Oligodendrogliomas: A Review

Sajeel Chowdhary, MD
H Lee Moffitt Cancer Center and Research Institute

Marc C Chamberlain, MD
H Lee Moffitt Cancer Center and Research Institute

Corresponding author:
Marc C Chamberlain, MD
H Lee Moffitt Cancer Center and Research Institute
Department of Interdisciplinary Oncology
Neuro Program
12902 Magnolia Drive
Ste 2010
Tampa, FL 33611
Tel: (813) 745-3295
e-mail: chambemc@moffitt.usf.edu

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Abstract:

Oligodendroglial tumors represent approximately 4-7% of all gliomas, however, in some series the incidence has been reported to be as high as 10-20% due to improved histological appreciation and recently recognized molecular signatures. Oligodendroglial tumors are classified as being low-grade oligodendroglial tumors (O), high-grade anaplastic oligodendroglial tumors (AO) or mixed oligo-astrocytic tumors. The mixed tumors can again be low- (OA) or high-grade (AOA). The recent EORTC and RTOG randomized trials have provided level 1 evidence regarding best management of these tumors. This review provides an overview of oligodendroglial tumors and discusses contemporary and evolving treatment strategies.

Introduction:

Oligodendroglial tumors are increasingly recognized as a result of improved histological appreciation and the presence of a molecular signature that characterizes these tumors.

Oligodendroglial tumors are a subtype of glioma and may be either low-grade (so-called oligodendroglioma: O), high-grade (so-called anaplastic oligodendroglioma: AO)
or as a component of a mixed malignant glioma (MMG). MMG may in addition, be either low- (oligoastrocytoma: OA) or high-grade (anaplastic oligoastrocytoma: AOA).

Supratentorial low-grade gliomas (LGG) comprise a group of primary central nervous system (CNS) neoplasms that includes both O and OA and which in adults, often become (>60%) become anaplastic. By contrast, in children, LGG even at time of recurrence typically remain low-grade.

The treatment of oligodendrogial tumors has been better defined since the recent completion of five randomized trials, three involving LGG including both O and OA and two concerned with AO and AOA.

**Definition:**

The classification of gliomas (of which oligodendrogial tumors are a subtype) is based upon the presumed cell of origin and the degree of malignancy. Classification systems are derived from two original pathological schemes. The first was first proposed by Bailey and Cushing and posited that gliomas were derived from transformation of normal glial cells at some point during their development [1]. The second system proposed by Kernohan was based upon the extent of observed anaplastic features such as mitoses, endothelial proliferation, cellular atypia, and necrosis [2]. Both of these classification schemes persist in revised form. The first is the foundation for the World Health Organization (WHO) classification published in 1993 [3], while the second continues to be used in modified form called the St. Anne-Mayo Clinic schema (Daumas-Duport system) [4]. Studies by Zulch directly resulted in the development of the WHO classification of CNS tumors [5]. The WHO classification from 2000 of brain
tumors from the is the most commonly pathological schema used for oligodendrogial and other CNS tumors[3].

LGG is a frequently used term, but it is not clearly defined by either of these classifications. These tumors have also been referred to as "benign" gliomas however neuro-oncologists recognize LGG as malignant albeit with the potential for relatively long survival. Although LGG have a more favorable prognosis than glioblastoma (GBM), they are only occasionally associated with prolonged (>10 years) survival and, over their natural history, frequently develop characteristics similar to more aggressive gliomas.

**Molecular biology:**

Kraus described shared allelic loss of chromosome 1p and 19q in both O and OA tumors suggesting a common origin of these tumors [6]. These losses most consistently mapped to the 19q and 1p regions, with allelic loss frequencies ranging from 40% - 86% for 19q and 50% - 83% for 1p.

Zhu has in addition reported loss of heterozygosity on chromosome 4 in O [7]. Reifenberger described losses on 9p and chromosome 10 in oligodendroglial tumors in particular anaplastic variants [8]. It is believed that the losses on chromosome 10 may encode for tumor suppressor genes as yet unidentified. It is now believed that the losses on chromosome 9p may encode for \(CDKN2A\) and \(CDKN2B\) [9,10]. The 19q and 1p losses are seen in both O and AO and are thus thought to be early important events in oligodendroglial tumorigenesis. Many studies have shown that pure O tumors commonly display allelic loss of 1p and 19q and astrocytic tumors contain \(TP53\)
mutations. Low grade OA tumors may either demonstrate an astrocytic (TP53) or oligodendroglial (1p/19g) genotype [9,10].

Cairncross further demonstrated that loss of chromosome 1p is a statistically significant predictor of chemosensitivity, and combined loss involving chromosomes 1p and 19q is statistically significantly associated with both chemosensitivity and longer recurrence-free survival after chemotherapy (alkylating agents) [10]. Multivariate and univariate analysis showed that losses involving 1p and 19q were associated with longer overall survival. CDKN2A gene deletions, found on 9p, were associated with worse prognosis, as well as ring enhancement on magnetic resonance images (MR) [10].

Di Rocco described the expression of the platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), and their receptors in oligodendroglial tumors [11]. They showed that the mitogen PDGF, which has been shown to have a role in neoplastic proliferation and is highly expressed in human glial tumors, is also expressed in O and may be acting in an autocrine stimulatory loop.

Chan examined the expression of VEGF and its receptors in oligodendroglial tumors [12]. This study revealed that VEGF, which has been shown to induce neovascularization in tumors, particularly in response to hypoxia, was expressed in all AO but only infrequently (1/3) in O. In addition, the VEGF receptors were highly expressed in the tumor vasculature of AO, but were weak or undetectable in O. Chan concluded that anaplastic progression of O may occur as a result of small zones of VEGF-expressing cells inducing early vascular proliferation, followed by an accelerated phase of angiogenesis closely associated with VEGF induction around areas of necrosis.
Fallon and Perry described the prognostic value of 1p, 19q, 9p, 10q and EGFR-FISH analyses in recurrent O [13]. Their data suggests that in O, 1p/19q tumor status was a predictor of patient survival, even after recurrence. Fallon described p16 deletions, most common with tumor progression. By contrast, 10q deletions and epidermal growth factor receptor (EGFR) amplifications were sufficiently rare in oligodendroglial tumors to suggest the possibility of an alternate tumor histology.

Walker recently described the molecular pathology and clinical characteristics of oligodendroglial neoplasms [14]. The authors investigated allelic imbalance at 1p36, 19q13, 17p13, 10p12-15, and 10q22-26 and p53 mutation in 100 consecutive oligodendroglial neoplasms. The -1p/-19q genotype, seen in 64%, 34%, 77%, and 30% of O, OA, AO, and AOA respectively, was inversely related to p53 mutation and 17p13 loss. Genotype was unrelated to tumor location and could not distinguish high-grade tumors that presented de novo from those that progressed from a previous lower grade malignancy. Presentation with seizures was more common in cases with the -1p/-19q genotype, and these remained stable for longer before treatment. In longitudinal samples, 74% retained their initial histological differentiation, whereas 29% showed new genetic alterations, the -1p/-19q genotype being acquired in three cases. Loss of 1p36 and 19q13, 17p13, chromosome 10, and p53 mutation were significantly associated with survival in Kaplan-Meier analysis (p < 0.01), and loss of 1p36 and 19q13 and loss of 17p13 retained significance in multivariate analysis. In this series, clinical differences in tumors with and without the -1p/-19q genotype support a genetic approach to aid diagnosis and prognostication for oligodendroglial neoplasms.
**Classification:**

LGG, considered by the WHO as predominantly Grade II gliomas in adults, occur approximately one-fifth as frequently as the more malignant gliomas. These tumors may develop in any CNS location. LGG in a broad spectrum term that comprises several tumor types including low-grade astrocytoma (LGA), O and OA.

Anaplastic oligodendroglial (AO) tumors are considered by the WHO as Grade III glioma as are AOA. As treatment differs, the treatment of O and OA will be discussed first followed by a discussion of AO and AOA.

**Low-Grade Oligodendrogloma**

**Incidence:**

Rubinstein described O as representing 4-7% of all intracranial gliomas [15]. By contrast, Burger reported a higher incidence of oligodendroglial tumors (10-15%) amongst all primary brain tumors [16]. Coons described O tumors as comprising 25% of all gliomas, a significantly higher proportion than previously recognized. [17]. O and OA are more common in males and most often present in patients in their 2nd to 4th decade of life.

**Clinical presentation:**

Not infrequently, there is a delay between identification of a tumor by imaging studies (and believed to represent a probable LGG) and the time that histological confirmation is obtained. LGG (including O and OA) are likely when patients present with a transient neurologic disturbance consistent with seizure, and imaging reveals a non-enhancing hemispheric mass that produces little mass effect.
Neurologic symptoms generally reflect either the location of the tumor (e.g. hemiparesis, ataxia) or the result of increased intracranial pressure (e.g. headache, nausea/vomiting or change in mental status).

Still controversial is how to best manage patients with non-enhancing presumed LGG. In patients who are otherwise neurologically normal aside from tumor-related seizures (well controlled on anti-epileptic drugs), many physicians are reluctant to recommend biopsy or resective surgery and propose a “watch and wait” approach. In patients with neurological deficits, maximum safe resection is recommended. In non-resectable tumors (i.e. eloquent region of brain), observation with or without a biopsy may be advocated. However regularly scheduled neuroimaging is recommended. In patients deferring histological diagnosis, careful observation is reasonable until either symptoms or neuroimaging findings worsen. Whether such a delay in diagnosis and treatment significantly affects outcome of LGG is discussed below.

**Radiology:**

Lee and Van Tassel described CT imaging characteristics of O [18]. O were most often supratentorial and as many as 60% of them calcified. Oligodendroglial tumors are commonly seen as a large, calcified, poorly to non-enhancing peripheral frontal tumors. Higher grade lesions (i.e. AO and AOA) more often enhance and are associated with hemorrhagic and necrotic areas. Among 831 consecutive patients with primary brain tumors, tumor contrast enhancement on CT was present in 96% of GBM, 87% of all high-grade gliomas, 57% of anaplastic gliomas, and 21% of LGG [19a, 19b]

Lee recently characterized MR features of O and OA and concluded these tumors were indistinguishable radiographically [20, 21]. The most common MR appearance was
an amorphous, stippled pattern with minimal enhancement on T1-weighted (T1W) images following gadolinium. Characteristic was the finding of a honeycomb pattern on T1W images which reflects the tumor matrix of O and has been described in only one other primary parenchymal intracranial tumor, the intraventricular neurocytoma. Contrast enhancement was commonly minimal if present, dot-like or lacy in appearance, or most often, absent. As with CT, robust contrast enhancement is most commonly associated with an anaplastic tumor i.e. AO or AOA. Calcification was present in the majority (58%) of O and OA.

**Pathology:**

O and OA appear as a sheet of round cells with a well-defined cytoplasmic membrane and an empty-looking cytoplasm (the so called fried egg appearance) [22]. Tumor cell density is usually low, but focal hypercellularity may be present. A rich thin-walled capillary network, calcification, and cortical invasion with perineuronal, perivascular, or subpial neoplastic cells (i.e. satellitosis) are often present. As is common of all LGA, accurate histological diagnosis may be challenging and not infrequently, neuropathologists disagree as to tumor subtype in a given patient.

**Survival:**

Although considered to have a somewhat more favorable prognosis than LGA, the behavior of O is similar, in that younger patients (i.e. < 40 years of age) with no neurological deficits and who undergo complete resection, have a better prognosis [23-26].

In adults, the majority of LGG eventually de-differentiate to a higher grade tumor [27-31]. In one series of 53 adults with supratentorial LGG, in whom the majority had
subtotal or gross total resection and postoperative RT, the median overall survival (OS) was 7.3 years with a five-year survival of 64% [28]. Deaths were generally due to evolution into an anaplastic astrocytoma or GBM. The median time to progression (TTP) was 4.5 years after the original surgery, and the survival from recurrence was only 12 months. In this and other studies, young age, good performance status, and the clinical presentation of an isolated seizure with an otherwise normal examination were generally good prognostic features [27, 32- 42]. Oligodendrogial tumors also abide by the before mentioned criteria for good prognosis (see below). On the other hand, CT contrast enhancement of the original tumor appears to predict a high likelihood of progression to a malignant lesion [28].

More recent data suggests that patients with O and OA have a prolonged natural history. In a retrospective review of 106 patients with O or OA, the majority of whom had either biopsy alone or subtotal resection, the median TTP was 5 years (range 0.5 to 14.2), and the median OS was 17 years [31]. Recurrence eventually developed in 68% of patients. Disease-free and OS did not differ with immediate or deferred therapy (see below).

**Treatment:**

The goals of treatment are symptom management, minimize treatment-related morbidity, prevent or delay tumor progression and deter malignant transformation (hypothetical).

**Symptomatic Management:**

Symptomatic management usually consists of headache and seizure management. Seizures associated with hemispheric O and OA can be a source of major morbidity and
are more refractory to medical management than idiopathic epilepsy [43]. Over one-half of patients with a short preoperative duration of seizures (less than one year) will have near complete or total resolution of seizures after tumor resection. Although it is difficult to definitively demonstrate that it is superior to a standard tumor resection, some surgical neuro-oncologists advocate seizure-type surgery with intraoperative recording to localize the seizure focus and permit resection of the source of refractory seizures [44,45].

**Surgical Management:**

In the absence of controlled prospective trials comparing surgical approaches, there are several surgical perspectives advocated [46,47]. The early surgery advocates recommend maximum safe resection at the time of diagnosis, regardless of symptoms. This approach is based upon the belief that complete resection improves survival and may decrease the rate of malignant transformation [48]. Intraoperative MR has been used to assist the surgeon identify small lesions and to improve the extent of tumor resection [49-51].

Trials by the European Organization for Research and Treatment of Cancer {EORTC} (discussed below) have demonstrated that the extent of surgical resection of LGG (including O and OA) favorably affects outcome [33,34,36,38, 53-56]. Alternatively, some neuro-oncologists have described excellent outcomes in patients who underwent biopsy only or in whom surgery is deferred [57].

**Radiotherapy:**

Karim described the efficacy of radiotherapy (RT) and the presence of a dose-response relationship for LGG in two multicenter randomized trials conducted by
the EORTC [58]. For the dose-response trial, 379 adult patients with cerebral LGG were randomized to receive irradiation postoperatively with either 45 Gy or 59.4 Gy. With 343 (91%) eligible and evaluable patients a minimum follow-up 50 months (median 74 months), there was no significant difference in terms of OS (58% for the low-dose arm and 59% for the high-dose arm) or the progression free survival [PFS] (47% and 50%) between the two arms of the trial. However, this prospective trial revealed important determinants of prognosis (see below). Importantly, EORTC trial 22844 did not demonstrate an advantage for low-dose versus high-dose RT (i.e. no advantage to high-dose RT).

Van den Bent updated the Karim study conducted by the EORTC (trial 22845) describing 314 adult patients with LGG [59]. Patients after surgery were assigned to either early RT of 54 Gy or deferred RT at the time of progression (control group). Patients with LGG, O and OA and incompletely resected pilocytic astrocytoma, with a WHO performance status 0-2 were eligible. 157 patients were assigned early RT and 157 were assigned to deferred RT. Median PFS was 5.3 years in the early RT group and 3.4 years in the control group (hazard ratio 0.59, 95% CI 0.45-0.77; \( p<0.0001 \)). However, OS was similar between groups: median OS in the early RT group was 7.4 years compared with 7.2 years in the deferred RT group (hazard ratio 0.97, 95% CI 0.71-1.34; \( p=0.872 \)). In the control group, 65% of patients received RT at progression. At 1 year, seizures were better controlled in the early RT group. It was concluded that early RT after surgery lengthens the period without progression but does not affect OS. Because quality of life was not studied, it is not known whether time to progression reflects clinical deterioration. RT could be deferred for patients with O and OA who are in a good
condition, provided they are carefully monitored.

An intergroup study conducted by the North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG), and Eastern Cooperative Group (ECOG) randomized 211 adults to low- versus high-dose RT [60]. There was no difference in the 5-year OS or PFS rates between the two dose groups in either study. Similarly in a small Phase II Southwest Oncology Group (SWOG) study randomized 60 adults with incompletely resected LGG to RT alone or RT plus lomustine (CCNU) chemotherapy [60]. There was no difference in outcome between the two treatments arms.

Shaw summarized the results of these four prospective clinical trials of supratentorial LGG in adults [60]. The data from nearly 1,000 patients treated on these studies addressed the following three current controversies in the RT management of patients with LGG. Optimum timing of RT, optimum RT dose and addition of chemotherapy to RT. The 5-year OS and PFS rates in these four studies ranged from 58% to 72% and from 37% to 55%, respectively. Significant prognostic factors included extent of surgical resection, histology, tumor size, and age.

Pignatti described prognostic factors in accordance with EORTC in adult patients with cerebral LGG, derived a prognostic scoring system, and validated results using an independent data set [42]. Cox analysis was performed on 322 patients from EORTC trial 22844 (construction set), and the results were validated on 288 patients from trial 22845 (validation set). Patients with pilocytic astrocytomas were excluded from this prognostic factor analysis. Multivariate analysis on the construction set showed that age ≥ 40 years, astrocytoma histology
subtype, largest diameter of the tumor ≥ 6 centimeters, tumor crossing the midline, and presence of neurological deficit before surgery were unfavorable prognostic factors for survival. The total number of unfavorable factors present can be used to determine the prognostic score. Presence of up to two of these factors identifies the low-risk group, whereas a higher score identifies high-risk patients. The validity of the multivariate model and of the scoring system was confirmed in the validation set. These factors can be used to identify low-risk and high-risk patients. These prognostic factors may help in defining further treatment on an individual basis.

Although relatively well tolerated, RT is not without potential long-term morbidities. A significant concern regarding RT is delayed neuropsychological sequelae [61-63]. It has been suggested that this complication is overstated [64] as cognitive decline is a function not only of RT, but also the tumor and antiepileptic drug use [63a]. Surma-aho in a single institution study of 51 patients undergoing resection for cerebral LGG, compared 28 who received post-surgery RT (but no chemotherapy or secondary surgery) to 23 patients who received no further therapy, including RT [61]. At a mean follow-up of seven years, the RT group performed significantly worse on tests of cognitive function, and had more severe MR-defined leukoencephalopathy, which correlated with poor memory. Kiebert in a follow-up study to EORTC 88245 described the effects of RT dose on cognitive decline [62]. An increased frequency of long-term adverse effects was noted in patients treated with a higher dose (59.4 Gy versus 45 Gy). Brown described a low frequency of cognitive decline in patients without tumor progression [65]. In a study by the NCCTG of 203 adults with supratentorial LGG treated with RT and periodically assessed with Feinstein
Mini Mental Status Exam (MMSE), minimal cognitive decline was seen. In patients without tumor progression, deterioration from baseline MMSE occurred at years 1, 2, and 5 in 8.2%, 4.6%, and 5.3% of patients. Patients with significantly impaired baseline MMSE (defined as less than 27), showed even greater declines in performance. However, the lack of discrimination of this tool for neurocognitive assessment (as contrasted with neuropsychological assessments) may have underestimated the number of affected patients.

**Chemotherapy:**

Oligodendroglial tumors, because of their infrequency, are often grouped with LGG in various clinical chemotherapy studies, with little distinction being made concerning histology-specific patient response to chemotherapy and survival. Assessing benefit from chemotherapy can be difficult to judge using standard brain tumor response criteria [66,67], as O and OA are typically non-enhancing, ill-defined, and difficult to measure [68]. Unequivocal clinical improvement that is unaccompanied by a significant reduction in tumor size may indicate benefit, while in some studies, functional imaging (e.g., with thallium-201 SPECT) appears to be a better predictor of tumor control and patient survival than CT or MRI [69]. Nevertheless, the end points of most LGG clinical trials are objective response rate and time to tumor progression. Increasingly recognized however, is the value of FLAIR and T2-weighted MR sequences, which objectively measure tumor and response to treatment. At this time however, there is no validated MR response criteria as contrasted with that commonly used for contrast enhancing gliomas.

**Adjuvant Chemotherapy:**
Eyre for SWOG reported the only randomized study of adjuvant chemotherapy for LGG that was unfortunately closed early due to poor accrual (70). Sixty adult patients with incompletely excised LGG were randomly assigned to receive radiotherapy (55 Gy over a total of 6.5-7 weeks) either alone or with CCNU (100 mg/m² every 6 weeks). Evaluation of patient age, extent of surgery, tumor grade, and performance status showed no significant differences between the treatment arms. The response rate, as judged by the disappearance or reduction in size of the tumor on CT/MR, was 79% for RT alone versus 54% for RT plus CCNU. The median survival time was 4.45 years for all patients, with no significant difference between treatment arms (p = 0.7). For the group as a whole, patient age and performance status were the most important prognostic parameters. The majority of patients receiving chemotherapy experienced moderate hematological toxicity. This study demonstrates that CCNU chemotherapy does not improve the results of RT in the treatment of incompletely excised LGG.

Buckner described a phase II trial of procarbazine, CCNU, and vincristine (PCV) as initial therapy for patients with O or OA [71]. Adult patients with residual tumor on MR following biopsy or subtotal resection of O or OA received up to six cycles of PCV. RT (59.4 or 54.0 Gy) began within 10 weeks of completing PCV or immediately, if there was evidence of tumor progression on PCV. Tumor tissue was analyzed by fluorescent in situ hybridization (FISH) for 1p and 19q deletion and by immunohistochemistry for p53 expression. Eight of 28 (29%) and 13 of 25 (52%) eligible patients demonstrated tumor regression as assessed by the treating physician and a blinded central neuroradiology reviewer, respectively. Myelosuppression was the predominant toxicity. Loss of 1p and 19q were associated with O but not for OA
(p = .009), were inversely associated with p53 detection, and were not associated with response to PCV (possibly because of the small sample size).

Quinn described a phase II trial of temozolomide (TMZ) in patients with progressive LGG not previously treated with RT [72]. TMZ was administered orally once a day (200 mg/m²/day) for five consecutive days. Treatment cycles were repeated every 28 days following the first daily dose of TMZ (5/28 schedule). Forty-six patients with LGG were treated. The objective response rate was 61% (24% complete response; CR and 37% partial response; PR), with an additional 35% of patients having stable disease (SD). Median PFS was 22 months (95% confidence interval [CI], 15 to infinity months) with a 6-month PFS of 98% (95% CI, 94% to 100%) and a 12-month PFS of 76% (95% CI, 63% to 92%).

Brada in a study of thirty LGA treated primarily with TMZ including 11 O and 2 OA tumors reported 3 PR, 14 minimal responses and 11 SD [73]. PFS at 3 years was reported as 66%. Quality of life (QOL) improvement at least in one domain was reported 96% of patients. In addition 54% of patients with epilepsy had reduction in seizure frequency. This small trial suggests TMZ has single agent activity in LGA, provides modest improvement in QOL and control of epilepsy. Recently Mollemann have demonstrated a positive correlation between 1p- 19q- allelic loss and tumor content of MGMT (i.e. O⁶-methylguanine DNA methyltransferase gene hypermethylation) [74]. The authors posits that oligodendroglial tumor sensitivity to alkylator-based therapy is a reflection of low to absent MGMT expression, a repair enzyme of alkylator chemotherapy.
Salvage Chemotherapy:

Recurrent O ands OA respond to various chemotherapies (Table 1), and in particular to PCV and TMZ [67,71,75-79].

Soffietti described a Phase II study to determine the benefits and toxicity of the PCV in patients with recurrent O and OA following either surgery alone or surgery with RT [76]. Patients were treated with up to six cycles of PCV, and response was evaluated by CT or MR. Sixteen of 26 patients (62%) responded to PCV, 3 (12%) experienced CR, 13 (50%) demonstrated a PR, 8 (31%) had SD and 2 (8%) had progressive disease. All symptomatic patients who responded and three with SD improved in seizure frequency, lateralizing signs, and symptoms of intracranial hypertension. The response rate for patients with enhancing lesions (74%) was significantly higher than that of patients with non-enhancing lesions (29%) (p < 0.05). Both O and OA responded to PCV, with complete responses occurring in association with pure O only. The overall median TTP was 24 months and was significantly longer for those with O compared with those with OA (32 versus 12 months) (p <0.001). Chemotherapy was well tolerated, with mild hematological toxicity and rare skin rashes being the most frequent sequelae.

Stege described a study suggesting that PCV chemotherapy may provide a reasonable alternative to RT for the initial treatment of large O and thereby permit deferred RT [80]. However, randomized trials will be needed to confirm the efficacy of this approach. The authors retrospectively studied the outcome of 16 patients with newly diagnosed O and 5 patients with recurrent O treated with PCV and deferred
RT. Loss of chromosome 1p and 19q was assessed using FISH with locus-specific probes. Three of five patients (60%) with recurrent tumors responded. Thirteen of the 16 newly diagnosed patients showed evidence of response with a median TTP of >24 months. Only one of these patients experienced disease progression while receiving PCV. Several patients showed a significant clinical improvement despite minimal MR response. The authors conclude that newly diagnosed patients with O and OA, with or without loss of 1p/19q, responded to PCV chemotherapy.

LGG are also responsive to second-line as well as first-line TMZ [72, 81, 82]. van den Bent described an EORTC Phase II trial (EORTC study 26971) of first-line chemotherapy with TMZ in recurrent O or OA. In this prospective, nonrandomized, multicenter trial, patients were treated with 200 mg/m\(^2\) of TMZ on the 5/28 schedule for 12 cycles. Patients with a recurrence after initial surgery and RT, and with measurable on MR were eligible for this study. Patients with large lesions and mass effect or with new clinical deficits were not eligible. Pathology and MR of all responding patients were centrally reviewed. Thirty-eight eligible patients were included. In three patients, pathology review did not confirm the presence of an O or OA. TMZ was generally well tolerated. The most frequent side effects were hematologic; only one patient discontinued treatment for toxicity. In 20 (52.6%) of 38 patients (95% exact confidence interval, 35.8% to 69.0%), a CR (n = 10) or PR to TMZ was observed. The overall median TTP was 10.4 months and 13.2 months for responding patients. At 12 months from the start of treatment, 40% of patients were still free from progression.

Quinn described a series of 46 patients (which included 20
with OA and 16 with LGA), only one of whom had received prior chemotherapy (PCV), 11 had a CR and 17 had a PR (objective response rate 63%) to TMZ [72]. Response rates for A and O were similar, and the one year PFS rate for all patients was 76%.

Hoang-Xuan reported a somewhat lower objective response rate in 60 previously untreated patients with O or OA treated with TMZ [83]. Although clinical improvement was noted in 51% (particularly in those with uncontrolled epilepsy), only 17% had an objective PR. Nevertheless, the 1-year PFS rate was similar to the prior study, 73%.

Chamberlain described a prospective Phase II study designed to establish the maximum tolerated dose and secondarily evaluate response rate to CPT-11 (irinotecan) in patients with recurrent O [84]. A 15% objective neuroradiographic response (all PR) was seen in this small cohort of patients with recurrent O having failed prior PCV and on cytochrome P450 enzyme inducing AEDs.

Peterson retrospectively analyzed patients with O treated with second, third, or fourth cytotoxic salvage regimens for recurrent O [85]. Despite the small number of patients, two noteworthy trends emerged from their data: first, PCV was a highly effective salvage treatment when used at tumor recurrence following non-PCV chemotherapy regimens, and second, the synergistic combination of VP-16 and CDDP may have anti-oligodendroglioma activity.

Lastly, Soffietti described a phase II study of second-line treatment with carboplatin for recurrent or progressive oligodendrogliarial tumors after PCV [86]. They concluded that when administered according to a monthly schedule, carboplatin exhibited modest activity in adult patients with recurrent or progressive oligodendroglioma or
oligoastrocytoma who experienced treatment failure after PCV chemotherapy.

**Anaplastic Oligodendroglioma**

**Incidence:**

AO and AOA represent 3.5% of newly diagnosed anaplastic gliomas and 15% of all oligodendrogial tumors [87]. Some have described AO and AOA as being the third most common high-grade glioma [88]. AO and AOA occur in males more frequently, and the peak occurrence is during the 5th and 6th decades [87].

**Clinical Presentation:**

Weir described a series of 63 patients with AO and stated that seizures were the most common initial symptom and occurred in 79% of patients [89]. 11% patients presented with headaches, 3% had weakness, 3% mental status changes. In this series, 48% of patients had hemiparesis, 39% papilledema and 31% had mental status changes.

**Radiology:**

Reiche described a study to define the pattern of contrast enhancement in MR and CT of oligodendrogial tumors and to compare this pattern with tumor grade [90]. 12 patients with O and 8 AO were reviewed. All AO showed tumor contrast enhancement on MR and CT. In addition, six O (50%) demonstrated MR contrast enhancement. In five O, tumor calcifications were detected by CT. Of the O, CT showed contrast enhancement in three 3 (33%) and no enhancement in six (67%), while in three cases post-contrast CT was not available. A comparison of contrast enhancement with tumor grade resulted in a p-value of 0.042 for MR and of 0.011 for CT. A combined statistical test of tumor grade and calcifications detected by CT compared with MR
contrast enhancement showed a significant correlation (p=0.014). This data demonstrates that differentiating O from AO based on the MR contrast enhancement is not possible.

**Pathology:**

AO and AOA are more cellular tumors in comparison to O, demonstrate increased nuclear pleomorphism, vascular proliferation, and areas of focal tumor necrosis, but high mitotic activity is required for the diagnosis of AO according to the current WHO classification [3,22]. AO and AOA tumors additionally develop astrocytic features [3,22]. These tumors have a propensity to include large entrapped reactive astrocytes as well as small tumor cells with eccentric non-fibrillar glassy cytoplasm strongly positive or glial fibrillary acidic protein (the so called minigemistocytes).

**Treatment:**

Treatment goals are similar to those of O (see above) however palliation of tumor-related signs and symptoms and disease control are of primary importance.

**Symptomatic treatment:**

Headaches and seizures are managed similar to that described for O and other gliomas [91]. The vasogenic edema that surrounds AO and AOA (and not seen in LGG) contribute significantly to morbidity. This results from disruption of the blood brain barrier, allowing protein-rich fluid to accumulate in the brain extracellular space. Tumor-related disruption in the blood brain barrier is caused by two major mechanisms; the local tumor production of factors that increase the permeability of tumor vessels (i.e. VEGF, glutamate, and leukotrienes) and the absence of tight endothelial cell junctions seen in tumor blood vessels [91]. Furthermore, because the brain is encased in the rigid cranium, unchecked cerebral edema may result in fatal herniation. The majority of patients with
AO/AOA and peritumoral edema can be adequately managed with corticosteroids. However, a reduction in elevated intracranial pressure (ICP) resulting from peritumoral edema may take several days with steroid therapy; thus, other therapies may be required when an acute reduction in ICP is required (i.e. mannitol, CSF diversion).

**Surgery:**

There are no prospective trials regarding the value of resective surgery for patients with high-grade gliomas including AO. However, the Brain Tumor Study Group in a retrospective analysis found a survival benefit for patients having small volume disease (measured by contrast-enhanced CT) following either initial surgery or at the completion of RT [92]. An often quoted paper is that by Lacroix (see below) which retrospectively evaluated the benefit of extent of tumor resection in patients with GBM [93]. This study found that in patients with an image verified complete or near complete resection (defined as (98%+ resection), survival was improved in patients with GBM. Additionally, the position of the National Cancer Center Network (NCCN) as promulgated in the CNS guidelines calls for maximum safe resection [94].

Quigley in a meta-analysis described the relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas [95]. They analyzed 20 reports comprising 5691 patients however, in only 4 reports was the extent of the surgical resection related to survival. In 2 of these four studies, it followed age, histology and performance status in prognostic importance. The 2 remaining studies however did not rank prognostic variables.

In a single institution retrospective study from MD Anderson Cancer Center, Lacroix described a multivariate analysis of 416 patients with GBM and evaluated
prognosis, extent of resection, and survival [93].

Five independent predictors of survival were identified: age, Karnofsky Performance Scale (KPS) score, extent of resection, and the degree of necrosis and enhancement on preoperative MR imaging studies. A significant survival advantage was associated with resection of 98% or more of the tumor volume (median OS 13 months, 95% confidence interval [CI] 11.4-14.6 months), compared with 8.8 months (95% CI 7.4-10.2 months; p < 0.0001) for resections of less than 98%. Using an outcome scale ranging from 0 to 5 based on age, KPS score, and tumor necrosis on MR imaging, Lacroix observed significantly longer survival in patients with lower scores (1-3) who underwent aggressive resections, and a trend toward slightly longer survival was found in patients with higher scores (4-5). Gross-total tumor resection is associated with longer survival in patients with GBM, especially when other predictive variables are favorable. This data, and that mentioned above, argue that near complete surgical resection has prognostic benefit for patients with high-grade gliomas and by extrapolation, AO. This area of treatment however remains controversial.

**Radiation:**

Two recently completed (though not yet published) randomized Phase III trials of AO and AOA are available and summarized below (see adjuvant chemotherapy) [96,97]. In brief, both randomized trials (performed by RTOG and EORTC) show no survival benefit when PCV chemotherapy is added to adjuvant RT (60 Gy given in accordance to RTOG guidelines). However in both trials, PFS was improved in the chemotherapy plus RT arms.
Chemotherapy:

Adjuvant Chemotherapy:

Cairncross recently reported on intergroup randomized clinical trial in which 291 patients with AO or AOA were randomized to upfront RT versus upfront iPCV followed by RT [96]. This study demonstrated that the addition of neoadjuvant iPCV to RT increased the PFS (1.9 years in the RT group versus 2.6 years in the PCV + RT group) but the overall survival in these groups did not significantly change (4.5 years in the RT group and 4.8 years in the PCV + RT group).

van den Bent reported a recent EORTC trial for AO in which 368 patients were randomized to RT followed by PCV or RT alone [97]. The median OS was 36.8 months in the RT + PCV arm and 30 months in the RT arm (not statistically different). Median PFS was 24.3 months in RT + PCV arm and 13.3 months in the RT only arm. Five-year OS was 41.9% in the RT + PCV arm and 35% in the RT only group.

These trials suggest that PCV chemotherapy has a modest benefit in the adjuvant treatment of AO and AOA (improving PFS only) however as both trials have been reported only in abstract form, further data and in particular response of 1p- and 19q-tumors are pending.

Abrey described a Phase II high-dose chemotherapy with stem cell rescue as initial therapy for AO and AOA [98]. Patients were treated iPCV followed by high-dose thiotepa with autologous stem cell rescue for patients with newly diagnosed AO or aggressive O. RT was deferred until evidence of tumor progression. Sixty-nine patients with a median age of 42 (range: 18-67) and a median Karnofsky Performance Score of 90 (range: 70-100) were enrolled. Sixteen patients had a prior diagnosis of O
and 16 had AO pathology. Only patients with neuroradiographically responsive tumors or without evidence of enhancing tumor after surgery and induction therapy were eligible to receive high-dose thiotepa. Thirty-nine patients (57%) completed the transplant regimen; their estimated median PFS is 69 months and median OS has not been reached. Twelve transplanted patients (31%) relapsed. Neither histology nor prior low-grade histology correlated with relapse; however, persistent non-enhancing tumor at transplant conferred an increased risk of relapse (p = 0.028). Thirty patients (43%) did not receive high-dose thiotepa for a variety of reasons most commonly because of stable or progressive disease (n = 21). How to interpret this study is problematic as no intent to treat analysis was presented and furthermore the trial was biased by an enrichment for small volume and responsive tumors.

Salvage Chemotherapy:

Bouffet reported on a small study of PCV for 23 patients with aggressive O or AO or AOA (Table 2) [99]. Sixteen (69%) responded to PCV with CR in two patients and PR in 14. Previously irradiated patients were as likely to respond to PCV as those previously not irradiated. An over 1-year history of seizures was the main clinical prognostic factor of response. All toxicities were manageable and no treatment related deaths occurred. van den Bent (Table 2) similarly described the response rate to PCV in patients with recurrent AO or AOA [100]. This was a retrospective, observational multicenter study. Patients treated with PCV or iPCV for a recurrent AO after surgery and RT with measurable disease were evaluated for response. Stabilized or responding patients received six cycles of PCV unless unacceptable toxicity occurred. Fifty-two patients were included; median TTP for the entire group was 10 months. In 17%
of patients a CR (TTP, 25 months) was obtained, and in 46% a PR (TTP, 12 months) was obtained. Median OS was 20 months.

Although treatment was discontinued for toxicity in seven patients (13%), it was generally well tolerated. The iPCV regimen was more toxic. Patients initially presenting with seizures and patients with tumor necrosis in histological specimens had a better response rate in contrast to patients who had their first relapse within 1 year of first treatment (surgery and RT).

Cairncross described a prospective National Cancer Institute of Canada Clinical Trials Group study of iPCV chemotherapy for AO (Table 2) [101]. In this single-arm multicenter Phase II study, patients with measurable, newly diagnosed or recurrent, contrast-enhancing AO were treated with up to six cycles of PCV. Central pathology and radiology review were mandatory, and rigorous response criteria based on imaging were used. Thirty-three patients entered the trial; nine were excluded subsequently, seven due to ineligible pathology. Eighteen of 24 eligible patients (75%) responded, nine completely (38%), four had stable disease (SD), and two progressed during the first cycle of PCV. Responses were observed in nine of 10 patients (90%) with a preexisting O and 10 of 15 (67%) with necrotic tumors, called GBM by some. Previously irradiated patients were as likely to respond to PCV as those newly diagnosed (11 of 15 [73%] versus seven of nine [78%]). The median TTP was 25.2 months for complete responders, and was 14.2 months or partial responders and 6.8 months for stable patients. Four ineligible patients also responded to PCV; all had gliomas with oligodendroglial differentiation. All responders, eligible or ineligible, were stable or improved neurologically, but nine of 22 (41%) experienced a decline in Eastern
Cooperative Oncology Group (ECOG) performance status of one grade while on PCV. Adverse events on treatment included a death from *Pneumocystis* pneumonia, a severe reversible encephalopathy due to procarbazine, an intratumoral hemorrhage, and a subdural hematoma. All other acute toxicities were anticipated and manageable. They concluded that AO were chemosensitive brain tumors, patients with these tumors respond predictably, durably, and often completely to PCV, and many tolerate a dose-escalated formulation.

In another study of PCV, Brandes described a phase II study of patients with AO and AOA recurrent after RT (Table 2) [102]. 37 patients were enrolled in this study. Of these, 23 had AO (62%) and 14 had AOA (38%). All patients received PCV and cycles were repeated every 6 weeks. There were 11 CR (29.7%) and 11 PR (29.7%) reported and 8 patients had SD (21.6%). The response rate was higher in patients with AO compared with patients with AOA (77.2% vs. 22.7%; P = 0.02). The overall median TTP was 12.3 months, 30.3 months in patients who achieved a CR, 19.1 months in patients who achieved a PR, and 6.1 months in patients with SD. The median TTP was 18.6 months in AO patients and 6.14 in AOA patients. There were no cases of severe toxicity reported although in 16 patients (43%) who were free of disease progression, PCV was discontinued because of toxicity or inadequate recovery after 2 weeks of delay.

Chinot evaluated the safety and efficacy of TMZ in patients with recurrent AO after RT and PCV chemotherapy (Table 2) [103]. Forty-eight patients with histologically confirmed AO or AOA who had received previous PCV were treated with TMZ (using the 5/28 schedule). Eight patients (16.7%) demonstrated a CR, 13 patients (27.1%) a PR (overall objective response rate, 43.8%), and 19 patients
(39.6%) SD. For the entire treatment group, median PFS was 6.7 months and median OS was 10 months. For objective responders, median PFS was 13.1 months and median OS was 16 months. For complete responders, PFS was more than 11.8 months and OS was more than 26 months. Response correlated with improved survival. Twelve patients developed grade 1/2 thrombocytopenia and three patients developed grade 3 or higher thrombocytopenia.

In another TMZ (5/28 schedule) study, van den Bent treated 30 recurrent AO (Table 2) [104]. Nine patients responded: 7 of 27 patients (26%) treated with TMZ and after prior PCV chemotherapy and 2 of 3 chemotherapy-naive patients (both CR). Median TTP in responding patients was 13 months.

**Conclusions:**

In summary, oligodendroglial tumors are increasingly recognized due to increased histological appreciation and the presence of molecular signatures that define these tumors. Oligodendroglial tumors are further stratified into low-grade (O), anaplastic (AO) or mixed low-grade (OA) and mixed high-grade (AOA) histiotypes. Pathology, radiology and cytogenetic studies play a complementary role in diagnosis, decision making and treatment.

Trials of LGG by the EORTC and RTOG that included O and OA have demonstrated that the extent of surgical resection favorably affects outcome. Most importantly, these trials further demonstrated there is no significant difference in survival between high- and low-dose up-front RT or early versus deferred RT except for an improvement noted in PFS with early RT. The benefit of adjuvant chemotherapy for
LGG is as yet not defined as the only randomized trial by SWOG (and using CCNU) showed no benefit. There are however single institution trials which demonstrate that adjuvant chemotherapy may delay the need for RT by 18-24 months. The role of salvage chemotherapy for recurrent O and OA is well established and furthermore, demonstrate that these tumors respond to a panoply of salvage regimens. Issues of controversy in the treatment of O and OA remain and include timing of and extent of surgery, how best to measure response (i.e. FLAIR MR sequence sequential changes) and the role (if any) of adjuvant chemotherapy. Adjuvant chemotherapy for low grade oligodendroglial tumors may like RT, improve seizure frequency [105].

AO and AOA represent 3.5% of newly diagnosed anaplastic gliomas and 15% of all oligodendroglial tumors. The treatment of these tumors has been clarified by the recent randomized trials reported by EORTC and RTOG. These trials somewhat surprisingly demonstrate that adjuvant chemotherapy (either adjuvant PCV or neoadjuvant iPCV) when combined with RT, does not improve survival and furthermore has only modest benefits with respect to PFS. Still unclear is whether genotyping of these tumors predicts for survival in these randomized trials (data not yet reported). Issues relating to the value of extent of surgical resection in AO and AOA may be defined as these large trials as they are further analyzed. Not clear is whether the benefit of concurrent TMZ and RT followed by post-RT TMZ as seen with GBM might also be of value for AO and AOA [106]. Similar to O, AO and AOA are responsive to a variety of salvage chemotherapies.

**Expert Opinion:**
Oligodendroglial tumors when surgically accessible should be completely resected as both the RTOG and EORTC low-grade glioma trials have demonstrated that the extent of surgical resection favorably influences outcome. Whether to observe or surgically resect a newly discovered and suspected O/OA in a neurologically intact patient remains controversial however our bias is to offer surgery when a complete resection is surgically feasible. The benefit of radiotherapy whether administered early or late is defined by the patients enthusiasm for early radiotherapy treatment and the fact that early radiotherapy lengthens progression free survival. Only one trial (SWOG) has examined the utility of adjuvant chemotherapy, CCNU, for LGG and the trial showed no survival benefit when combined with radiotherapy versus radiotherapy only. Our bias is to defer adjuvant chemotherapy for O and OA unless treated on an investigational trial. However, at time of recurrence, O/OA often respond (or stabilize) to salvage chemotherapy suggesting further trials using upfront chemotherapy (i.e. TMZ) are warranted.

Anaplastic oligodendrogliial tumors (AO and AOA), show an improvement in time to tumor progression when treated with adjuvant PCV and radiotherapy when compared to radiotherapy alone. However survival in both groups (RT with or without PCV) is similar though outcome in patients with 1p-, 19q- tumors is still immature. Our bias is to use adjuvant chemotherapy as we believe delaying time to tumor progression results in a better quality of life for patients but recognize there is modest data to support this perspective. When possible, we treat AO/AOA in an adjuvant setting with both chemotherapy and radiotherapy on an investigational trial. Notwithstanding that AO/AOA respond to a variety of chemotherapies at time of recurrence, we advocate
enrollment onto phase 1 and 2 trials as new anti-glioma therapies are needed and best defined in this setting.

**Five Year View:**

Several developments are likely in the next several years regarding the treatment of oligodendroglial tumors. Most likely an understanding of the molecular oncology of chromosome 1p and 19q allelic loss will be defined. Understanding the association between 1p-, 19q- allelic loss and treatment response, will likely lead to new avenues of targeted treatment for oligodendroglial tumors.

Because of the shorter natural history of AO/AOA (mOS 3-4 years), new adjuvant phase 2 trials are nearing completion. Both standard (5/28) and dose-dense (7/14: 7 days on, 7 days off) adjuvant TMZ phase 2 trials are underway and when completed, will likely stimulate interest in the development of a new randomized phase 3 trial for these tumor types. The role of small molecular inhibitors such as platelet derived growth factor receptor inhibitors (i.e. imatinib or Gleevec) is an active study by the North Central Cancer Treatment Group for recurrent oligodendroglial tumors. Trials such as this will likely lead to novel targeted therapies for oligodendroglial tumors, an area of study as yet relatively unexplored and ripe for investigation.

Lastly, it is also likely that a new multicenter randomized LGG trial will be initiated and incorporate experience gained with TMZ in the treatment of GBM. This randomized trial will almost certainly have one arm using concurrent TMZ and RT followed by TMZ similar to the EORTC/NCIC treatment now accepted as standard of
care for GBM. The RTOG has recently initiated a phase 2 trial for high-risk LGA that incorporates both upfront RT and concurrent TMZ followed by TMZ which hopefully will better define the role of adjuvant chemotherapy in the treatment of LGA.

**Key Issues:**

1. Oligodendrogial tumors are increasingly recognized and often associated with a molecular phenotype, allelic loss of 1p and 19q.
2. The treatment of low-grade gliomas including oligodendrogliomas and oligoastrocytomas has been the subject of 4 randomized trials.
3. Radiotherapy dose and timing of radiotherapy have been defined by the abovementioned trials and suggest early treatment delays time to tumor progression but has no effect on overall survival when compared to delayed radiotherapy. Further, a radiotherapy dose of 50-54 Gy appears to offer the best response and least neurotoxicity. Lastly, the inclusion of CCNU to early radiotherapy with respect to survival is similar to that of radiotherapy alone.
4. The treatment of anaplastic oligodendrogial tumors has been the subject of 2 randomized trials.
5. Both trials demonstrate that upfront PCV chemotherapy delays time to tumor progression but has no effect on overall survival when compared to radiotherapy.
6. The majority of recurrent oligodendroglial tumors respond to a variety of chemotherapies including both alkylator- and antimetabolite-based chemotherapy.

**Table 1.**

Oligodendroglioma; Response to chemotherapy.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Median Response [%]</th>
<th>Median response Duration [mons]</th>
<th>Author/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV</td>
<td>60-80</td>
<td>12-18</td>
<td>Soffietti 1998</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>40</td>
<td>6-7</td>
<td>van den Bent 2003</td>
</tr>
<tr>
<td>Taxol</td>
<td>15</td>
<td>10</td>
<td>Chamberlain 1995</td>
</tr>
<tr>
<td>VP-16/CDDP</td>
<td>40</td>
<td>11</td>
<td>Peterson 1996</td>
</tr>
<tr>
<td>Melphalan</td>
<td>55</td>
<td>6</td>
<td>Chamberlain 1988</td>
</tr>
<tr>
<td>CPT-11</td>
<td>15</td>
<td>6</td>
<td>Chamberlain 2002</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>13</td>
<td>3</td>
<td>Soffietti 2004</td>
</tr>
</tbody>
</table>
Table 2.
Chemotherapy for Anaplastic Oligodendroglioma

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Chemo regimen</th>
<th>Prior chemo</th>
<th>CR</th>
<th>PR</th>
<th>Total</th>
<th>TTP</th>
<th>Med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cairncross 1994</td>
<td>24</td>
<td>PCV</td>
<td>-</td>
<td>9</td>
<td>9</td>
<td>18(75%)</td>
<td>16.3 mons</td>
<td>NR</td>
</tr>
<tr>
<td>Kim 1996</td>
<td>32(1)</td>
<td>PCV</td>
<td>-</td>
<td>10</td>
<td>19</td>
<td>29(91%)</td>
<td>15.4 mons</td>
<td>NR</td>
</tr>
<tr>
<td>Bouffet 1998</td>
<td>23</td>
<td>PCV</td>
<td>-</td>
<td>2</td>
<td>14</td>
<td>16(69%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>van den Bent 1998</td>
<td>52</td>
<td>PCV</td>
<td>-</td>
<td>9</td>
<td>24</td>
<td>33(63%)</td>
<td>10 mons</td>
<td>20 mons</td>
</tr>
<tr>
<td>Brandes 2004</td>
<td>37(2)</td>
<td>PCV</td>
<td>-</td>
<td>11</td>
<td>11</td>
<td>22(59%)</td>
<td>12 mons</td>
<td>31 mons</td>
</tr>
<tr>
<td>Triebels 2004</td>
<td>24</td>
<td>PCV</td>
<td>TMZ</td>
<td>2</td>
<td>24</td>
<td>26(17%)</td>
<td>6 mons</td>
<td>NR</td>
</tr>
<tr>
<td>Chinot 2001</td>
<td>48</td>
<td>TMZ</td>
<td>all</td>
<td>8</td>
<td>13</td>
<td>21(44%)</td>
<td>6.7 mons</td>
<td>10 mons</td>
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<tr>
<td>Brandes 2001</td>
<td>9</td>
<td>TMZ</td>
<td>PCV</td>
<td>1</td>
<td>12</td>
<td>13(22%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>van de Bent 2001</td>
<td>3</td>
<td>TMZ</td>
<td>-</td>
<td>2</td>
<td>0</td>
<td>2(66%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>TMZ</td>
<td>PCV</td>
<td>0</td>
<td>7</td>
<td>7(26%)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

CR: complete response; PR: partial response; PCV: Procarbazine, CCNU, Vincristine; TMZ: Temozolomide; TTP: Time to tumor progression; NR: Not reported; OS: Overall survival.
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|---|
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Study demonstrated that anaplastic oligodendrogliomas are chemosensitive brain cancers that respond predictably, durably, and often completely to PCV.


Treatment with intensified PCV in addition to radiotherapy in anaplastic oligodendrogliomas increased the time to progression but the overall survival was unchanged.

97. **van den Bent MJ et al. First analysis of EORTC trial 26951, a randomized phase III study of adjuvant PCV chemotherapy in patients with highly anaplastic oligodendroglioma. In abstract form presented at ASCO 2005.**

Addition of PCV to RT improved time to tumor progression in AO but overall survival was not affected.


