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Oligodendroglioma: clinical study and survival analysis correlated with chromosomal anomalies

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Object. Demonstration of the loss of chromosomes 1p and 19q in the presence of a brain neoplasm marks the emergence of genotype as a prognostic indicator. The authors report gene expression data for oligodendroglioma and correlate genotype with response to therapy. Gene expression subgroups may represent distinct types of disease.

Methods. Eighty-seven cases of supratentorial oligodendroglioma were selected from 145 cases treated in a single center between January 1990 and December 2001. Fluorescence in situ hybridization was used to determine the status of chromosomes 1p and 19q. Parameters evaluated included clinical data and radiological and histological features. Univariate and multivariate analyses were performed and a probability value less than 0.05 was considered significant.

The patients included 48 women and 39 men. The overall mean age at presentation was 45 years for women and 36 years for men ($p = 0.006$). The univariate analysis identified the following as favorable prognostic factors: younger patient age ($p = 10^{-5}$), female sex ($p = 0.0025$), seizure as a presenting symptom ($p = 10^{-5}$), normal clinical examination ($p = 10^{-5}$), absence of lesion enhancement on neuroimaging studies ($p = 0.0231$), lack of histological necrosis ($p = 0.0003$), absence of mitoses ($p = 0.0014$), 1p and 19q deletions ($p = 0.0001$), absence of recurrence ($p = 0.0021$), and adjuvant radiotherapy and/or chemotherapy ($p = 10^{-5}$). The multivariate analysis identified patient age ($p = 10^{-5}$) and chromosomal anomalies ($p = 0.002$) as independently linked to survival. Three molecular subtypes emerged: oligodendroglioma with 1p and 19q deletions, oligodendroglioma demonstrating polysomia and a lack of meaningful response to radiotherapy or chemotherapy, and oligodendroglioma with no 1p-9q deletion in which partial response was seen.

Conclusions. According to our data, oligodendrogliomas could be divided into three molecular subtypes. Although chemotherapy seems efficient for managing this tumor, additional studies should be conducted to compare the efficacy of radiotherapy and chemotherapy.

KEY WORDS • oligodendroglioma • fluorescence in situ hybridization • 1p-19q deletion • polysomia • prognosis

Recent studies have shown that the combined loss of chromosomes 1p and 19q is a genetic predictor of chemosensitivity and prolonged overall survival in oligodendroglioma.[5,6,40,44] Fifty to seventy percent of oligodendroglial tumors are characterized by a loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q),[3,5,6,15,34,40,44] and practically all tumors with this combined loss of 1p and 19q respond to chemotherapy.[6,15] The demonstration of this correlation made genotyping of brain tumors a useful indicator of therapeutic outcome.[6,44]

Chromosomal studies are performed using several techniques[3,17,18,31,34,40] including FISH. Fluorescence in situ hybridization is a molecular cytogenetic investigation that uses recombinant DNA technology to analyze both metaphase and interphase cells. Because it can assess both dividing and nondividing cells, FISH can make an important contribution to retrospective studies.[19,29,34]

The possibility that gene expression subgroups may represent distinct types of a disease[2,6,12–14,42] has led us to describe gene expression data for oligodendroglioma in relation to its biological behavior and its response to therapy.

Abbreviations used in this paper: CI = confidence interval; CT = computerized tomography; FISH = fluorescence in situ hybridization; MR = magnetic resonance; WHO = World Health Organization.

CLINICAL MATERIAL AND METHODS

The surgical pathology files of the neurosurgery department of Rennes University Hospital were searched for cases of oligodendroglioma. Records of patients who presented between January 1990 and December 2001 were selected. All patients were initially admitted to the neurosurgery department for surgical procedures and histological diagnosis.

Histopathological Analysis

All initial histological specimens were reviewed for confirmation of the original diagnosis by a single neuropathol-

ogist who was blinded to patient data except for presence or absence of contrast enhancement.

The definition of oligodendroglioma was that according to the WHO.[15] The histological parameters that were evaluated included necrosis, vascular proliferation, mitosis, and cell density. Cellularity was defined as low, moderate, or high according to the presence or absence of neuropil between tumor cells. Necrosis was recorded as present when observed in at least one area in the total histological samples examined. Mitosis counts were performed in the most mitotically active area of the tumor at high-power magnification. The single highest mitosis count per 10 hpf was recorded. Endothelial proliferation was defined as low rate when confluence between endothelial cells was observed and as high rate when glomeruloid aspects were observed.

All tumors were classified according to both WHO[20] (Grades II and III) and St. Anne (Grades A and B) classifications.[9,10] Tumors were classified as low grade (A-II) when two criteria were present. These included no or few mitoses ($<$ 5/hpf), low or moderate cellular density, and/or a low vascular proliferation rate. Specimens were classified as high grade (B-III) if they showed high cellular density, intense vascular proliferation, numerous mitoses, and necrosis (and contrast enhancement for the St. Anne grading system).

Immunohistochemical studies involving glial fibrillary acidic protein, neurofilament, and Ki-67 stains were performed on all tumors. The presence of vascular endothelial growth factor, p27, p18, and MIB1 were retrospectively assessed in 84 specimens. Glial fibrillary acidic protein staining was always negative except in astrocytic areas ($<$ 20% of the total sample examined). Staining for neurofilament was negative and that for Ki-67 was usually positive.

Fluorescence in Situ Hybridization Analysis

Fluoresence in situ hybridization was used to evaluate allelic losses of chromosomes 1p36 and 19q13 on formalin-fixed paraffin-embedded tissue specimens (M. Le Calve, et al., manuscript in preparation). The study was performed as previously described,[29,39] and the molecular biology team was blinded to the clinical data and follow up. Individual samples embedded in paraffin blocks were examined histologically, and blocks predominantly composed of neoplastic cells were selected. Hematoxylin and eosin–stained slides served as a guide for the fluorescence microscopic study that was performed on interphase nuclei of 5-μm-thick paraffin sections, and was performed according to the Vysis procedure (Vysis, Inc., Des Plaines, IL). The DNA probes were developed from different bacterial artificial chromosome clones specific to 1p36, 19q13, 1q23, and 19p23. Plasmid DNA extraction was performed according to the Qiagen protocol (Plasmid Midi Kit; Qiagen, Valencia, CA). Probes were directly labeled with either spectrum red (Vysis, Inc.) for 1p36 and 19q13 or spectrum green (Vysis, Inc.) for 1q23 and 19p23 by using the Nick Translation Kit (Vysis, Inc.). Probes were tested on normal metaphases for their specificity before being applied to paraffin sections, and the technique was first tested on 12 normal samples from our nervous tissue database.

For each specific chromosome probe, hybridization signals were scored from a minimum of 200 nonoverlapping nuclei. Counting was only effective when the nuclei showed clear signals and all fluorescent dots showed similar intensity. Deletions were defined as samples demonstrating one signal over more than 50% of the nuclei. Polysomia was confirmed on either chromosome when more than 10% of nuclei exhibited three or more signals for one or both probes.

Patient Population

Of 145 newly diagnosed oligodendrogliomas, 33 tumors with neoplastic astrocytes or an astrocytic component of more than 20% of the total cells were classified as oligoastrocytomas and were excluded from the study. Twenty-five cases were excluded because the diagnosis was based on stereotactic biopsy sampling, which may not necessarily sample a representative specimen of the lesion. The charts of the remaining 87 patients with supratentorial oligodendroglioma were reviewed. Clinical data systematically assessed included patient age, sex, presenting symptom, duration of symptoms, neurological examination at admission, and tumor location.

All patients underwent either CT (with and without contrast agent) and/or MR imaging (with and without gadolinium) studies performed before surgery and repeated within 72 hours after surgery.

All patients underwent subtotal or gross-total resection. The neuroimaging studies were reanalyzed when available (69 patients) to confirm the presence or absence of contrast enhancement of the tumor and the quality of the resection; otherwise the operative record and data obtained by the neurooncology staff were consulted.

Total excision was performed if there was no residual enhancement for the high-grade nor hypodensity or hyposignal for the lower-grade lesions; otherwise subtotal excision was performed.

Survival time was measured from the date of surgery until death or the last clinical evaluation before January 12, 2004. The mean follow-up period from surgery was 61 $\pm$ 40 months (range 3–160 months), and no patients were lost to follow up. In 19 patients the date of death was obtained from the local record office. Neither quality of life nor the Karnofsky Performance Scale score was evaluated. No patient experienced leptomeningeal dissemination or distant metastasis.

All patients were treated surgically, and all patients included in the study survived the procedure. Adjuvant therapy was not performed in 21 patients (24%); 36 (41%) received radiotherapy or chemotherapy, 29 (33%) only radiotherapy, and one patient only chemotherapy.

The median physical radiation dose was 54 Gy (range 45–60 Gy) with no dose difference related to age or sex. The number of chemotherapy-associated "cures"[11] was variable, with a mean of five cures (range three–15). A combination regimen of procarbazine, lomustine, and vincristine was the most commonly used.

Statistical Analysis

The statistical values were computed using available software (SPSS Version 12.0 for Windows; SPSS, Inc., Chicago, IL). Correlations of categorical variables were investigated using the Pearson correlation test. Bilateral associations showing statistical significance at a probability level of 0.05 were considered in our analysis.

The survival analysis first consisted of computing Kaplan–Meier survival curves to estimate the mean and median survival for each parameter. The survival curves were compared using univariate Cox regression analysis after checking for the proportionality of hazard and crude hazard ratios with their 95% CIs and by using both the generalized Wilcoxon and the log-rank (Mantel–Cox) tests, with a probability value less than 0.05 considered statistically significant.

Time to progression was analyzed using the Kaplan–Meier model, and patients with or without local progression were considered for analysis of this variable, the event being recurrence.

A multivariate Cox analysis was performed using Wald criteria and both forward and backward regression.

RESULTS

The data for our study population are summarized in Table 1.

Age and Sex Distribution

The 87 patients included 48 women (55%) and 39 men (45%). The overall mean age at presentation was 41 ± 15 years (range 5–73 years). The women were older (mean 45 ± 16 years [range 11–73 years]) than the men (mean 35 ± 13 years [range 5–67 years]), and this difference was statistically significant ($p = 0.006$).

The chromosomal anomaly distribution was homogeneous with regard to sex and age.

Clinical Features

Seizures were the most frequent presenting symptom (66%) compared with other presenting symptoms, including signs of intracranial hypertension, neurological deficit, and mental deterioration. Seizure remained the most frequent presenting symptom, even when adjusted to chromosomal findings, and was most often linked to a normal neurological examination (50 of 59 cases), whereas other presenting symptoms were usually linked to an abnormal neurological examination (21 of 28 cases).

The mean duration of symptoms before tumor detection was 16.5 months (range 1 day–132 months) when seizures appeared at onset and 8 months (range 1–102 months) for other presenting symptoms. The interval between onset and diagnosis was longer in patients younger than 50 years (16 months) than in those older than 51 years (7 months). Adjusted to chromosomal anomalies, the mean duration of symptoms was shorter in patients with polysomia (5 months) than in patients with 1p and 19q deletions (15 months) or without such deletions (16 months).

The most commonly involved anatomical site was the frontal lobe (59%), with a significant statistical correlation between location and first symptom. In 40 frontal locations (74%) the presenting symptom was epilepsy. There was no correlation between chromosomal anomalies and onset, neurological examination, or location.

Neuroimaging Features

Contrast enhancement on neuroimaging studies correlated with both presenting symptoms and findings at the clinical examination. Enhancing lesions were most frequent in patients who presented with symptoms other than seizure. In patients with epilepsy as the first symptom, the rates of enhancing and nonenhancing lesions were similar regardless of age.

Of 28 patients whose neurological examination demonstrated abnormal findings, 26 (93%) had enhancing lesions, and there was no difference when the findings of the neurological examination were normal (28 of 59 patients had nonenhancing lesions). No correlation existed between chromosomal anomalies and neuroimaging features.

Molecular Analysis

The FISH assay revealed three categories of patients: the first group with a 1p and/or 19q deletion, the second group with no 1p or 19q deletion, and the third group in which polysomia was observed.

Histological Features

Of the clinicopathological correlations observed, we focused on the link between vascular proliferation and neuroimaging enhancement. This correlation was positive in 78% of cases. In 54 cases with histological vascular proliferation imaging enhancement was evident, and in 14 cases a lack of vascular proliferation and imaging enhancement was observed. In 22% of cases, the correlation was negative. In 16 patients with vascular proliferation no imaging enhancement was demonstrated and three tumors that enhanced on neuroimages had no vascular proliferation. None of the histological parameters was linked to specific chromosomal anomalies.

Thirty-two tumors (36%) were histologically classified as low-grade oligodendroglioma (WHO Grade II), and the remaining 53 tumors (54%) represented anaplastic tumors (Grade III). When tumors were graded by the St. Anne classification, 14 (16%) were classified as Grade A and 73 (84%) as Grade B. The discrepancy between the two grading systems is due to a misclassification of some intermediate grades representing benign histological features and imaging enhancement. There was no relationship between the WHO or St. Anne grade and the chromosomal findings.

Patient Survival

Univariate Analysis. Table 2 shows the survival time according to clinicopathological features and treatment modalities. Thirty-two deaths (37%) were recorded (nine patients with Grade II and 23 with Grade III lesions compared with five patients with Grade A and 27 with Grade B lesions).

The median follow-up period was 53 months. The mean overall survival was 107 ± 40 months (range 3–160 months). The overall median survival was not reached.

Men survived longer than women; however, after adjustment for age there was no difference in survival between the two sexes. Age was of prognostic value. Seizures were of good prognostic value compared with other presenting symptoms. Findings of the neurological examination were of prognostic value. Patients with normal neurological findings survived longer than patients with neurological deficits. Patients with enhancing lesions had worse outcomes than those with nonenhancing lesions. Tumor location alone was not predictive of survival. Of the histological fea-

TABLE 1

*Clinical and pathological findings, molecular genetic characteristics, and outcomes in the patient population**

Variables	No. of Patients	Age (yrs)			Sex		CT/ MRI		Chromosomal Anomalies		
		< 25	26–50	≥ 51	M	F	NE	E	1p/19q Deletion	No Deletion	Polysomia
total no. of patients	87	13	51	23	39	48	30	57	50	18	19
age 0–25 yrs	13				8	5	7	6	5	7	1
age 26–50 yrs	51				26	25	19	32	34	5	12
age ≥ 51 yrs	23				5	18	4	19	11	6	6
male	39	8	26	5			15	33	26	6	7
female	48	5	25	18			15	24	24	12	12
seizure	57	10	37	10	29	28	26	31	35	11	11
other presenting symptoms	30	3	14	13	10	20	4	26	15	7	8
examination											
normal	59	13	38	8	29	30	28	31	35	10	14
abnormal	28	0	13	15	10	18	2	26	15	8	5
location of tumor											
frontal	51	8	30	13	24	27	19	32	27	12	12
other	36	5	21	10	15	21	11	25	23	6	7
CT/MRI											
NE	30	7	19	4	15	15			15	6	9
E	57	6	32	19	24	33			35	12	10
cellularity											
weak–moderate	47	9	29	9	22	25	25	22	22	11	14
intense	40	4	22	14	17	23	5	35	28	7	5
absent	64	9	41	14	29	25	30	34	38	12	14
present	23	4	10	9	10	13	0	23	12	6	5
vascular proliferation											
absent	17	4	10	3	7	10	14	3	7	4	6
present	70	9	41	20	32	38	16	54	43	14	13
mitoses											
<5 cells/hpf	64	12	40	12	32	32	29	35	38	12	14
>5 cells/hpf	23	1	11	11	7	16	1	22	12	6	5
grading											
WHO Grade II	32	7	21	4	15	17	21	11	13	7	12
WHO Grade III	55	6	30	19	24	31	9	46	37	11	7
St. Anne Grade A	14	4	8	2	6	8	14	0	4	4	6
St. Anne Grade B	73	9	43	21	33	40	16	57	46	14	13
excision											
total	49	7	29	13	24	25	17	32	24	14	11
subtotal	38	6	22	10	15	23	13	25	26	4	8
treatment											
surgery alone†	21	8	12	1	13	8	14	7	11	7	3
surgery & radiotherapy†	29	2	11	16	7	22	10	20	18	7	5
surgery & radiotherapy & chemotherapy†	36	3	27	6	19	17	6	30	21	4	11
outcome											
dead	32	0	14	18	8	24	6	26	10	8	14
alive	55	13	37	5	31	24	24	31	40	10	5
no recurrences	50	10	26	14	28	22	17	33	33	12	5
recurrences	37	3	25	9	11	26	13	24	17	6	14

* E = enhanced; NE = nonenhanced.

† One patient had only surgery and chemotherapy and was not included.

tures, absence of necrosis and mitoses were related to survival and had statistical significance. Tumor grade, as determined using either the WHO or St. Anne grading system, had no statistically significant effect on patient survival; however, WHO grading was of prognostic value with regard to the chromosomal anomaly (Fig. 1).

A review of the records did not reveal why some patients underwent postoperative radiotherapy and others did not, nor the timing of chemotherapy. This therefore raises the question of whether selection bias occurred. The distribution of treatment modalities according to patient age and clinical examination was inconsistent. The median ages were 30, 40, and 50 years for the groups treated by surgery, surgery plus radiotherapy and chemotherapy, and surgery plus radiotherapy, respectively. In most patients who underwent surgery and radiotherapy the clinical examination yielded abnormal findings in contrast to those patients treated by surgery alone, in whom the findings were normal. We therefore did not conduct a comparative study of the different treatment modalities.

The extent of resection (mean survival 109 months for total excision compared with 101 months for subtotal excision), even adjusted to chromosomal anomalies, was not of prognostic value. The overall mean survival period for the

TABLE 2

*Survival period according to clinical parameters**

Parameter	No. of Patients	Groups	Overall Survival (mos)				
			Mean ± SE	95% CI	Median ± SE	95% CI	p Value
age (yrs)	13	0–25	censored		—	—	0.0000†
	51	25–50	122 ± 9	105–139	—	—	
	23	>50	34 ± 6	22–47	20 ± 9	3–37	
sex	48	female	86 ± 11	65–107	82 ± 29	26–138	0.0025†
	39	male	124 ± 8	108–141	—	—	
clinical onset	57	seizures	128 ± 8	113–143	—	—	0.0000†
	30	other symptoms	55 ± 9	38–72	33 ± 10	14–52	
neurological examination	59	normal	120 ± 7	106–134	—	—	0.0000†
	28	abnormal	68 ± 13	42–93	27 ± 9	10–44	
neuroimaging enhancement	57	present	95 ± 9	77–113	93		0.0231†
	30	absent	124 ± 10	105–142			
tumor location	51	frontal	114 ± 9	96–132	—	—	0.2553
	36	nonfrontal	80 ± 9	63–98	—	—	
mitoses	64	<5/hpf	120 ± 8	104–135	—	—	0.0008†
	23	>5/hpf	70 ± 14	43–97	27 ± 5	17–37	
necrosis	64	absent	122 ± 8	106–137	—	—	0.0003†
	23	present	66 ± 13	40–92	28 ± 9	11–45	
St. Anne Grade	14	A	104 ±17	72–136	—	—	0.8674
	73	B	107 ± 8	91–123	—	—	
WHO Grade	32	II	114 ± 10	94–134	—	—	0.1799
	55	III	100 ± 9	82–119	—	—	
excision	49	total	109 ± 10	90–128	—	—	0.9564
	38	subtotal	101 ± 10	81–121	—	—	
treatment modalities	87	overall survival	107 ± 7	93–122	—	—	
	66	surgery & radiotherapy	94 ± 9	77–111	93		
	37	surgery & chemotherapy	118 ± 11	97–139	—	—	
chromosomal anomalies	50	1p-19q deletion	130 ± 9	113–146	—	—	0.0001†
	18	no 1p-19q deletion	83 ± 14	56–109	—	—	
	19	polysomia	51 ± 10	31–71	—	—	
time to disease progression	87	overall	92 ± 8	76–108	72		
	37	w/ chemotherapy	115 ± 11	93–137	—	—	
	66	w/ radiotherapy	101 ± 9	82–119	—	—	

* SE = standard error; — = not reached or not applicable.
† Statistically significant.

entire group was 107 months. The overall survival adjusted to radiotherapy or chemotherapy indicated that chemotherapy improved overall survival, but radiotherapy did not.

Survival adjusted to chromosomal anomalies was 130 months for both 1p and 19q deletions (Fig. 2 *left*). Survival adjusted both to chromosomal anomalies and radiotherapy showed no benefit from radiotherapy (Fig. 2 *center*), whereas chemotherapy did improve survival (Fig. 2 *right*).

In our paper, we use the term local progression rather than recurrence. Even when macroscopic resection is total, complete histological removal is seldom achieved due to the infiltrative growth pattern of oligodendroglioma. All tumor progression occurring in the immediate vicinity of the primary tumor indicated a poor prognosis.

The overall mean survival period of patients with no local progression was 128 months compared with 77 months in those with local progression ($p = 0.0021$). The rate of local progression stratified to chromosomal anomalies was 33% in the single chromosome deletion and no-deletion groups compared with 74% in the polysomic group ($p = 0.008$). The death rate was 20% for 1p-19q deletion, 44% for no 1p-19q deletion, and 73% for polysomia ($p = 0.005$).

The overall mean time to local progression was 92 months, and there was no difference between total excision (mean 93 months) and subtotal excision (mean 87 months). Radiotherapy improved the overall mean time to progression (101 months) although not to a statistically significant extent, whereas chemotherapy did so significantly (mean 115 months). The mean time to progression adjusted to chromosomal anomalies was 107 months for patients with 1p-19q deletions (Fig. 3 *left*). Radiotherapy, adjusted to chromosomal anomalies in the 1p-19q deletion group, significantly improved time to progression (mean 122 months; Fig. 3 *center*). Chemotherapy, adjusted to chromosomal anomalies, also significantly improved the time to progression in patients with 1p-19q deletions (mean 145 months; Fig. 3 *right*).

Statistical Analysis

The predictive power of chromosomal anomalies was further assessed by logistic regression. The Cox regression model showed that only age ($p < 10^{-5}$) (OR 1.026, 95% CI 1.049–1.074) and chromosomal anomalies for no deletion ($p < 0.002$; OR 3.5, 95% CI 4.3–9.2) and for polysomia with 1p-19q deletion as a reference group (OR 7.4, 95% CI 3–13.7), were independently linked with survival.

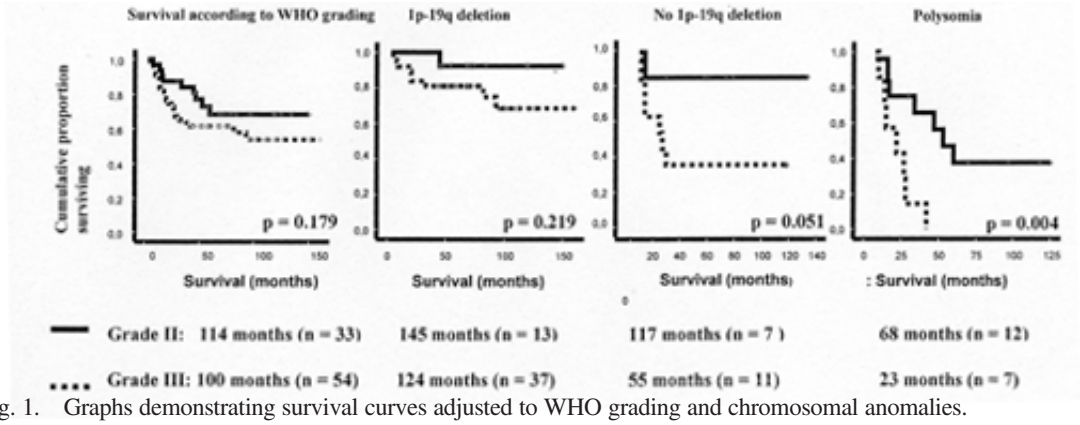

Fig. 1. Graphs demonstrating survival curves adjusted to WHO grading and chromosomal anomalies.

For time to progression, none of the prognostic factors analyzed emerged as independent prognostic factors.

DISCUSSION

Oligodendrogliomas constitute approximately 2 to 9% of all primary brain tumors[25,30,43] and 25 to 33% of all glial tumors.[10,14] In the US, the annual incidence of all oligodendroglioma was reported to be 0.3 per 100,000 individuals in 1995.[8] It is well known that several investigators have come to different conclusions when clinical, pathological, and treatment modalities have been correlated with survival. This is possibly due to the lack of biological markers for accurate diagnosis,[13,34] absence of an accepted grading system or unambiguous malignancy criteria, and use of different therapeutic modalities.[14,34,37] In a single-center population-based retrospective–prospective study, we investigated and compared chromosomal assay with clinical and histopathological features and treatment modalities in 87 oligodendrogliomas. Univariate and multivariate analyses yielded disparate prognostic factors. Some of these merit emphasis.

Clinical Data

The overall patient population in this series is similar to other oligodendroglioma case series[7,10,11,23,24,26,28,30,37,43] except that in this study there were more women than men.[38,47] In most studies, age was found to affect survival using either univariate[7,16,23,24,26,37,38,49] or multivariate analysis.[6,25,33,51] It has been shown that the observed survival distribution was significantly different from the corresponding expected age–sex matched survival curves of a normal reference population.[37] In our data, age emerges as an independent prognostic factor.

The effect of age may distort the effect of sex on survival because the median age of the women in this series was 10 years older than that of the men. When sex is adjusted to age, it has no statistical value. Therefore, the sex difference in survival is only a statistical bias attributable to the older age of women.

In most series, seizure was the most common presenting symptom, ranging in incidence from 35 to 91% of patients;[7,10,11,28,30,33,38,43] it was reported as a prognostic factor.[10,25,30,45] There was a strong correlation between the mode of presentation and clinical examination. Seizures are most often found in patients whose neurological examination was normal, in both younger and older patients in contrast to abnormal neurological examination which is most often associated with other presenting symptoms and older age. Seizure is a statistically significant prognostic factor independent of chromosomal anomalies.

Furthermore, clinical status was also reported to be statistically significant in relation to survival.[7,9,21,26,27,30,43,45,49] Patients without neurological deficits fared better. Moreover, permanent neurological deficits probably represent a factor of comorbidity in older patients. Our data confirm that the frontal lobe is the principal tumor location,[7,10,11,28,30,33,37,38,43,49,51,52] although this has neither prognostic significance[7,9,11,16,22,24] nor is it linked to chromosomal anomalies, as reported previously.[52]

Radiological Features

Although imaging studies provide valuable information, none has proven specific for oligodendroglial differentiation. Of the imaging features, radiological enhancement was closely related to vascular proliferation and both were considered criteria for diagnosis of malignancy and assessment for prognosis.[9,25,26,37,46] In our series, enhancement emerges as a prognostic factor, and its clinical significance merits discussion. Some patients underwent CT scanning and others MR imaging. Thus the evaluation was not uniform. Furthermore, in 22% of cases there was no relationship between enhancement and malignancy (some low-grade oligodendrogliomas showed enhancement and some anaplastic ones did not). Nevertheless, as reported previously,[10] 93% (26 of 28) of our patients with neurological deficits had enhancing tumors. Thus, from our own experience, and as demonstrated previously,[6,15] we only attribute a malignant value to enhancement if necrosis is also present (ring enhancement).

Pathological Features

Numerous attempts have been made to identify characteristics of prognostic significance, and the literature has presented the conflicting views of authors regarding the influence of individual pathological features on survival. Therefore, immunohistological features linked to a poor outcome included necrosis, high mitotic activity, increased cellularity, nuclear atypia, cellular pleomorphism, micro-

vascular proliferation, and the presence of vascular endothelial growth factor, MIB1, and other biological markers.[6,9,11,13,14,21,22,24,27,30,33,41,46] In our series, we could only relate survival to mitosis and necrosis by using univariate analysis.

Recent investigators have demonstrated that these basic pathological features, which are also used for grading oligodendrogliomas, are in themselves unreliable[14] and have different intrinsic impact on survival. Their influence is highly variable in the previous series as demonstrated by the variable results of the series including patients with the same pathological features.[7,9,11,16,23,25,26,30,37,43,46,47,51]

The lack of correlation between histopathological and molecular analyses (as shown in Table 1) suggests that the histological group of oligodendroglioma defined by the two pathological grading systems is genetically heterogeneous. This may explain the varying results observed in previous studies in which histopathological features were the sole prognostic factors. Therefore, genetic analysis may be a particularly useful tool for classifying oligodendroglioma.[14,34,48] Molecular genetic assay does not foretell the end of traditional histopathological analysis, however, but rather it will enhance its interpretation.[48]

Molecular Assay

Fluorescence in situ hybridization may not detect genetic events that do not result in a change in copy number, specifically loss of one allele followed by duplication of the remaining allele.[31] Some knowledge of the abnormality is necessary to select the appropriate probes.[19] Nonetheless, as reported in anaplastic oligodendroglioma,[15] our series demonstrates that oligodendroglioma may be divided into the following three distinct therapeutic and prognostic subgroups based on molecular biology: 1) oligodendroglioma showing 1p-19q deletion with a favorable prognosis; 2) polysomic oligodendroglioma characterized by a lack of meaningful response to both radiotherapy and chemotherapy with a particularly ominous prognosis and a high rate of recurrence and death; and 3) oligodendroglioma with no 1p-19q deletion, which are intermediate between the first two molecular subtypes depending on histological grading.

The incidence of 1p-19q deletion does not differ in specimens from primary and metastatic lesions,[40] and it has been shown that malignant progression is associated with the loss of 10q,[15,17,35,36] 9p,[3,4] and the accumulation of multiple genetic anomalies.[3,4,17,35,36]

A subset of 196 genes are differentially expressed between WHO Grades II and III, and 209 genes are differentially expressed between oligodendroglioma with and without 1p loss.[34] In addition, detailed analysis of the messenger RNA expression of oligodendroglioma has shown a preponderance of larger-sized transcripts for several genes that may represent a fundamental difference in oligodendroglioma tumorigenesis.[50]

We can speculate that the entire group, and specifically those patients with no 1p-19q deletion and polysomia, may have other chromosomal anomalies. Thus, the distinct survival rate and response to treatment observed within the molecular subgroups may be improved by identification of new basic molecular differences in the future.

Treatment Modalities

The issue of how to treat oligodendroglioma adequately is still a matter of debate.[1,2,7,8,12,16,32,47,51] Authors of some reports have indicated that a more complete resection of tumor is associated with increased survival.[7,11,16,21,27,37] Our data have not confirmed this, as the survival period was not affected by residual tumor. We did not compare treatment modalities because of statistical bias. Nonetheless, from the review of the patients treated by excision alone, we can infer that, in younger patients with an asymptomatic low-grade oligodendroglioma and 1p-19q deletion, total resection is adequate and adjuvant treatment should be deferred until the tumor progresses because all such patients are still alive.

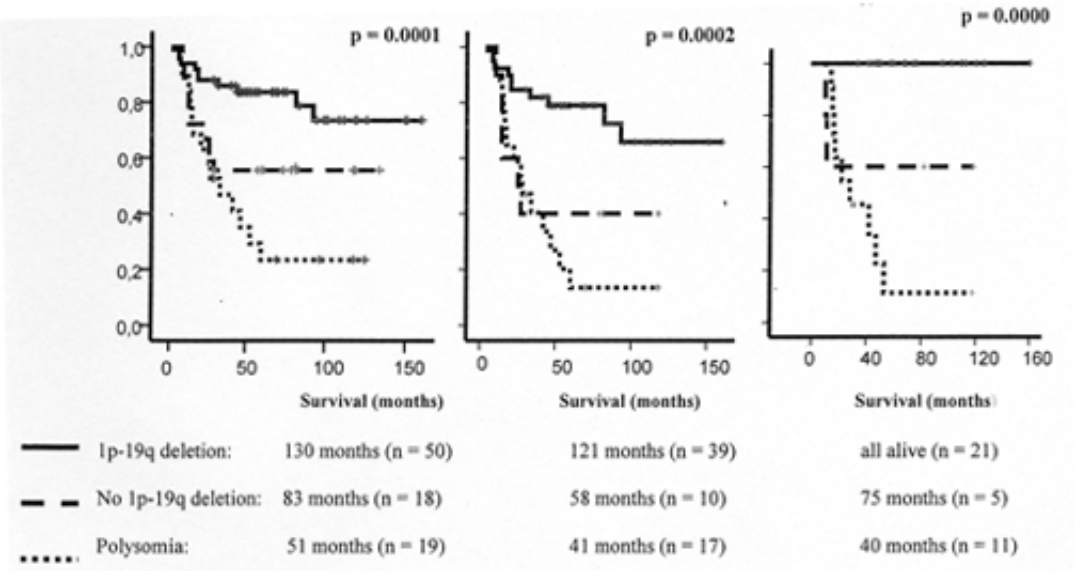

Fig. 2. Graphs demonstrating overall survival curves adjusted to chromosomal anomalies alone *(left)*, chromosomal anomalies and radiotherapy *(center)*, and chromosomal anomalies and chemotherapy *(right)*.

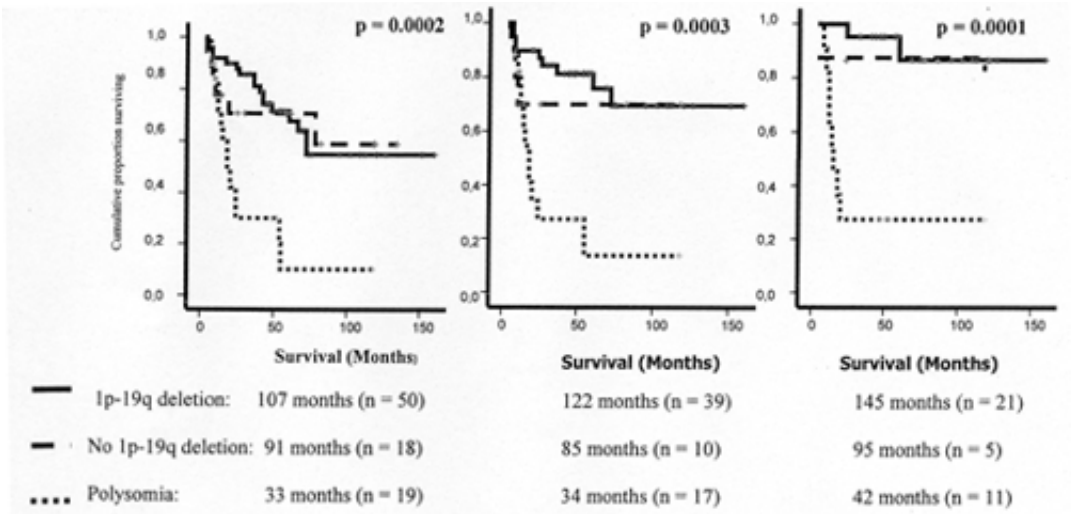

Fig. 3. Graphs demonstrating overall time-to-progression curves adjusted to chromosomal anomalies alone *(left)*, chromosomal anomalies and radiotherapy *(center)*, and chromosomal anomalies and chemotherapy *(right)*.

The role of radiotherapy has been questioned, and there is no demonstration in the literature that radiotherapy is always effective in treating oligodendroglioma.[7,11,14,27,37,38,43] Findings from the present series suggest that there is no beneficial effect of radiotherapy alone on survival, even when age, clinical data, histological grading, and type of surgery are considered; however, radiotherapy prolongs the overall time to progression.

Because the timing of radiotherapy in the postoperative setting is unclear, it could be argued that any survival benefit derived from radiotherapy in the immediate postoperative period could be biased by its effect on local progression.

Our data confirm that chromosomal deletions of 1p-19q are associated with better survival and response to chemotherapy. The survival curves show a plateau in patients with 1p-19q deletions treated by adjuvant chemotherapy, which also prolongs the time to progression; however, radiation therapy and chemotherapy improved neither survival nor the free time to progression in patients who did not have 1p-19q deletion and polysomia, although the patient numbers were limited.

In the literature, the response rate of oligodendroglioma to chemotherapy ranges from 60 to 100%,[4,6,12,14,15,32] and the response rate is similar according to histological grade.[8,12,21]

CONCLUSIONS

This study reveals three molecular subgroups of oligodendroglioma which have clinically different outcomes. Although combined therapy of surgery, radiotherapy, and chemotherapy is currently considered one of the standard treatments of oligodendrogliomas, a comparative prospective randomized study between surgery plus radiotherapy and surgery plus chemotherapy seems necessary for evaluating oligodendrogliomas with 1p-19q deletion and those without these chromosomal anomalies.

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Dedication

This article is dedicated to the patients who died of oligodendroglioma.

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