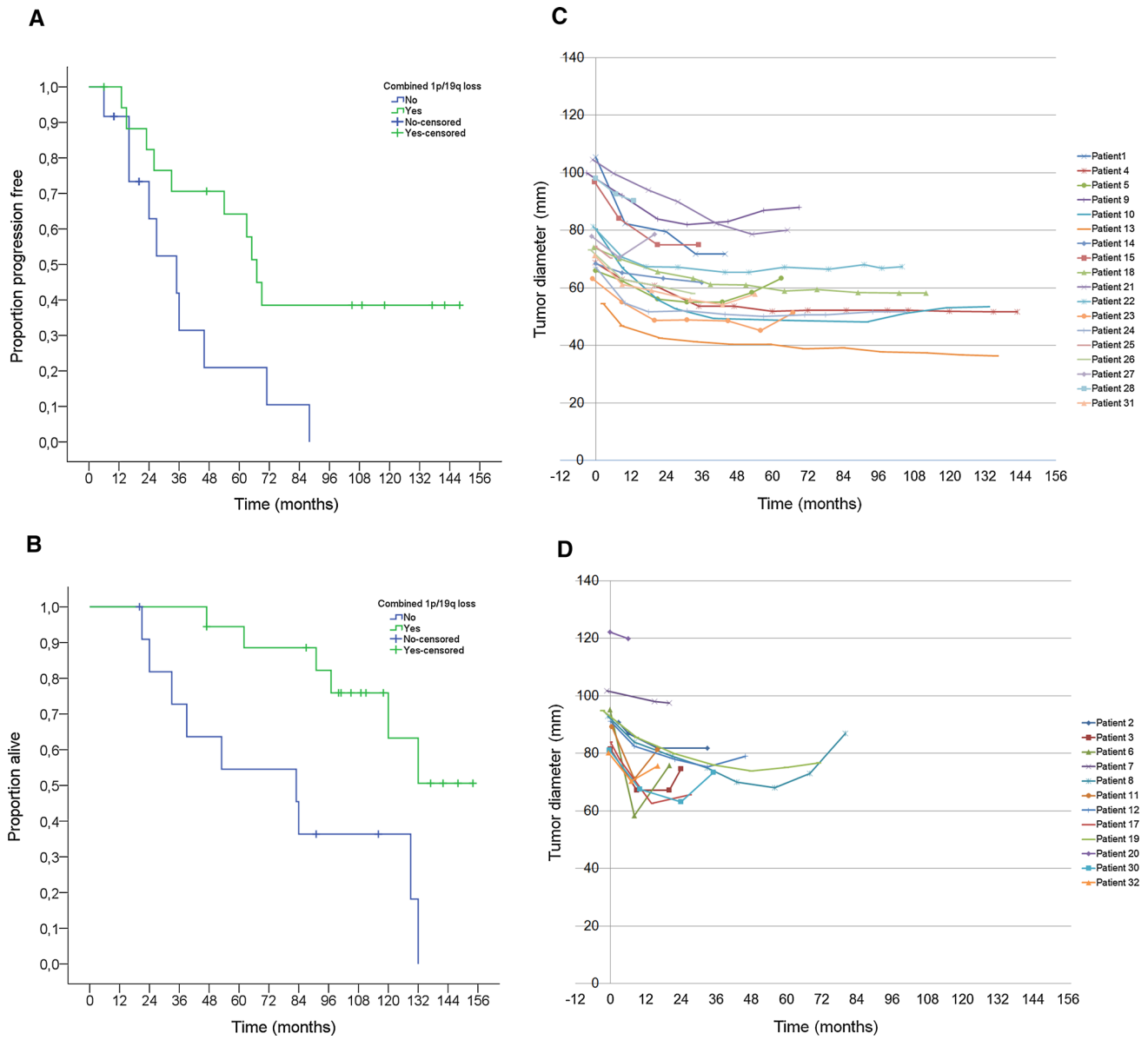

Fig. 1 Overall survival, progression free survival and mean tumor diameters plotted over time from the start of the treatment with upfront procarbazine, CCNU (lomustine) and vincristine (PCV) chemotherapy in patients with large low-grade oligodendroglial tumors. **a** Progression free survival curves; **b** Overall survival curves; **c** Mean tumor diameters of patients with combined loss of 1p and 19q. **d** Mean tumor diameters of patients without combined loss of 1p and 19q

patients), the results show a long lasting PFS and OS after treatment with upfront PCV in patients with large low-grade OD or OA. Outcome was particularly favorable in patients with combined 1p and 19q loss, with 34 % of these patients still being free from progression after 10 years.

Furthermore this is the first study to show long term follow-up of growth kinetics in these patients. We observed a decrease in the MTD during the PCV treatment in all patients with a median DEV of −11.7 mm/year, very similar to that observed by others [20]. During PCV treatment MTD increase did not occur, and after discontinuation of the PCV an ongoing and prolonged MTD decrease for a median of almost 3 years was observed in the 18 patients with combined 1p/19q loss. In 4 patients the MTD continued to decrease for more than 6 years (Fig. 1c).

Outside neuro-oncology interest in tumor growth kinetics has also increased. A recent study shows a near-lineal relationship between growth kinetics and survival in phase I studies, questioning the value of classical categorical responses [21]. In several studies in LGG, the MTD was found to be of use in monitoring growth of both untreated and treated LGG, improving our understanding of the clinical behavior of these tumors [14, 20, 22–24].

Table 4 Treatment after progression in patients treated with upfront PCV chemotherapy for large low-grade oligodendroglial tumors

Events after PCV chemotherapy	N (%)
Died without further treatment	3 (9)
Death related to brain tumor	1 (3)
Death unrelated	2 (6)
Ongoing response	7 (22)
Further treatment after progression	22 (69)
RT only	3 (9)
RT and one line chemotherapy (mainly TMZ)	6 (19)
RT and 3 lines of chemotherapy	1 (3)
RT, TMZ and re-RT	1 (3)
RT, TMZ, resection and re-RT	1 (3)
TMZ only	1 (3)
TMZ and RT	7 (22)
Resection, TMZ and RT	2 (6)

PCV procarbazine, *CCNU* (lomustine) and vincristine, *RT* radiotherapy, *TMZ* temozolomide chemotherapy

The optimal method of assessing outcome (RANO vs. MTD) in LGG patients remains to be defined [13]. Of note, others have shown, with tumor volume measurements, that in untreated LGG an increase in growth rate is a common early indicator of malignant transformation [25]. Somewhat surprisingly, we found an increase of the MTD presaged the progression only in 3 out of 22 patients and most patients progressed with enhancement on the MRI scan suggestive of malignant dedifferentiation without a prior increase in growth rate. Others have demonstrated an increase in mutations in LGG patients progressing after TMZ chemotherapy [26]. This suggests that at a certain point in time after chemotherapy new mutations induce malignant dedifferentiation leading to more aggressive clinical behavior. Another series showed that LGG patients with a fast response after RT had worse survival, but in the present study a fast response (DEV faster than the medium of −11.7 mm/year) was not prognostic [22].

The rationale for the present choice for upfront chemotherapy was our wish to postpone RT and the associated delayed cognitive disturbances in LGG patients. In our cohort of patients with large OD requiring large RT treatment volumes (estimated more than 50 % of the cerebral hemispheres), RT could be delayed for a considerable period of time in all patients. Furthermore, the patients remained in very good condition and most were able to do work at their previous level until progression. Had these patients with large tumors and long survival (especially patients with 1p/19q loss) been treated with RT it is not unlikely that they would have suffered from cognitive deterioration due to the RT. A previous study in long term survivors with LGG showed that long-term survivors who received RT showed a progressive decline in cognition, whereas patients who did not have RT had a stable cognitive status over time [10]. Similarly, neuropsychological evaluation in cohort of 37 long term survivors of the EORTC study 26951 (all irradiated) showed that out of the 27 patients still free from progression since initial treatment 30 % were severely cognitively impaired, 41 % were employed and 81 % lived independently [27]. The impact of RT on the cognitive functioning in long term survivors of LGG remains poorly understood, but the patients in the present cohort that remained free from progression continued to do well even after many years of follow-up. This supports an approach in which RT is delayed as long as this is safely possible. Although, one of the limitations of this study is the lack of data on the outcome of the epileptic seizures, while the control of epilepsy in LGG is an important issue [28].

Until recently, standard treatment for LGG requiring postsurgical treatment was either RT or chemotherapy. This may however be changing. An early report of the Radiation Therapy Oncology Group (RTOG) study 9802 on adjuvant PCV chemotherapy in LGG showed that for those patients surviving at least 2 years the addition of PCV to RT conferred a considerable survival advantage, suggesting a delayed OS benefit for the addition of PCV chemotherapy to RT [29]. An update on the more mature data of this study has been announced and it is expected that adjuvant PCV to RT prolongs survival significantly compared with radiation therapy alone.(National Cancer Institute press release: www.cancer.gov/newscenter/newsfromnci/2014/RTOG9802) This may imply that RT with adjuvant chemotherapy will become the next standard therapy in high-risk LGG.

These latest results of the RTOG 9802 study results in a complicated dilemma, putting the patient between Scylla and Charybdis. Where on the one hand early RT with adjuvant chemotherapy may prolong survival, on the other hand it could lead to cognitive decline and loss of quality of life in the long run, especially in large LGG with long survival (like the OD with 1P/19 loss in the present study). The alternative approach with chemotherapy alone may compromise survival however. Further studies are needed to clarify whether patients with large OD or OA with 1p/19q loss are form a quality of survival perspective better off with upfront chemotherapy, and preservation of RT for recurrences after chemotherapy. It needs no further explanation that the phase III studies addressing these issues with their inherent long follow-up are extremely difficult to conduct. This appears however be the most relevant next question in LGG, apart from better drugs to treat these patients.

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Conflict of interest W.T., C.C.D., W.N.M.D., P.A.E.S.S., A.A.A.C.M.W., J.E.C.B. and I.H. report no disclosures. M.J.B. has served on the speakers' bureau of MSD.

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