

## Role of exclusive chemotherapy as first line treatment in oligodendroglioma

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### Abstract

**Purpose** The optimal therapy of oligodendrogliomas remains uncertain. Although chemosensitive, these tumors are not chemocurable. We investigated whether chemotherapy delays the need for radiation therapy (RT) without decreasing length and quality of survival.

**Methods and materials** Among 89 patients treated for oligodendrogliomas at the Centre Léon Bérard of Lyon from 1982 to 1999, 59 patients fitted inclusion criteria, having had centrally reviewed pure oligodendroglioma requiring treatment. According to the WHO's classification 35 patients had Grade III and 24, Grade II oligodendrogliomas.

**Results** According to the intent to treat, patients were retrospectively classified in three groups as exclusive RT (Group 1), radio-chemotherapy (Group 2), or exclusive

chemotherapy (Group 3). Median progression-free survival (PFS): was 47 months [95% confidence interval (CI) 39–56], and median overall survival (OS) was 109 months (95% CI 83–134). In univariate analysis, PFS was correlated with frontal location and WHO classification; OS was correlated with frontal location and Post-operative Karnofsky performans status both appearing as independent prognostic factors for OS in multivariate analysis. There was no significant difference between the treatment groups with regard to PFS ( $P = 0.82$ ) and OS ( $P = 0.64$ ). In the group of patients treated with exclusive chemotherapy the 5-year PFS and OS rates were 44 and 71%, respectively.

**Conclusion** Front-line exclusive chemotherapy results in prolonged OS in patients with confirmed pure oligodendroglioma. Whether this strategy improves quality of life remains debatable.

**Keywords** Oligodendroglioma · Chemotherapy · Radiotherapy

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### Introduction

The optimal therapy of gliomas is unclear [1]. Five randomized concordant studies demonstrate that radiotherapy of high-grade gliomas increases survival [2–6]. Two concordant meta-analyses show a 10% survival advantage at 1 and 2 years for patients receiving nitrosoureas compared to those who do not [7, 8]. However, in these studies, high-grade oligodendrogliomas were not segregated from high-grade astrocytomas. No clear guideline exists for the treatment of high-grade oligodendrogliomas.

For low-grade gliomas, the situation is even less clear. The European Organization for Research and Treatment of Cancer (EORTC) randomized trial [9] showed no overall

difference in 5-year survival comparing therapy comprising post-operative irradiation of 54 Gy with irradiation at recurrence. Median survival was 7.4 years in the radiotherapy group and 7.2 years in the control group [HR 0.97, 95% confidence interval (CI) 0.71–1.34;  $P = 0.872$ ]. However, median progression-free survival (PFS) was 5.3 years in the group receiving early radiotherapy versus 3.4 years in the control group (HR 0.59 and 95% CI 0.45–0.77;  $P < 0.0001$ ). Randomized prospective trials conducted by the EORTC [10] and Radiation Therapy Oncology Group (RTOG) [11] demonstrated lower-dose radiotherapy (45 and 50.4 Gy) to be as effective as higher doses (59.4 and 64.8 Gy). Again, oligodendrogliomas were not segregated from other gliomas. Neither optimal timing nor optimal dose of radiation is clearly defined in treatment of low-grade gliomas. Nor is there a randomized study evaluating the role of chemotherapy in these low-grade glial tumors.

Oligodendrogliomas demonstrate better prognoses than other gliomas. With equivalent treatment, patients with oligodendrogliomas survive longer than those with astrocytomas. In a review of the RTOG 83-02, Donahue et al. reported a median survival of 7.3 years in patients with anaplastic oligodendrogliomas or anaplastic mixed tumors versus 3.4 years for those with pure anaplastic astrocytomas  $P = 0.019$  [12].

Cairncross et al. showed that LOH foci on 1p and 19q were predictors of good response to chemotherapy in anaplastic oligodendrogliomas [13]. In adults, combined 1p and 19q deletion has been observed in 83% of pure oligodendrogliomas, 63% of anaplastic oligodendroglioma, 56% of mixed low-grade glioma and 52% of anaplastic mixed oligoastrocytoma. Those patients also had longer overall survival (OS) (172 months vs. 105 months without deletions) [14].

Oligodendrogliomas are considered chemosensitive tumors irrespective of grade [15–25], but the optimal timing and final contribution of chemotherapy to OS remains unknown. Addition of chemotherapy to radiotherapy in first-line treatment of oligodendrogliomas increased disease-free survival (DFS) but had no impact on OS [26, 27]. No study in the current literature evaluates the impact of front-line radiotherapy in the subgroup of oligodendrogliomas that respond to chemotherapy. So, is it possible to treat a subgroup of patients exclusively with chemotherapy?

Prospective trials with baseline cognitive testing have shown small but measurable incidence of cognitive deficits after focal moderate dose radiotherapy, and therefore efforts to delay the possibility of this late toxicity are reasonable [28–30]. Thus, to determine if radiotherapy could be post-poned without adversely affecting survival, the authors' retrospectively analyzed three types of first-line strategies used in one oncology center in 59 centrally reviewed pure oligodendrogliomas requiring treatment.

The first group underwent radiotherapy alone; the second, radiotherapy followed by chemotherapy; and the third, exclusive chemotherapy.

## Methods and materials

### Patients

We retrospectively reviewed the records of all patients with oligodendrogliomas who received adjuvant treatment at Centre Léon Bérard from 1982 to 1999. Only patients followed with modern imaging techniques [computed tomography (CT) and/or magnetic resonance (MR) imaging]. Most patients were operated in one of the neurosurgical units and most initial pathology was examined in the Department of Neuropathology of Hôpital Wertheimer (Lyon, France), and central review for all patients was performed by an experienced neuropathologist (AJ). The Neuro-oncology Committee of the Centre Léon Bérard designed post-operative treatment. Active treatment was undertaken in two situations. High-grade oligodendrogliomas (Grade III according to WHO's classification) were treated directly after pathological diagnosis, but in Grade II tumors, active treatment was undertaken in case of clinical progression (deficit and/or resistant epilepsy) and/or radiological progression (increase in volume and/or apparition on contrast enhancement). In the latter group, there was usually no new histological proof of grading. Radiotherapy was delivered in the Radiotherapy and Neuro-oncology Unit of Centre Léon Bérard. Regular follow-up was performed either by the neuro-oncology team of Centre Léon Bérard or by a member of the ONCOR network. The response evaluation to chemotherapy is based on MacDonald's criteria [31].

### Radiation therapy

Involved field radiotherapy was administered at 60 Gy in 2.0 Gy, 5 days a week using a technique with multiple fields. All patients had CT planning and provisional dosimetry. Planning target volume (PTV) varied according to date of treatment. From 1982 to 1994, the gross target volume (GTV) was defined by CT; after 1994, by MR imaging. Patients were discharged home after 1-week hospital stay or as soon as feasible thereafter. Concomitant prevention of edema was delivered as required using steroids and/or mannitol.

### Chemotherapy

Patients were scheduled to receive six cycles of PCV chemotherapy that included CCNU (110 mg/m<sup>2</sup>) or BCNU

(150 mg/m<sup>2</sup>) on day 1; procarbazine (60 mg/m<sup>2</sup>) on days 8–21; and vincristine (1.4 mg/m<sup>2</sup>, maximum dose: 2 mg) on days 8 and 28. The cycles were scheduled at 6-week intervals. Concomitant edema prevention using both steroids and/or mannitol was delivered as required.

The grouping of patients depended on the initial intention to treat. In the group treated with either exclusive radiation therapy (RT) or combined radio-chemotherapy (RT-CT), failure was defined as recurrence of tumor during or after therapy. In the group receiving exclusive CT the intent to treat was to discontinue treatment only in those patients who showed complete disappearance of contrast enhancement after 4–6 courses of chemotherapy. The strategy was considered to have failed if contrast enhancement persisted after chemotherapy, and these patients received immediate radiotherapy.

#### Review of histology

The pathology was reviewed centrally by an experienced neuro-pathologist using different classifications. Hematoxylin and eosin-stained slides of paraffin-embedded tumor tissue were examined for the presence of oligodendroglial and astrocytic components. Mixed oligoastrocytomas were excluded. Mixed oligoastrocytomas are defined as tumors which contained both neoplastic oligodendroglial and astrocytic elements, with neoplastic astrocytic elements comprising at least 25% of the mixed glioma. Tumors were also graded as either low-grade or malignant, based on the presence or absence of elevated mitotic activity, significant nuclear pleomorphism, vascular neogenesis, and necrosis. In the identification of high-grade tumors, great emphasis was placed upon the presence or absence of vascular neogenesis. Vascular neogenesis was identified in all tumors designated malignant, with the exception of two small tumor samples containing few blood vessels, but displaying marked nuclear pleomorphism and significantly elevated mitotic activity. Ancillary diagnostic techniques, including immunohistochemistry, were selectively employed.

#### Statistical analysis

The end point of interest was survival time, with two criteria, PFS and OS. PFS was defined as the time from the date of start of treatment to the date of disease progression or death or to the date of last follow-up for patients alive with no indication of disease progression. OS was defined as the time from the date of start of treatment to the date of death or to the date of last follow-up for patients alive at last contact. Follow-up was completed in April 2006; median follow-up was 81 months. Survival curves were

estimated using the Kaplan–Meier method [32] and compared with the log-rank test.

#### Univariate analysis

To evaluate the relation between survival and baseline characteristics, variables were included in univariate Cox proportional hazard regression models [33]. Age was included in the models as a dichotomous variable with the value zero for patients under 45 years (median value of the series) or one otherwise.

#### Multivariate analysis

Independent prognostic variables of PFS and OS were, respectively, identified by Cox regression analysis using a backward stepwise procedure to eliminate non-influential variables. We used a stepwise modeling algorithm with a significance level of 0.10 for entering and of 0.05 for removing explanatory variable.

## Results

Eighty-nine patients fit inclusion criteria. Review of pathology excluded 30 patients. Of these 30, no slides were available for 20 patients; the diagnosis was changed for five patients (one case each, chordoid glioma, ependymoma, cavernoma, meningioma, and astrocytoma); and the diagnosis after histology review was mixed tumor for five patients. Thus, the diagnosis of pure oligodendroglioma was confirmed in 59 cases, and analysis was restricted to these 59 patients. Characteristic of those 59 patients are described in Table 1 (Table 1).

Patients were 29 men and 30 women. Median age at diagnosis was 45 years (21–72 years). Thirty-three patients presented with only seizure at diagnosis, nine with headache, five with headache and seizure, and 12 with focal deficit. The predominant localization was frontal (25 patients), followed by occipital (14), temporal (10), parietal (6), thalamic (3), and brainstem (1). Sixteen underwent total gross removal (surgeon's description) of the tumor, whereas 43 underwent biopsy or incomplete resection.

According to the WHO classification [34] determined at the time of histological review, 35 patients had Grade III and 24 Grade II oligodendrogliomas. Among the 24 Grade II oligodendrogliomas, nine patients with inoperable tumors were treated because of symptoms and five patients with inoperable tumors were treated because of contrast enhancement. Seven were treated at the time of unresectable recurrence with no new biopsy. Two patients were treated after surgery because of contrast enhancement on

**Table 1** Comparison of patient characteristics among three treatment groups

Factors	Radiotherapy ( <i>n</i> = 11) number (%)	Chemotherapy and radiotherapy ( <i>n</i> = 16) number (%)	Exclusive chemotherapy ( <i>n</i> = 32) number (%)	Total
Sex				
Male	5 (45.5)	8 (50.0)	16 (50.0)	29 (49.2)
Female	6 (54.5)	8 (50.0)	16 (50.0)	30 (50.8)
Age (years)				
≤45	7 (63.6)	8 (50.0)	16 (50.0)	31 (52.5)
>55	4 (36.4)	8 (50.0)	16 (50.0)	28 (47.5)
WHO tumor grade				
II	3 (27.3)	2 (12.5)	19 (59.4)	24 (40.7)
III	8 (72.7)	14 (87.5)	13 (40.6)	35 (59.3)
Smith tumor grade <sup>a</sup>				
A/B	4 (36.4)	2 (13.3)	18 (58.1)	24 (42.1)
C	7 (63.6)	13 (86.7)	13 (41.9)	33 (57.9)
Daumas-Duport tumor grade				
A	1 (9.1)	–	5 (15.6)	6 (10.1)
B	10 (90.9)	16 (100)	26 (81.3)	52 (88.1)
Frontal location				
Yes	5 (45.5)	7 (43.8)	13 (40.6)	25 (42.4)
No	6 (54.5)	9 (56.3)	19 (59.4)	34 (57.6)
Complete surgical removal				
Yes	3 (27.3)	6 (37.5)	7 (21.9)	16 (27.1)
No	8 (72.7)	10 (62.5)	25 (78.1)	43 (72.9)
Post-operative Karnofsky performance status				
90–100	4 (36.4)	6 (37.5)	20 (62.5)	30 (50.8)
≤80	7 (63.6)	10 (62.5)	12 (37.5)	29 (49.2)
Epilepsy <sup>a</sup>				
Yes	3 (30.0)	10 (62.5)	11 (35.5)	33 (57.9)
No	7 (70.0)	6 (37.5)	20 (64.5)	24 (42.1)
Time from diagnosis to treatment (months)				
≤12	8 (72.7)	14 (87.5)	16 (50.0)	38 (64.4)
>12	3 (27.3)	2 (12.5)	16 (50.0)	21 (35.6)

<sup>a</sup> Data were missing for two patients

preoperative MRI. One patient was treated with chemotherapy for a tumor classified Grade II according to WHO classification. He was treated after multidisciplinary discussion because of an elevated mitotic activity in a small part of the tumor. After central review this tumor remains classified Grade II.

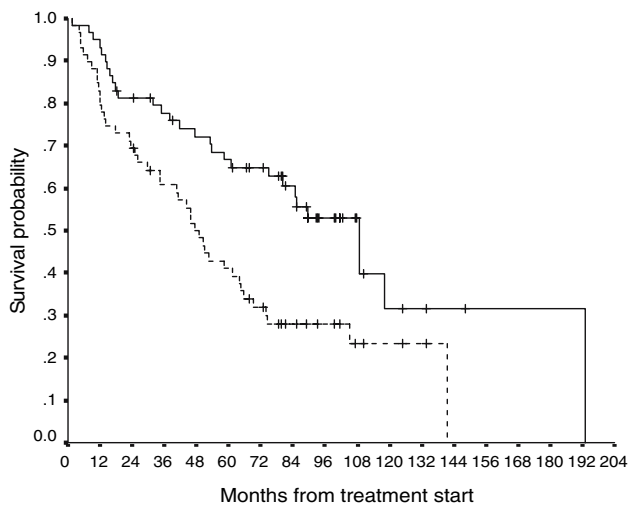
Twenty-one were treated after 12 or more months of observation after diagnosis of oligodendroglioma.

According to current knowledge and to neuro-oncology multidisciplinary decisions, the intent to deliver adjuvant therapy varied with time. Group 1 included 11 patients treated between 1982 and 1996 with exclusive radiotherapy. Group 2 included 16 patients treated between 1988 and 1999 with chemotherapy followed by radiotherapy. Group 3 included 32 patients treated between 1994 and 1999 with exclusive chemotherapy. The median PFS and OS for the series were 47 and 109 months, respectively

(Fig. 1). In univariate analysis, PFS was correlated with frontal location and WHO classification and OS was correlated frontal location and Post-operative Karnofsky performance status (KPS) (Table 2). After multivariate analysis, these factors appear as independent prognostic factors for PFS and OS (Table 3).

The 5-year PFS was 32% in Group 1 (RT); 41% in Group 2 (RT-CT), and 44% in Group 3 (CT). The difference is not significant ( $P = 0.67$ ; Fig. 2). In addition, there was no significant difference between the three groups with regard to OS. Five-year OS was 51% for Group 1, 68% for Group 2, and 71% for Group 3 ( $P = 0.86$ ; Fig. 3).

Patient characteristics (gender, age, frontal localization, complete surgery, and time from diagnosis to treatment) were well balanced between the three groups (Table 1). However, the histological type and Karnofsky index were more favorable in group 3 (CT). The rate of Grade III



**Fig. 1** Kaplan-Meier curves for progression-free (*solid line*) and overall survival (*dotted line*). The *tick marks* represent censored data

tumors according to WHO classification was only 41% in group 3 (CT) compared to 81% in the groups 1 and 2 (receiving radiation).

In Group 1 (RT), all 11 patients completed radiotherapy and experienced no tumor progression while on radiotherapy. Two remain non-progressive (9 and 3 years after treatment). Tumor recurred in nine patients, eight of whom required a second-line treatment because of tumoral evolution and the ninth receiving no second-line treatment because of low Karnofsky performance status at the time of recurrence. Second-line treatment was PCV in five patients, fotemustine (Muphoran<sup>®</sup>) in two patients, eight drugs in 1 day in one patient. Two patients were alive 24 and 108 months after recurrence, and six patients died 2, 3, 10, 42, 46, and 57 months after recurrence.

In Group 2 (CT + RT) all 16 patients completed intended treatment. Six remain non-progressive, four had no second-line treatment because of low-performance status, and six had second-line treatment, consisting of further surgery plus chemotherapy in two patients, chemotherapy in four patients. Chemotherapy comprised (Temodal<sup>®</sup>), in two patients, Muphoran (fotemustine), in four patients. One of whom is alive 2 months after recurrence and the others died 8, 13, 36, 48, and 50 months after recurrences.

In Group 3 (CT), three of 32 patients had progression during or immediately after first-line treatment and received RT as salvage treatment. Nine patients did not relapse. Four patients had no treatment at the time of tumor recurrence because of poor performance status. Nineteen patients required a second-line treatment for tumor evolution. Four patients received exclusive chemotherapy (comprised Temodal), two of whom were alive 24, and 36 months after recurrence and the others died 24 and 30 months after recurrence. Of 15 patients receiving

radiotherapy for recurrence eight patients were alive, respectively, 24, 36, 42, 48 (three patients), 60, and 66 months after recurrence, and seven patients died 4, 6, 13 (two patients), 24, 28, and 36 months after radiation. In the group 3 (CT), 19 patients were treated for low-grade oligodendrogliomas according to WHO classification, and 13 were treated for High-grade oligodendrogliomas. In the group 3 (CT) the 5 years OS for low-grade is 66% (CI 95% 52–80); and 62% for high grade (CI 95% 47–75). The 5 years PFS for low grade is 32% (CI 95% 21–43); and 38% for high grade (CI 95% 25–51). Those differences are not statistically significant. Sixteen patients of group 3 were treated with exclusive chemotherapy after 12 or more months of observation after diagnosis of oligodendroglioma. Five-year PFS is 42% (CI 95% 29–55) compared to 35% (CI 95% 21–49) for patients receiving chemotherapy <1 year before diagnosis. Five-year OS is 66% (CI 95% 52–80) compared to 63% (CI 95% 48–78) for patients receiving chemotherapy <1 year before diagnosis.

## Discussion

Any study reporting on a cohort of oligodendrogliomas has its own biases. Our study was designed to deal with a population as homogeneous as possible. Central review for all patients was performed by an experienced neuropathologist. Patients younger than 18 years were excluded because of differences in survival between patients according to age [35–40]. Inclusion criteria were the need for treatment in patients with confirmed oligodendrogliomas and included only pure oligodendrogliomas confirmed after review. According to WHO classification this study includes Grade III, and clinical aggressive Grade II. Clinical aggression was defined as increasing symptoms or tumor size or occurrence of contrast enhancement. Such inclusion criteria are similar to that used by Abrey et al. [41].

The prognostic factors in this series were consistent with those reported in the literature. In the present series Karnofsky index was prognostic factor for survival. Higher survival was associated with frontal location and grade of tumor according to WHO classification as reported in other series [42, 43] and absence of neuro-logical symptoms [44–49].

Demonstration of the unique chemosensitivity of oligodendrogliomas has opened the way to considerable research and hope. Cairncross and MacDonald and their colleagues were the first to report on a high-response rate of 75% to PCV chemotherapy for patients with enhancing recurrent oligodendroglioma [50, 51]. Genetic alterations were shown to correlate significantly with chemosensitivity and OS of oligodendroglioma in several uncontrolled or

**Table 2** Results of the univariate survival analysis testing 11 factors for significant impact on progression-free and overall survival, respectively

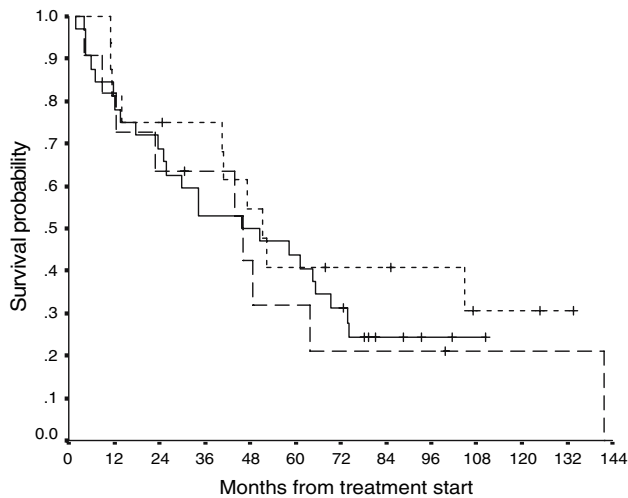
Factors	Progression-free survival			Overall survival		
	5-year rate (%)	Median and 95% CI (months)	<i>P</i> -value	5-year rate (%)	Median and 95% CI (months)	<i>P</i> -value
Sex						
Male	40	51 (37–66)	0.84	68	85 (59–111)	0.73
Female	42	46 (19–72)		66	14 (82–136)	
Age (years)						
≤45	39	49 (43–55)	0.51	71	109 (73–144)	0.99
>45	45	30 (0–77)		62	118 (52–185)	
WHO's tumor grade						
II	70	74 (62–86)	0.019	83	109 (108–109)	0.17
III/IV	21	41 (19–62)		56	85 (38–132)	
Smith's tumor grade						
I/II	62	65 (53–78)	0.18	74	109 (76–142)	0.71
III/IV	25	41 (22–60)		62	85 (66–104)	
Daumas Duport's tumor grade						
A	57	65 (17–113)	0.34	71	–	0.79
B	39	47 (34–61)		66	109 (84–133)	
Frontal location						
Yes	55	65 (49–80)	0.04	92	–	0.0006
No	31	34 (11–58)		48	58 (40–76)	
Complete surgical removal						
Yes	34	47 (15–80)	0.31	68	89 (43–118)	0.87
No	43	49 (36–61)		66	109 (82–135)	
Post-operative KPS						
90–100	50	51 (31–72)	0.41	83	109 (75–142)	0.015
≤80	31	44 (17–71)		50	58 (14–103)	
Epilepsy						
Yes	45	52 (28–77)	0.62	64	109 (46–172)	0.18
No	36	47 (26–69)		66	89 (64–115)	
Time from diagnosis to treatment (months)						
≤12	40	47 (37–58)	0.62	67	109 (72–145)	0.83
>12	43	51 (8–94)		66	109 (58–159)	
Treatment strategy						
Radiotherapy	32	46 (13–79)	0.67	51	85 (29–141)	0.86
Chemotherapy and radiotherapy	41	51 (37–65)		68	89 (66–113)	
Exclusive chemotherapy	44	46 (12–79)		71	109 (61–156)	

*CI* confidence interval, *KPS* Karnofsky performance status

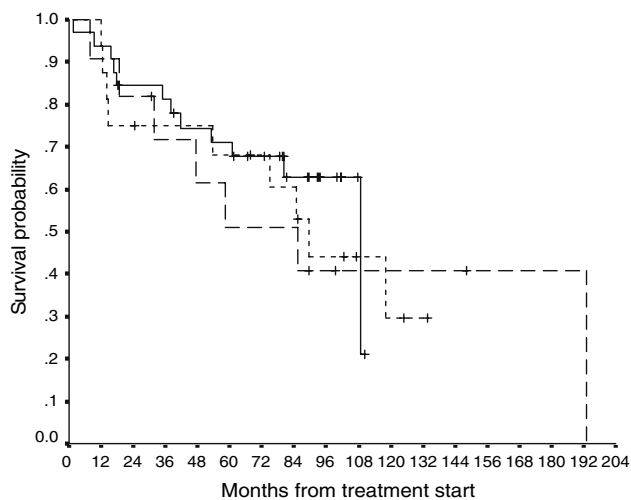
**Table 3** Results of the multivariate analysis for progression-free survival and overall survival, respectively (*n* = 59)

Factors	Progression-free survival			Factors	Overall survival		
	Hazard ratio	95% CI	<i>P</i> -value		Hazard ratio	95% CI	<i>P</i> -value
Who's tumor Grade II	2.48	1.28–4.84	0.007	Post-operative KPS ≤ 80	2.47	1.10–5.55	0.028
Frontal location	2.20	1.16–4.18	0.016	Frontal location	4.16	1.67–10.39	0.002

Abbreviation: *CI* confidence interval



**Fig. 2** Kaplan–Meier curves for progression-free survival according among patients in the three treatment groups. The tick marks represent censored data on patients who were alive without progression of disease. Large dotted line represents group 1 (exclusive radiotherapy), small dotted line group 2 (chemotherapy followed by radiotherapy), and solid line group 3 (exclusive chemotherapy).  $P = 0.67$  for the comparison among the groups



**Fig. 3** Kaplan–Meier curves for overall survival according among patients in the three treatment groups. The tick marks represent censored data on patients who were alive at last follow-up. Large dotted line represents group 1 (exclusive radiotherapy), small dotted line group 2 (chemotherapy followed by radiotherapy), and solid line group 3 (exclusive chemotherapy).  $P = 0.86$  for the comparison among the groups

retrospective studies, but also in two recent phase III prospective trials [52–56]. The PCV chemotherapy regimen has been the standard treatment in case of recurrence after radiotherapy. Talianky-Aronov et al. reported a series of 20 patients treated with Temozolomide for newly diagnosed anaplastic oligodendrogliomas. Clinical improvement was observed in 60% of the patients and objective

radiological response in 75% of the patients [57]. Several phase II trials investigated the role of Temozolomide (Temodal) in patients with recurrent anaplastic oligodendroglioma after prior RT. In the study EORTC 26971 High-response rates of 53% (26% complete responses) were observed with first-line chemotherapy [58]. In contrast Temozolomide has demonstrated response rates of 25–43% in second-line studies after prior radiotherapy and PCV [59, 60]. Most patients who responded to second-line treatment had also responded to first-line PCV chemotherapy, but some patients who do not respond to PCV may still respond to TMZ [61]. Triebel reported a 50% PFS after PCV in Temozolomide resistant oligodendrogliomas [62]. Franceschi et al. evaluate Temozolomide for prior Temozolomide responders. Objective response or stable disease was achieved in 43% patients [63]. A second line of chemotherapy may also be discussed for patients relapsing after first line. In case of low grade Oligodendroglioma response have been published [64, 22].

In the present series, patients receiving exclusive chemotherapy as first-line treatment, the 5-year PFS and OS rates were 44 and 71%, respectively. When analysis is limited to the 13 patients treated for Grade III oligodendroglioma (according to the WHO's classification), the 5 years OS and DFS are, respectively, 62 and 38%.

To our knowledge, there is no publication assessing the role of exclusive chemotherapy in high-grade oligodendrogliomas naïve of radiotherapy. Abrey et al. reported a series of 69 newly diagnosed oligodendroglioma treated with first-line chemotherapy including PVC and thiotepa high dose in case of response to PVC. Thirty-nine above 69 patients received thiotepa high dose; their 2 years DFS is 78% [65].

In the present series patients receiving exclusive radiotherapy as first-line treatment, the 5-year PFS and OS rates were 32 and 51%, respectively, study. OS are reported in literature between 50 and 83% [66–68]. In the retrospective series reported by Celli et al. RT helped the 65 patients with neuro-logic signs (5-year survival rate, 11% vs. 53%;  $P = 0.002$ ) [69]. Lindergaard et al. found that irradiation appears not to be of benefit after “total” removal. In this series patients with partly removed lesions appeared to benefit from post-operative radiotherapy; the median survival period after subtotal tumor resection was 37 months with and 26 months without radiotherapy ( $P = 0.0089$ ) [70]. Shaw et al. analyzed of the subset of 63 patients who underwent subtotal resection alone or with RT showed that the median survival was 2 years for the eight patients with subtotal resection alone; 4 and 7 years for the 26 patients with surgery and low-dose (<5,000 cGy) RT; and 7.9 years for the 29 patients receiving surgery and high-dose RT ( $\geq 5,000$  cGy) [71, 72]. In similar retrospective studies

post-operative radiotherapy increased survival for several authors [73, 74] and had no impact [75, 76].

The respective indications for RT and chemotherapy are not well defined. Two multiinstitutional randomized trials have been performed to determine the contribution of PCV to OS and PFS of patients with newly diagnosed high-grade oligodendrogliomas. The RTOG 9402 study compared exclusive radiotherapy to dose-intensive PCV administered immediately before radiotherapy. The EORTC 26591 investigated the value of six cycles of PCV after radiotherapy compared with exclusive radiotherapy. In both studies PFS is better after association of radiotherapy and chemotherapy but OS is not significantly modified [21, 22]. In both studies 80% of patients assigned to the radiotherapy only group received chemotherapy at recurrence. The absence of benefit in OS may be a result of the efficacy of chemotherapy at the time of recurrence. It is regrettable that these randomized trials did not include an arm using exclusive chemotherapy, with OS and quality-of-life end points. In fact, these patients may well respond to RT, which, for small-volume tumors, may be the simpler therapeutic choice [77].

The EORTC 22845 [78] experience with low-grade gliomas has led to important conclusions: because radiotherapy delays progression, delaying radiotherapy results in lower PFS. However, radiotherapy delivered at relapse results in equivalent OS. It remains to be proven that delaying radiotherapy does not extend the field of radiation. It will be crucial to understand if delaying radiotherapy improves quality of life. Only Q-TWIST analysis in a randomized setting may be able to answer such a question [79].

In this series, PFS and OS did not differ significantly among the three treatment groups. As usual for retrospective studies, there are obvious biases. Initial prognostic factors were less favorable in the group of patients treated with exclusive RT. They had higher tumor grades. In all groups, second-line treatment was delivered at time of relapse, suggesting a similar philosophy of successive medical teams.

Our findings of 5-year OS of 71% and 5-year PFS of 44% after exclusive chemotherapy suggest that exclusive front-line chemotherapy is an efficient treatment. Exclusive chemotherapy with careful follow-up did not seem to reduce survival in our patients. First-line exclusive chemotherapy with PCV was advised as an option in the French “standard option and recommendations” [1]. Delaying radiotherapy with careful follow up seems possible but RT is a major treatment of oligodendroglioma. The search for 1p 19q deletion that was not available during the period of our study, may modify such conclusions in the future: selection of patients with molecular biology may isolate subgroups that would benefit more of this strategy.

Therefore, it may be suggested that, despite inevitable biases, this study may serve as a foundational randomized study for further strategies.

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