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PCV for Oligodendroglial Tumors: In Search of Prognostic Factors for Response and Survival

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ABSTRACT: ***Background:*** We report survival and pretreatment prognostic factors for survival and chemosensitivity in 53 oligodendrogliomas treated with PCV (procarbazine, lomustine and vincristine) chemotherapy. ***Methods:*** A total of 53 patients with histologically proven oligodendroglioma, anaplastic oligodendroglioma or oligo-astrocytoma and treated with PCVwere extracted from the London Regional Cancer Center database. A retrospective review was conducted to evaluate overall survival and pretreatment prognostic factors for survival and chemosensitivity. ***Results:*** The median survival time from diagnosis was 123.6 months. The overall five- and ten-year survival rates were 72.7% and 52.7% respectively. Age <40, seizure as an initial symptom, absence of cognitive deficit and presence of a homogeneous hypodense lesion without contrast enhancement on the initial pretreatment CT scan were all factors independently associated with favorable outcome. The presence of increased cellularity, pleomorphism, mitosis, vascular proliferation and grading as an anaplastic lesion using these surrogates on pathological assessment, were all associated with an unfavorable outcome in univariable analysis. In multivariable analysis, only the anaplastic grading and presence of increased cellularity were significant determinants of unfavorable survival. The only factor adversely associated with chemosensitivity was the presence of a focal symptom at presentation. ***Conclusion:*** Overall survival is significantly longer in oligodendroglial lesions than in fibrillary astrocytic tumors. A two tier grading system using standard morphological features seems accurate in predicting outcome in these patients. The presence of a neoplastic astrocytic component does not seem to impact the outcome. No clinical, radiological or pathological factor could be identified to reliably predict chemotherapy response.

RÉSUMÉ: PCV dans le traitement des tumeurs oligodendrogliales: à la recherche de facteurs pronostiques de la réponse et de la survie. ***Introduction:*** Nous rapportons des données sur la survie et les facteurs pronostiques de survie et de chimiosensibilité avant traitement chez 53 patients porteurs d'oligodendrogliomes traités par chimiothérapie au PCV (procarbazine, lomustine et vincristine). ***Méthodes:*** 53 patients porteurs d'un oligodendrogliome prouvé par anatomopathologie, un oligodendrogliome anaplasique ou un oligo-astrocytome et traités au PCVont été identifiés dans le registre du London Regional Cancer Center. Une revue rétrospective a été effectuée pour évaluer la survie générale et les facteurs pronostiques de survie et de chimiosensibilité avant traitement. ***Résultats:*** La survie médiane à partir du moment du diagnostic était de 123.6 mois. Le taux de survie général après 5 et 10 ans était de 72.7% et 52.7% respectivement. Un âge inférieur à 40 ans, une crise convulsive comme symptôme initial, l'absence de déficit cognitif et la présence d'une lésion hypodense homogène sans rehaussement du contraste au CTscan initial avant traitement étaient tous des facteurs associés de façon indépendante à un bon pronostic. La présence d'une cellularité accrue, de pléomorphisme, de mitoses, de prolifération vasculaire et le fait que la lésion soit classifiée comme anaplasique au moyen de ces marqueurs à l'examen anatomopathologique ont tous été associés à un pronostic défavorable à l'analyse univariée. À l'analyse multivariée, seule la classification de la lésion comme étant anaplasique et la présence d'une cellularité accrue étaient des déterminants significatifs d'une survie défavorable. Le seul facteur associé négativement à la chimiosensibilité était la présence d'un symptôme focal comme mode de présentation. ***Conclusion:*** La survie générale est significativement plus longue chez les patients atteints de lésions oligodendrogliales que chez ceux qui ont des tumeurs astrocytaires fibrillaires. Un système de classification à deux niveaux basé sur les caractéristiques morphologiques standards semble fournir un pronostic précis chez ces patients. La présence d'une composante astrocytaire néoplasique ne semble pas influencer le pronostic. Aucun facteur clinique, radiologique ou anatomopathologique prédisant la réponse à la chimiothérapie n'a pu être identifié.

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Three major histological types of diffuse infiltrative tumors are recognized by the World Health Organization's classification of gliomas: astrocytomas, oligodendrogliomas and oligo-astrocytomas.[1] These tumors are further classified by subtypes (mainly for astrocytomas) and by histological grading.[2-5] Oligodendrogliomas constitute approximately 5% of all primary brain tumors in traditional reports,[6,7] although more recent

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studies have reported a much higher incidence (25 to 33% of all primary brain tumors) based on expanded diagnostic criteria. According to these studies, oligodendrogliomas would be under-diagnosed to a significant degree.[8-10]

Recognizing the difference in biological behavior and chemotherapy response rate among gliomas, recent studies have emphasized the importance of clearly differentiating oligodendrogliomas from other primary brain tumors.[10] Several reports have established anaplastic oligodendroglioma as a responsive tumor to alkylating agents, most notably to the procarbazine, lomustine and vincristine (PCV) regimen initially described by Levin et al.[11-14] More recently, low-grade oligodendroglioma[15,16] and mixed tumors[17,18] were also found to be responsive to the same regimen. Furthermore, Kirby et al[19] have shown that this regimen can be safely administered before radiation treatment without adversely impacting overall survival.

Even though an overall response rate of up to 75% has been reported in anaplastic oligodendrogliomas treated with this regimen, some patients experienced only minimal or no response at all.[12] Since the PCV regimen is not without side-effects,[20] and other chemotherapy options for oligodendrogliomas have emerged in recent years (carboplatin, etoposide phosphate, temozolomide, thiotepa, melphalan), it would be important to identify, before the initiation of treatment, the patients that are more likely to respond to the PCV regimen.[21,22] Although a recent molecular genetic study has identified allelic loss of chromosomes 1p and 19q as being predictive of chemotherapy response in anaplastic oligodendrogliomas, no pretreatment clinical or histological factor has been found to be predictive of chemotherapy response.[23]

The present retrospective study was conducted with the primary purpose of investigating pretreatment clinical, radiological and histological variables, and their possible predictive relationship to PCV chemotherapy treatment and survival.

Methods and materials

In an attempt to identify pretreatment prognostic factors for PCV chemotherapy response and survival, patients with a diagnosis of oligodendroglioma or oligo-astrocytoma treated with PCV at the London Regional Cancer Center (London, Ontario, Canada) between 1979 and 1997 were identified. Of a total of 143 patients, 53 treated with the PCV or intensive PCV regimen and with complete follow-up information were identified. These 53 patients constitute the basis of this report.

A retrospective review of the medical records was conducted, and the following data were sought: patient epidemiological data, pretreatment clinical and radiological characteristics, histological diagnosis and variables, type of surgical procedure, chemotherapy and radiotherapy treatment details. When data were unavailable from the medical report, it was recorded as missing. Pretreatment performance status was excluded from the analysis because of incomplete data.

Statistical analysis

Survival curves were generated using the Kaplan-Meier method with death due to disease as the end point. Cox regression analysis was used to investigate the association of independent variables with survival. A stepwise regression was employed to identify factors that were independently predictive of survival. Although potentially important prognostic factors may have been excluded, only variables for which at least 50 cases were available were considered as candidates for this multivariable model in order to maintain statistical power.

All but six cases responded to chemotherapy or remained stable. Associations with pretreatment prognostic factors were evaluated using Fisher's exact two-tailed test. With so few subjects not responding to chemotherapy, no attempt was made to develop a multivariable model. Probability values of <0.05 were considered statistically significant. The analysis was conducted using two different groupings, to address divergent opinions regarding the meaning of "stable disease": 1) chemotherapy response/stable disease vs. progression 2) chemotherapy response vs. stable disease/progression.

PCV chemotherapy

PCV regimen was initially reported by Levin et al.[13] Cairncross and Macdonald[11,24] then developed an intensified version (I-PCV).

The total number of cycles administered varied from patient to patient, and was dependent on several factors but, most notably, on the patient's susceptibility to side effects. Each cycle was repeated every six weeks. Doses in subsequent cycles were reduced or the interval between cycles lengthened for hematological and other toxicities, using standard criteria.

Inclusion criteria

Patients included in this series had histologically proven anaplastic oligodendroglioma, anaplastic oligo-astrocytoma, or aggressively behaving low-grade oligodendroglioma or oligo-astrocytoma (as defined by Macdonald et al[15]). They generally had good functional status. Moreover, all patients included had to be assessable for response on imaging modality (MR or CT scans).

Results

Descriptive data

Fifty-three of 143 patients identified with a diagnosis of oligodendroglioma, anaplastic oligodendroglioma, oligo-astrocytomas and anaplastic oligo-astrocytomas were treated with at least one course of PCV, and had complete follow-up data. Of these 53 patients, 29 were male, 24 female. Table 1 delineates the recorded symptoms at presentation.

Although some patients had MRI in order to complete the initial radiological assessment, all patients had CT as an initial imaging procedure. Since the study period covers a significant pre-MRI interval, most of the patients in this study did not undergo a preop MRI (n=42). Therefore, CT characteristics were used for analysis in this study, in order to maintain consistency in reporting data.

As previously reported by other groups, a frontal predominance was found in tumor location (Table 2). There was no side predilection: 25 lesions were right-sided, 25 left-sided and three were classified as bilateral. Other pertinent CT scan descriptives are listed in Table 2.

All the patients in this report were operated on before any adjuvant treatment was initiated. Most patients (n=42) had a subtotal resection, whereas seven patients underwent a gross

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Table 1: Symptoms at presentation

Seizure	38	72%
Headache	11	21%
Cognitive deficits	11	21%
Focal symptoms	8	15%
Visual symptoms	4	7.5%

Visual symptoms refer to visual symptoms related to increase intracranial pressure. Visual field deficits are classified in focal symptoms.

Table 2: Pretreatment CT scan data

Tumor Location		
Frontal	34	
Parietal	7	
Temporal	17	
Occipital	2	
Deep structures	7	
CT Scans Characteristics		
Density	Heterogeneous	Homogeneous-hypodense
	29	17
Calcification	Present	Absent
	24	22
Cystic component	13	25
Mass effect	33	12
Enhancement	20	21

Data not listed in the radiology report were not reported, and are therefore considered as "missing value" in the analysis. Deep structures refer to basal ganglia.

Table 3: Pathology

Pathological diagnoses			
Oligodendroglioma	23		
Anaplastic oligodendroglioma	21		
Oligo-astrocytoma	5		
Anaplastic oligo-astrocytoma	3		
Pathological specifics as reported			
	None to mild	**Severe**	
Cellularity	11	16	
Pleomorphism	26	25	
	None	**Mild/moderate**	**Severely increased**
Mitoses	21	21	10
	Yes	**No**	
Vascular proliferation	18	34	
Necrosis	14	38	
Halo artifact	39	2	
Calcification	24	28	
Chicken wire vascular pattern	30	23	
Peri-neuronal satellitosis	20	33	
Astrocytic component	14	38	

Unavailable data in the pathological report are considered as "missing values" in the analysis.
Peri-neuronal satellitosis could be detected only in samples containing cortical tissue.
Astrocytic component refers to the presence of neoplastic astrocytes in the sample.

Table 4: Treatment characteristics

	Gross total resection	**Subtotal resection**	**Biopsy**
Surgery	7	42	4
	Whole brain	**Opposite field**	**Wedge pairs**
Radiation	10	13	18
	1-3 cycles	**4-6 cycles**	**> 6 cycles**
PCV	21	30	2
	Yes	**No**	
Steroids	11	42	

Unavailable data are considered as missing values in the analysis.
Steroids signify that patients were treated with steroids at the initiation of PCVtreatment, which could act as a confounding factor when response to chemotherapy is assessed.

total resection as assessed by the surgeon and postoperative scan. Only four patients underwent a stereotactic biopsy. For purposes of statistical analysis, these four patients were included in the subtotal resection group.

At our center, and in agreement with recent reports,[10,25] oligodendroglial tumors and mixed tumors are graded using a two-tier system. The pathological diagnoses and histo-pathological variables routinely assessed are listed in Table 3. Using the so-called typical features of oligodendrogliomas,[10] and looking at cellularity, pleomorphism, mitoses, vascular proliferation and necrosis, a final diagnosis and grading using a two-tier system were obtained. According to this system, 23 lesions were classified as oligodendrogliomas, 21 as anaplastic oligodendrogliomas, five as oligo-astrocytomas and three as anaplastic oligo-astrocytomas. To be considered a mixed tumor, a lesion had to display a neoplastic astrocytic component, but no formal fractional threshold was used.[10]

All the patients in this series were treated with at least one cycle of PCV, and received a mean of 3 cycles (median = 4 cycles). In rare instances (n=4), chemotherapy had to be discontinued because of acute side effects. More often, however, chemotherapy was discontinued because of documented tumor progression (n=15) or because of cumulative hematological toxicity (n=11). Seventeen patients received other forms of chemotherapy, with limited success, most often after PCV failure. Twenty-eight patients were initially treated with the I-PCV protocol, whereas 25 received the standard PCV protocol.

Most patients were also treated with radiotherapy (n=48). The

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average dose was 55 Gy. Twenty-four patients underwent radiation treatment before chemotherapy. In that situation, chemotherapy was usually used as a salvage treatment for recurrent or progressive disease, after surgery and routine irradiation. One patient underwent radiation treatment simultaneously with chemotherapy, whereas 23 patients were treated with PCVchemotherapy before radiation. In recent years, it has been common practice at the London Regional Cancer Center to administer neoadjuvant chemotherapy as a primary modality after surgery, and withhold radiotherapy for progression or for consolidation after chemotherapy in high-grade lesions.

Table 4 summarizes treatment characteristics. Because of consistency in treatment options used in this series, treatment factors were not considered in the statistical analysis. This topic will be the focus of a subsequent paper looking at a broader series of patients having been submitted to different treatment modalities.

Patients under dexamethasone treatment while initiating PCV chemotherapy typically had a significant mass effect caused by the tumor and/or peri-tumoral edema. The medication was titrated in accordance to clinical and/or radiological improvement.

Response to treatment and disease specific survival

Overall, six patients (11.5%) progressed on PCV, 13 patients (23%) remained stable during treatment and 34 (65%) showed prolonged chemotherapy response as evidenced by decrease in tumor size and/or decreased enhancement on CT/MRI, and clinical improvement. The radiological response criteria used in the reports were those defined by Macdonald et al.[26]

Median patient follow-up was 62.6 months (2 months to 174.5 months) for this series. Median survival time from diagnosis was 123.6 months (Figure). The overall five and ten year survival rates were 72.7% and 52.7% respectively. At last follow-up, 24 patients (45%) had progressed and eventually died of their disease. Three (5.6%) patients had documented progressive disease and were still alive, two (3.8%) died of unrelated conditions, and one patient (1.9%) suffered lethal treatment complications. In the whole series, 22 patients (41%) experienced, and were still experiencing at last follow-up, a regression and/or stabilization in their disease, and one patient (1.9%) was still showing no sign of residual disease. The median interval between diagnosis and PCV use was 49 months for the whole series, and this delay did not correlate with response (p=0.09) or survival (p=0.26). Looking at a possible relationship between response and the progression-free interval or survival, there was no evidence of an association when the analysis was carried using the grouping of *No response/Stable disease vs. Response*. When looking at *No response vs. Stable disease/ Response,* an association was suggested (p=0.017 for disease specific survival, p=0.002 for progression-free interval). However, there were only six events in the *no response group*, and this finding might not be valid.

Survival by pretreatment prognostic factors

Univariable associations which cause specific survival are reported in Table 5. As reported in other studies,[27-30] younger age was predictive of better survival, as was initial presentation with seizures. On the other hand, the presence at diagnosis of a clinically significant alteration in cognitive function was found to adversely impact survival (p=0.032). Formal quantitative

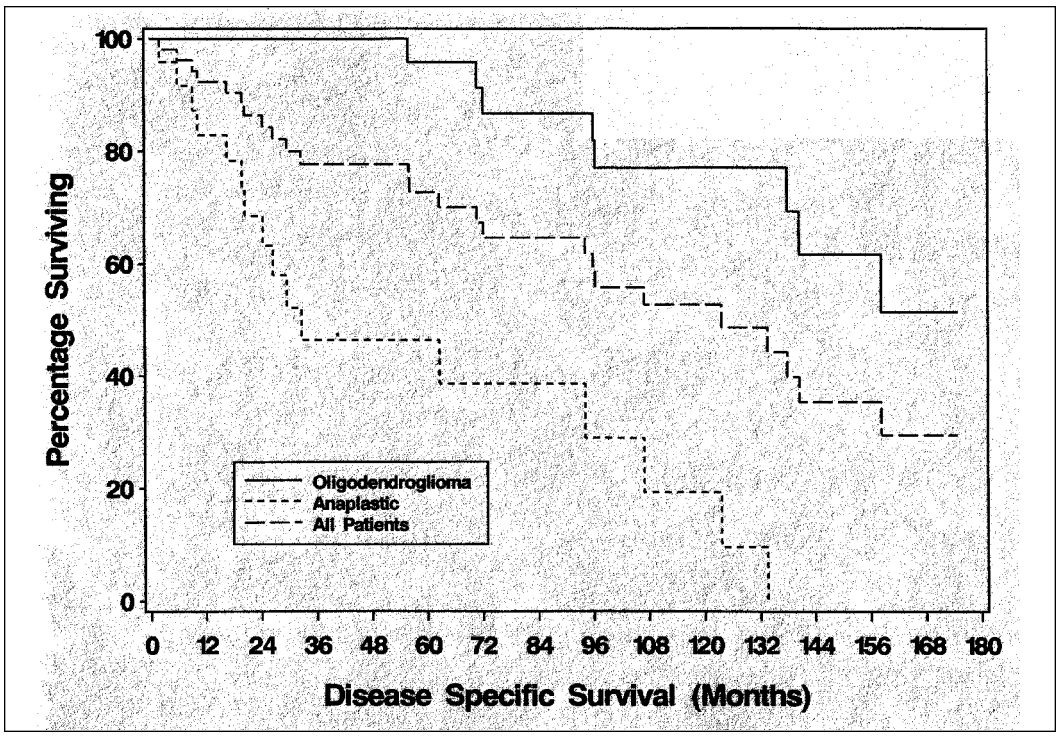

Figure: *Overall disease specific survival and overall survival by histological diagnosis*

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Table 5: Statistical correlation between each parameter studied and disease specific survival in univariable analysis.

Prognostic factor	Risk ratio	95% CI	P value
Gender (M vs. F)	0.572	0.255, 1.287	0.177
Age at diagnosis (<40 vs. ≥40)	2.328	1.026, 5.285	0.043
Symptom interval prior to diagnosis (<2 vs. ≥2 Months)	0.937	0.420, 2.092	0.874
Headache (No vs. Yes)	2.509	0.974, 6.460	0.057
Seizure (No vs. Yes)	0.160	0.060, 0.426	<0.001
Cognitive symptoms (No vs. Yes)	2.633	1.087, 6.379	0.032
CTtomographic location: Frontal No vs. Yes)	1.002	0.439, 2.289	0.996
CT topographic location: Temporal (No vs. Yes)	0.777	0.321, 1.880	0.576
Hemisphere involved (right only vs. left)	1.015	0.457, 2.254	0.970
Density of tumor at CT(hypodense vs. hyperdense/heterogeneous)	0.233	0.068, 0.794	0.020
CT - Calcification (No vs. Yes)	1.236	0.510, 2.994	0.639
CT - Presence of mass effect (No vs. Yes)	2.677	0.906, 7.909	0.075
CT- Presence of cyst (No vs. Yes)	1.872	0.606, 5.786	0.276
CT- Contrast enhancement (No vs. Yes)	5.888	2.053,16.889	0.001
Final pathological diagnosis -grading (oligo+ oligo-astro vs. anaplastic)	10.118	3.590,28.520	<0.001
Pathology - Cellularity of specimen (none/mild/moderate vs. severe)	2.573	1.115, 5.941	0.027
Pathology - Pleomorphism (none vs. mild/moderate/severe)	4.039	1.576,10.349	0.004
Pathology - Mitoses (none vs. mild/moderate/severe)	3.040	1.230, 7.512	0.016
Pathology - Vascular proliferation (No vs. Yes)	4.402	1.861,10.413	<0.001
Pathology - Necrosis (No vs. Yes)	3.710	1.647, 8.360	0.002
Pathology - Calcification (No vs. Yes)	2.061	0.900, 4.719	0.87
Pathology - Neoplastic astrocytic component (Yes vs. No)	1.086	0.424, 2.780	0.864
Treatment - Total # PCV cycles received (1-3 vs. > 3 cycles)	0.852	0.380, 1.909	0.697
Steroids administered with first cycle of PCV(No vs. Yes)	3.798	1.656, 8.712	0.002

Table 6: Factors associated with disease specific survival in the multivariable model

Prognostic factor	Risk ratio	95% CI	P value
Symptoms interval prior to diagnosis (<2 vs. ≥2 Months)	0.322	0.115, 0.903	0.031
Final pathological diagnosis - grading (oligo/oligo-astro vs. anaplastic)	58.136	11.131, 303.638	<0.001
Pathology - Cellularity of specimen (none/mild/moderate vs. severe)	5.053	1.657, 15.408	0.004
Pathology - Calcification (No vs. Yes)	3.137	1.165, 8.447	0.024

neuro-cognitive data were not routinely obtained in these patients. In the given context, cognitive function refers to clinically assessable cognitive surrogates such as memory, personality, speech, calculus, attention and concentration.

Tumor density, expressed here as the difference between a uniformly hypodense lesion and a lesion with mixed signals, was a significant prognostic factor. Patients with homogeneous hypodense lesion were found to have better prognosis (p=0.02). Neither the presence of calcification, nor that of cysts, was found to be of any prognostic significance. The presence of enhancement was strongly associated with an adverse prognosis (p=0.001).

Cellularity, pleomorphism, the presence of mitosis, vascular proliferation and necrosis were all found to be significantly associated with an adverse outcome. Since only tumors with oligodendroglial differentiation were considered in this report, the pathological diagnosis was mostly the reflection of the grade, and was found to be highly associated with survival (p<0.001) (see Figure).

Multivariable analysis for disease specific survival

The four factors presented in Table 6 were the only significant independent prognostic factors at p level <0.05. Prediagnosis symptoms interval ≥2 months was the only significant clinical variable and was associated with a favorable outcome. Interestingly, the three other significant variables were

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pathological variables: final diagnosis, cellularity of specimen and finding of calcification were statistically significant. To maintain statistical power, the surrogate "final diagnosis" was analyzed after the following grouping: oligodendroglioma/oligoastrocytoma vs. anaplastic oligodendroglioma/anaplastic oligoastrocytoma. This surrogate therefore reflected primarily the tumor grade. Anaplastic grade was, as expected, associated with an adverse outcome. An earlier analysis of these four groups could not demonstrate any influence on survival of the presence of an astrocytic component (data not shown). Interestingly, the cellularity of the specimen, recognized for its subjectivity and interobserver variability,[8] was also found to be adversely associated with survival. The presence of calcification in the specimen was found to be a prognostically favorable variable.

Pretreatment factors associated with chemosensitivity

Median progression free interval from PCV initiation was 90.7 months. When the data sets were grouped for analysis in response/stable disease vs. no response, the presence of focal symptoms as a pretreatment clinical variable was adversely associated with chemosensitivity (Table 7). No pretreatment factor possibly predictive of chemotherapy response was associated with the second analysis, looking at groups no response/stable vs. chemo response. Total number of PCVcycles as a treatment variable was associated with chemosensitivity in both analysis, but this association is probably the reflection of a treatment bias. The grading was not found to influence chemoresponsiveness. Tumors that were graded as oligodendroglioma and treated (so-called aggressive lesions radiologically, with low grade histology) responded as well as anaplastic lesions; of a total of ten such lesions, eight responded radiologically (partial response/complete response).

Discussion

Disease specific survival

The median survival time from diagnosis in our series was 123.6 months. The overall five- and ten-year survival rates were 72.7% and 52.7% respectively. Given the fact that this series includes low grade and anaplastic oligodendroglial lesions, it is not surprising that these results appear to be superior to those generally reported.[20,30-37] Histological criteria for diagnosis and grading of oligodendrogliomas are still disputed, and this probably explains in part the variability in results when survivals from retrospective series are reported.[8-10,25] Generally, a median survival of ten years for low-grade, and five years for anaplastic oligodendroglioma is accepted.[38] The longer survival for this series might reflect a selection bias, since only patients treated with PCV were included. Arguing for a selection bias in this series is the high percentage of patients who presented with seizure (72%), a clinical factor typically associated with a favorable outcome in many studies, including the present report ($p<0.001$). The usual incidence of seizures reported as a presenting sign in oligodendroglial lesion series is typically around 50%.[38]

On the other hand, a significant number of patients diagnosed with a low-grade oligodendroglial-based lesion were followed serially with scans (either MR or CT) without showing any signs of progression after surgery, deferring further treatment. These good outcome patients were therefore excluded from this series.

The presence of cognitive deficit at presentation was associated with an unfavorable survival. One might be tempted to attribute this finding to the location of the lesion, its mass effect, and/or its possible unresectability. However, 87% of the patients in this series did not have gross total resection. Moreover, tumor location and the presence of a significant mass effect, as assessed on initial CT scan were not found to impact on survival in this report. We did not find the favorable survival association with frontal localization reported in some series.[27,39] Interestingly, a deep-seated localization, expected to be an adverse prognostic finding for survival (since it virtually eliminates all chances of a gross total resection and tends to compromise patients function sooner in disease evolution) was not found to be so in this series.

The presence of a heterogeneous lesion on initial CTscan was associated with an adverse outcome when compared to a uniformly hypodense lesion, highlighting the more quiescent biological activity of the latter. This comes as no surprise, since the precontrast hyperdense lesions were included in the heterogeneous lesions group; this finding on CT scan is known to be associated with hypercellularity.[40] Contrast enhancement on initial CTscan was strongly associated ($p=0.001$) with shorter survival in the univariate analysis. Enhancement on initial CT scan and seizure as presenting symptoms, although significant in univariate analysis, were not found to be so in the multivariate model. These surrogates were, however, highly correlated with grade, which was found to be significant as a prognostic factor in univariate and multivariate analysis. This only emphasizes the finding in some recent studies that contrast enhancement on CT or MR scan can be used as an adjunct for the grading of oligodendroglioma.[25]

Since all the tumors included in this series were oligodendrogliomas, the accuracy in diagnosis criteria could not be assessed. The diagnosis of oligodendrogliomas is an area of great controversy, and there is no consensus as to what are the best criteria to recognize these lesions. The same can be said on the grading of these tumors. Most of the grading systems dedicated to the classification of glial tumors apply mainly to fibrillary astrocytomas.[3,6,41] They are generally of little value in the evaluation of oligodendroglial tumors, where they do not always produce prognostically relevant information. Classification specifically designed for oligodendrogliomas have therefore been put forward by some authors. Smith[42] introduced, in 1983, a four tier grading scheme for oligodendrogliomas, but not all of its five histopathologic features were found to be independently significant determinants for tumor progression. His system was later modified by Kros[43] to a three-tier system, which was more predictive of survival. In 1992, Shaw[37] reported on the lack of statistical significance of a four-tier grading system, and recommended a two-tier system. More recently, Daumas-Duport[25] also recommended a two-tier system based on a comprehensive review of 153 "pure" oligodendrogliomas. In our study, using a two tier system based on the recognition of cellularity, pleomorphism, mitoses, vascular proliferation and necrosis, the grading was found to be highly predictive of survival in both univariable and multivariable analysis ($p<0.001$).

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Table 7: Statistical association between pretreatment factors and chemotherapy response. (Yes/Stable Disease vs. No response)

Prognostic Factor	Category	f/n (%)	PValue
Gender	Male	25/28 (89.3%)	>.999
	Female	21/24 (87.5%)	
Age at diagnosis	<40	24/26 (92.3%)	0.668
	≥40	22/26 (84.6%)	
Symptom interval prior to diagnosis	<2 Months	28/32 (87.5%)	>.999
	≥2 Months	18/20 (90.0%)	
Headache	No	36/42 (85.7%)	0.582
	Yes	10/10 (100.0%)	
Visual symptoms	No	43/48 (89.6%)	0.397
	Yes	3/4 (75.0%)	
Seizures	No	11/14 (78.6%)	0.325
	Yes	35/38 (92.1%)	
Cognitive symptoms	No	37/41 (90.2%)	0.595
	Yes	9/11 (81.8%)	
Focal symptoms	No	41/44 (93.2%)	0.04
	Yes	5/8 (62.5%)	
CTtopographic location - Frontal	No	15/19 (79.0%)	0.175
	Yes	31/33 (93.9%)	
CTtopographic location - Temporal	No	32/35 (91.4%)	0.379
	Yes	14/17 (82.4%)	
CTtopographic location - Parietal	No	39/45 (86.7%)	0.58
	Yes	7/7 (100.0%)	
CTtopographic location - Occipital	No	45/50 (90.0%)	0.219
	Yes	½ (50.0%)	
CT topographic location - Deep Structures	No	39/45 (86.7%)	0.58
	Yes	7/7 (100.0%)	
Hemisphere involved with tumour	Right Only	21/25 (84.0%)	0.411
	Left Side Involvement	25/27 (92.6%)	
Density of tumour at CT	Hyperdense/Heterogeneous	24/28 (85.7%)	0.281
	Hypodense	17/17 (100.0%)	
CTcalcification	No	20/22 (90.9%)	>.999
	Yes	21/23 (91.3%)	
CT- presence of cyst	No	24/25 (96.0%)	0.107
	Yes	10/13 (76.9%)	
CT- presence of mass effect	No	11/12 (91.7%)	>.999
	Yes	28/32 (87.5%)	
CT- contrast enhancement	No	19/21 (90.5%)	>.999
	Yes	17/19 (89.5%)	
Type of surgery	Biopsy/Subtotal	39/45 (86.7%)	0.58
	Gross Total	7/7 (100.0%)	
Final pathological diagnosis	Oligo	27/28 (96.4%)	0.079
	Anaplastic	18/23 (78.3%)	
Cellularity of specimen	None/Mild/Mod	32/35 (91.4%)	0.348
	Severe	12/15 (80.0%)	
Pleomorphism	None	18/19 (94.7%)	0.387
	Mild/Mod/Severe	26/31 (83.9%)	
Mitoses (None vs. Mild/Moderate/Severe)	None	19/21 (90.5%)	>.999
	Mild/Mod/Severe	26/30 (86.7%)	
Vascular proliferation	No	31/33 (93.4%)	0.168
	Yes	14/18 (77.8%)	
Necrosis (No vs. Yes)	No	34/38 (89.5%)	0.638
	Yes	11/13 (84.6%)	
Pathology - fried-egg fixation artefact	No	2/2 (100.0%)	>.999
	Yes	35/38 (92.1%)	
Pathology - calcification on specimen	No	23/28 (82.1%)	0.199
	Yes	23/24 (95.8%)	
Pathology - neoplastic astrocytic component	No	33/37 (89.2%)	0.661
	Yes	12/14 (85.7%)	
Total # PCV cycles received	1-3	15/21 (71.4%)	0.003
	>3	31/31 (100.0%)	
Steroids given with first cycle of PCV(No vs. Yes)	No	38/41 (92.7%)	0.101
	Yes	8/11 (72.7%)	

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The literature has presented conflicting views regarding the influence on survival of individual histological morphologic features. Pleomorphism, mitosis, cell density and necrosis were found to be independently significant prognostic factors in certain studies, but not in others.[8-10,31,42-46] In univariable analysis, cellularity (p=0.027), pleomorphism (p=0.004), mitoses (p=0.016), vascular proliferation (p<0.001) and necrosis (p=0.002) were all found to be significant prognostic determinants for survival in the present report. In multivariable analysis, only the cellularity of specimen was significant (p=0.004). Mib-1 staining was not routinely done at our institution, but was instead used selectively in specimens with difficult interpretations. Numerous studies now support the routine use of objective proliferative index techniques for grading purposes.[39,47-51]

In a previous report, Macdonald et al[15] defined the term aggressive oligodendroglioma, referring to oligodendroglioma with an aggressive clinical behavior, regardless of the histopathological grading. On serial imaging scans (CT/MRI) following the surgical procedure, those lesions would either show an increase in size, or an increase or *de novo* appearance in contrast enhancement. At this institution, only patients with aggressively behaving lesions are treated with PCV, and therefore, regardless of the grading listed in Table 3, all patients included in this series were considered as having aggressive oligodendrogliomas and treated with PCV.

Noteworthy is the lack of influence of a significant neoplastic astrocytic component in the tumor. Therefore, neoplastic astrocytic cells would not adversely influence the prognosis of an oligodendroglial tumor. This finding, combined with the report by the Radiation Therapy Oncology Group that the simple presence of a neoplastic oligodendroglial component in fibrillary astrocytic tumor was sufficient to confer a better prognosis, might actually be helpful in redefining the concept of mixed tumor.[10,52,53]

Since all the patients in this report were treated with a fairly constant combination of surgery and PCV chemotherapy before or after radiation, treatment variables were not considered in the analysis (see Table 4 for details). The only factor considered was the use of steroids at initiation of PCV treatment, and was shown to be an adverse prognostic factor, probably reflecting the presence of a significant mass effect at chemotherapy initiation.

Prognostic factors predictive of chemotherapy response

For the reason already mentioned, we could only look at association between pretreatment factors and chemotherapy response (Table 7). The association between chemotherapy response and total number of PCV cycles administered is intuitively a treatment bias: if the patient is unresponsive to PCV, the treatment will obviously be discontinued.

The only other factor associated with chemotherapy response was the absence of a focal symptom at initial presentation (p=0.04). If validated, this association could be related to the morphological tumor type, as described by Daumas-Duport et al.[9] According to this scheme, there would be three different macroscopic morphologic patterns of tumor growth:

- Solid tumor tissue - Structure type 1
- Isolated infiltrative tumor cells (permeating intact brain parenchyma)- Structure type 3
- A combination of both- Structure type 2

Oligodendrogliomas would present either as structure type 2 or 3.[9] Structure type 3 (infiltrative parenchyma without a mass) was associated, in a study by the same group, with a better prognosis than type 2.[25] Type 2, because it is not only infiltrating the brain parenchyma but also distorting it by its mass effect, is more susceptible to produce focal symptoms. This form of tumor (type 2) might be less prone to respond to chemotherapy. This in turn could be related to the intrinsic biology of this morphologic subtype, or to a chemotherapy delivery issue (vascularization). It would also be interesting to investigate the possible relationship between these morphologic tumor types, chemo-sensitivity and molecular genetic anomalies, more specifically the allelic loss of chromosomes 1p and 19q.

Conclusion

Gliomas with oligodendroglial differentiation are chemosensitive tumors. The PCV regimen is a reliable and easy to administer chemotherapy combination for the treatment of these lesions. So far, it is the gold standard treatment to which any new modalities should be compared. Overall survival is significantly longer in oligodendroglial lesions than in fibrillary astrocytic tumors. A two tier grading system using standard morphological features seems accurate in predicting outcome in these patients. The presence of a neoplastic astrocytic component does not seem to impact the outcome. No reliable pretreatment factor predictive of chemotherapy response could be identified in this series, and so clinical and histological variables should not be used as reliable surrogates in the decision process to administer chemotherapy in these patients. Further molecular genetic studies are required, and these studies might yield standardized guidelines that will incorporate molecular genetic analysis as an integral part of the therapeutic decision process in patients with primary brain tumors.

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