Cerebral Oligodendroglioma: Prognostic Factors and Life History

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THE RECORDS OF 137 patients with supratentorial oligodendroglioma treated surgically between 1953 and 1986 were reviewed. The tumors were rated histologically benign or malignant. In the 105 patients followed up with a minimum observation time of 5 years to December 1991, the mean postoperative survival was 90.2 months (standard error, 9), the median 64 months (standard error, 9.6), the 5-year survival rate 52.4%, and the 10-year survival rate 24%. Sixteen possible prognostic factors, broken down into two or more variables each, were considered in the survival study on univariate methods (5-year survival rate, survival curves, and Cox's hazard function) and on multivariate analysis according to Cox's stepwise proportional hazards model. The latter showed that variables correlated positively with survival were benign histological findings (*P*, 0.000), postoperative radiation therapy (*P*, 0.004), and time of operation from 1977 to 1986 (*P*, 0.044) in 105 patients of the whole series, and period of surgery from 1977 to 1986 (*P*, 0.000), subtotal or total surgical resection of the tumor (*P*, 0.001), and radiation therapy (*P*, 0.005) in the subgroup of 79 patients operated on for benign tumors. However, the most interesting point to emerge from the study was the relevance of admission clinical status to the survival of patients who did not receive radiation therapy and to the prognostic response of those who did. Of the 40 patients with seizures and negative neurological status—Clinical Syndrome A—the 10 who did not receive radiation therapy had survived as long as the 30 who did (5-year survival rate, 80 versus 67%; *P*, not significant; median survival, 122 versus 85 months; Breslow and Mantel-Cox *P*, not significant), whereas of the 65 patients with intracranial hypertension and/or neurological deficits—Clinical Syndrome non-A—the 18 who did not receive radiation therapy had short survival times, and the 47 who did fared significantly better (5-year survival rate, 11 versus 53%; *P*, 0.002; median survival, 32 versus 64 months; Breslow and Mantel-Cox *P*, 0.000). These findings were not significantly affected by the exclusion of malignant neoplasms and in the group of benign tumors, in which the histological characteristics have not been found to be significantly different between those with A and those with non-A clinical syndrome, did not depend on different frequencies of subtotal or total tumor removal. In fact, multivariate analyses for benign tumors only demonstrated that the variables that correlated with survival were radiation therapy (*P*, 0.000) and preoperative history less than 12 months (*P*, 0.006) in 47 patients with Syndrome non-A, and subtotal or total surgical removal of the tumor (*P*, 0.005) and additional operations (*P*, 0.027) in 32 patients with Clinical Syndrome A. These results supply a reasonable explanation for the better survival and the unresponsiveness to radiation therapy of our patients who received surgical treatment since the introduction of computed tomography from 1977 to 1986. On the basis of this review, we believe that patients with cerebral oligodendrogliomas, when histologically benign, should be classified by clinical status at admission in two groups, and that treatment should be organized and survival assessed on that basis. It seems that the two clinical syndromes correspond to different periods in the life history of the tumor. (Neurosurgery 35:1018–1035, 1994)

Key words: Brain neoplasm, Clinical features, Oligodendroglioma, Outcome, Radiation therapy, Surgical removal

Oligodendroglioma is rare in the spinal cord (24) and uncommon in the brain, accounting for 1 to 4% of intracranial primary tumors and 4 to 8% of cerebral gliomas (5, 14, 17, 29, 43, 46, 47, 54, 58, 59, 77, 81), although higher frequencies, 9.6 and 18.8%, respectively, are reported by Zulch (83). Since 1929, when Bailey and Bucy (3) described the first series of 13 patients with cerebral oligodendroglioma, a large body of evidence has been published in the attempt to pinpoint the prognostic factors. Even now, however, the prognosis after surgery is uncertain and the role of radiation therapy controversial. The small number of cases reported in each series and the retrospective nature of surgical series spanning long periods are considered to explain the discordance of results. And yet more rigorous prospective studies of such an uncommon tumor are not easy to organize. We report here our experience in one of the largest retrospective series published to date. Besides the evaluation of prognostic factors, this review permits analysis of patients treated before and after the introduction of computed tomography.

PATIENTS AND METHODS

One hundred thirty-seven consecutive patients with cerebral oligodendroglioma received surgical treatment in the neurosurgery division of the Department of Neurological Sciences of La Sapienza University, Rome, between 1953 and 1986. After exclusion of patients who died in the postoperative period or later as a result of the operations, those lost to follow-up or unknown about postoperative radiation therapy (9 patients), and those irradiated for the first time at second operations (7 patients, excluded to have a more equal comparison of prognosis after surgery alone versus after surgery plus postoperative radiation therapy), there remained 105 patients with a minimum observation period of 5 years to December 1991 and with follow-up gathered from the patients, if living, or from the next of kin, if the patients had died, for the survival study.

Histological evaluation

Histological findings were reviewed, and according to the two-tiered World Health Organization scheme (82), the tumors were allocated to two groups, benign and malignant. Arbitrarily, we considered oligodendroglioma as benign when, at most, mitoses were 5 per 10 high-power (magnification ×400) fields, nuclear pleomorphism was moderate, and vascular endothelial proliferation minimal, and as malignant or anaplastic when the above-mentioned histological features were more pronounced or necrosis was associated with them. Moreover, benign oligodendroglioma was classified pure if all or nearly all of the cells were oligodendroglial (about 80% or more) and mixed if the astrocytic component was significant (more than about 20%).

Clinical features, tumor characteristics, and surgical results in 137 patients (*Table 1*)

One hundred patients were diagnosed and treated surgically in the period from 1953 to 1976 and 37 in the period from 1977 to 1986, that is, before and after the introduction of CT. Median patient age at admission was 42 years, and the mean length of preoperative history 41.3 months (median, 18 months). The most frequent onset symptom was seizure (63.5%), followed by headache (32%). At admission, epilepsy was reported by 72.2% of the patients; papilledema was observed in 47.4%; a neurological deficit, usually motor, in 35%; and a mental disorder in 13.8%. The most frequent tumor sites were the frontal lobes, 37.2%; 64.9% of the tumors were in the anterior regions (frontal, temporal, and frontotemporal), and 8% in the midline and deep structures.

Reexamination of the radiological evidence was possible for only some of the patients. Tumor calcifications were imaged on the plain-cranium radiographs in 52.5% (21 of 40) patients. In histologically benign tumors, the radionuclide scans showed positive results for 7 of 10 patients, cerebral angiography showed a tumor blush or pathological vascularity in 8 of 29 patients and CT scanning showed mild and poorly defined tumor enhancement after intravenous contrast in 7 of 12 patients.

The aim of surgical treatment in all cases was the removal of as much of the tumor tissue as possible; on the evidence of the surgical reports, removal was partial in 69.3%, subtotal (doubtful radicality) in 17.5% and total (tumor clearly separable from the cerebral tissue or lobectomy reputedly extending beyond the tumor confines into the sound parenchyma) in only 8% of the patients. Biopsy was performed only in 7 patients who had tumors in critical areas. Surgical mortality was 9.4% during the hospital stay but rose to 11.6% if we include 3 patients discharged with a Karnofsky Performance Status (KPS) score of less than 40, who died a few months later because of severe neurological deficits or infections attributable to the operations. Of the other patients, 28 (20.4%) had KPS scores of 50 to 70, and 93 (67.9%) had KPS scores of 80 to 100.

The patients were grouped by clinical onset, progression of the symptoms, and signs recorded at admission. The resulting five groups, each characterized by a clinical syndrome, were as follows: 1) 44 patients (32.1%) with histories of seizures who were neurologically healthy at admission; 2) 19 patients (13.8%) with seizures at onset of the disease followed by symptoms of intracranial hypertension, the grounds for admission (with or without neurological deficits); 3) 24 patients (17.5%) with seizures at onset followed by neurological deficits, almost always motor, the grounds for admission (without intracranial hypertension); 4) 44 patients (32.1%) with symptoms of in-

TABLE 1. Clinical Features, Surgical Findings, and Operative Results in 137 Patients Operated on for Cerebral Oligodendroglioma (1953–1986)

	Whole Series	Clinical Syndrome on Admission[a]				
		A	B	C	D	E
No. of patients	137	44	19	24	44	6
Period of surgery, 1977–1986	37	19	4	1	9	4
Sex (M/F)	1.07	1.20	1.70	0.60	1	2
Age (yr)						
Mean at onset of disease	35.2	34.4	35.9	35.3	34.9	42
Mean on admission	38.9	39	42.1	41.6	35.5	43
Median on admission	42	39.5	44	44.5	35.5	43.5
No. ≤ 15 yr	12	2	2	1	7	
No. > 40 yr	71	21	13	16	18	3
Preoperative history (mo)						
Median	18	36	60	54	5	1
Mean	41.3	48.3	74.5	75.2	5.60	8.10
Clinical features on admission						
Seizures	99	44	19	24	10	2
Intracranial hypertension	65		19		44	2
Neurological deficit	48		9	24	14	1
Mental changes	19	2	5	4	6	2
Side						
Right	80	27	12	16	23	2
Left	46	16	3	8	15	4
Median	11	1	4		6	
Location[b]						
F	51	16	8	6	20	1
FT	20	11	3	2	3	1
T	18	8	1	1	8	
FP	15	2	2	10	1	
P-PO-PT	22	6	1	5	6	4
M/D	11	1	4		6	
Surgical removal						
Biopsy	7	2	1	2	2	
Partial	95	20	17	18	34	6
Subtotal	24	15	1	3	5	
Total	11	7		1	3	
Histological findings						
Pure	53	16	7	10	19	1
Mixed	54	19	9	10	12	4
Anaplastic	30	9	3	4	13	1
Karnofsky score on discharge						
0 (operative mortality)	13	2	3	2	6	
≤40	3			1	2	
50–70	28	2	4	11	8	3
80–100	93	40	12	10	28	3

The period of surgery is related to before (1953–1976) and after (1977–1986) the availability of CT scan.

[a] A, seizures and normal neurological status; B, seizures at onset followed by intracranial hypertension (with or without neurological deficit); C, seizures at onset followed by neurological deficit (without intracranial hypertension); D, intracranial hypertension at onset (with or without other symptoms or signs); E, other initial symptoms (stupor from tumoral hemorrhage, frontal or parietal syndrome, focal deficit).

[b] F, frontal; FT, frontotemporal; T, temporal; FP, frontoparietal; P-PO-PT, parietal, parieto-occipital, parietotemporal; M/D, median/deep.

tracranial hypertension at onset (with or without neurological deficits, some with one or two epileptic episodes shortly before admission); and 5) 6 patients with heterogeneous clinical onset (neurological deficits, psychic disorders without intracranial hypertension, and stupor caused by intratumoral bleeding). These groups, based on clinical criteria, were also marked by other differences, for example, the frequency of subtotal or total tumor removal.

Postoperative radiation therapy and additional operations

Of the 105 patients followed up, 77 received postoperative radiation therapy, all after the first operations. Dose information was obtained from a little over half the patients irradiated, 54.5% (42 of 77 patients); 30 patients had received doses of less than 50 Gy (5 patients in and after 1977) and 12 doses of 50 Gy or more (11 patients in and after 1977). Although most of these 42 more recently treated patients received megavoltage irradiation on more or less generous brain volumes, specific information about treatment technique is known only for the patients operated on in and after 1977. Radiation sources used were the cobalt-60 apparatus and, in a few, a linear accelerator; the target volume was irradiated by two to four fields, encompassing the tumor with a margin of 2 to 3 cm on the basis of a CT scan; the total dose was delivered in a single daily fraction of 180 to 200 cGy, five times per week, for 5 to 6 weeks. Two of 77 patients irradiated underwent successful second operations for symptomatic pathologically documented radionecrosis.

Of the 105 patients considered for the survival study, 28 had undergone second operations for clinical recurrence of the tumors, after a mean interval of 60 months (median, 48.5 months; range, 1–15 years).

Statistical analysis

The endpoint of this study was postoperative survival. The prognostic significance of individual factors was evaluated by comparing the 5-year survival rates, by comparing the computer-generated survival curves estimated by the method of Kaplan and Meier (31) with the group survival differences assessed using both the generalized Wilcoxon (Breslow) and the log-rank (Mantel-Cox) tests, and according to the proportional hazards method as proposed by Cox (13). Multivariate survival analysis, based on Cox's hazard function, was performed with forward and backward stepwise procedures to determine the independent variables most positively associated with survival. Computations for survival curves and for Cox models were done by means of the BMDP statistical computer program (18). The χ^2 test, Fisher's Exact Test or Woolf's Test, as appropriate, were used for the 5-year survival comparison or for simple comparisons of the frequency of the variables in subsets of patients. $P \leq 0.05$ was taken as the significance level. For easy comparison, continuous variables were analyzed as specific categories, such as age (younger than and older than 40), duration of preoperative history (less than and more than 12 months), and year of surgery (before and after 1977).

RESULTS

The cumulative 5-year survival rate in the 105 patients considered was 52.4% and the 10-year rate 24%. Mean survival was 90.2 months (standard error [SE], 9) and median survival 64 months (SE, 9.6). Eighty-four patients died as the result of tumor recurrence, with a mean survival of 61.8 months (range, 4 months to 16.1 years; median, 50 months). Twenty-one patients with survival times greater than 5 years were censored, that is, they had not died of tumor, because 18 were alive when last observed, and 3 had died from causes other than the intracranial disease (myocardial infarct, suicide, and an accident). The longest survival time was 26.6 years in a woman who is still living.

The significance of 16 possibly prognostic factors, each broken down into two or more variables, was assessed on these 105 patients. On univariate analyses (comparison of 5-year survival rates and of survival curves and Cox's proportional hazards model; *Tables 2 and 3A*), numerous variables had positive influences on prognosis in at least one of the tests used, but only a few—period of operation from 1977 to 1986, temporal site, Clinical Syndrome A, benign histological findings, and postoperative radiation therapy—passed all tests. Sex, preoperative history, side, seizures, and mental disorders never attained a significance level. On multivariate analysis, only three variables—benign histologic findings, postoperative radiation therapy, and time of operation from 1977 to 1986—were selected by the best-fitting Cox model, each with $P \leq 0.044$ (*Table 3A*). On the other hand, Cox's univariate and multivariate analyses of the subgroup of 79 patients operated on for histologically benign oligodendrogliomas showed that subtotal or total surgical resection of tumor was significantly positive for survival, in addition to period of surgery from 1977 to 1986 and radiation therapy, all three variables with $P \leq 0.005$ (*Table 3B*).

To get a more accurate idea of the effectiveness of postoperative radiation therapy, we compared the survival values of all irradiated and nonirradiated patients with respect to each of the principal variables considered (*Table 4*). In line with the outcome for the series as a whole, radiation therapy improved the survival values, sometimes significantly, concordantly for one and other variables of most factors, except for the variables of some groups, namely time of operation from 1977 to 1986 and 1953 to 1976, preoperative history more than and less than 12 months, tumor site—temporal and nontemporal and Clinical Syndrome A and non-A (the latter representing other like clinical groups). Indeed, the survival of the irradiated patients was similar to that of the nonirradiated patients in the first variable of each of these four factors and definitely longer in the second; therefore, the response to radiation therapy was nil in the first and very significant in the second. On checking these patients, we were able to pinpoint Clinical Syndrome A and non-A as the variables conditioning survival and response to radiation therapy. The long survivals of the nonirradiated patients were in fact attributable to the high frequency or predominance of the good prognoses of the patients with Clinical Syndrome A (present in about 80% of the patients who underwent surgery in the period from 1977 to 1986 and of those with temporal tumor sites, whereas of the patients with preoperative histories exceeding 12 months, the eight with Syndrome A had a 5-year survival rate of 87 versus 14% for the seven with non-A syndrome; P, 0.000; median, 94 versus 33 months; Breslow and Mantel-Cox P, 0.000). On the other hand, the short survivals of nonirradiated patients and the significant response to radiation therapy were always attributable to a predominance of Clinical Syndrome non-A (for example, the

TABLE 2. Five-Year Survival Rate and Survival Curves According to 16 Possibly Prognostic Factors (105 Patients)

Factor (Variables)	No. Patients	Five-Year Survival Rate		Survival Curves Based on the Kaplan-Meier Method		
		%	*P* value	Median survival time (mo)	*P* values	
					Breslow	Mantel-Cox
Period of surgery						
1953–1976	75	44	0.006	50	0.015	0.026
1977–1985	30	73		95		
Age						
≤40 yr	52	63	0.024	81	NS	0.017
>40 yr	53	42		50		
Sex						
M	52	44	NS	50	NS	NS
F	53	60		78		
Preoperative history						
0–12 mo	51	49	NS	57	NS	NS
13–60 mo	30	45		76		
>60 mo	24	54		62		
Location						
F	34	50	NS	58	NS	NS
FT	19	32		48		
T	14	79		115		
FP	12	50		50		
P-PO-PT	19	68		81		
M/D	7	29		48		
T	14	79	0.032	115	0.022	0.038
All other sites	91	48		58		
Side						
Right	64	58	NS	72	NS	NS
Left	34	47		55		
Median	7	29		48		
Intracranial hypertension						
Present	43	40	0.028	48	0.020	NS
Absent	62	61		76		
Seizures						
Present	79	54	NS	72	NS	NS
Absent	26	46		50		
Neurological deficit						
Present	34	35	0.015	44	0.002	0.045
Absent	71	61		81		
Mental changes						
Present	14	43	NS	49	NS	NS
Absent	91	54		72		
Clinical syndrome						
A	40	70	0.012	86	0.001	0.016
B	13	31		48		
C	18	39		39		
D	30	47		51		
E	4	50		67		
A	40	70	0.005	86	0.001	0.028
Non-A (B+C+D+E)	65	42		48		

For abbreviations, see *Table 1*. Survival rates and curves do not differ statistically by site, except temporal, by clinical syndrome, except A or between subtotal and total removal. NS, not significant.

TABLE 2. Five-Year Survival Rate and Survival Curves According to 16 Possibly Prognostic Factors (105 Patients)—*Continued*

Factor (Variables)	No. Patients	Five-Year Survival Rate		Survival Curves Based on the Kaplan-Meier Method		
		%	*P* value	Median survival time (mo)	*P* values	
					Breslow	Mantel-Cox
Surgical removal						
Biopsy	5	40	NS	45	NS	NS
Partial	71	48		57		
Subtotal	20	65		87		
Total	9	67		177		
Partial	71	48	NS	57	0.023	0.012
Subtotal-total	29	66		111		
Histological findings						
Pure	35	69	NS	96	NS	NS
Mixed	44	59		70		
Benign	79	63	0.000	84	0.000	0.000
Anaplastic	26	19		35		
Karnofsky score on discharge						
50–70	23	35	0.047	38	NS	NS
80–100	82	57		72		
Radiation therapy						
Yes	77	57	0.042	76	0.009	0.018
No	28	36		37		
<50 Gy	30	57	NS	70	NS	NS
≥50 Gy	12	58		83		
Second operation						
Yes	28	71	0.013	85	0.015	NS
No	77	44		55		

frequency of this syndrome was 63 to 85% in nonirradiated and irradiated patients in the time of operation from 1953 to 1976, with a preoperative history of less than 12 months and with nontemporal tumor sites). In the 40 patients of the series who had Clinical Syndrome A, the 5-year survival rate of those not receiving radiation therapy was 80 versus 67% for those who did (*P*, not significant [NS]), and the median survival was 122 versus 85 months (Breslow and Mantel-Cox *P*, NS), whereas in the 65 patients with Clinical Syndrome non-A, the differences were very great, that is, the 5-year survival rate in the patients who did not receive radiation therapy was 11 versus 53% for those who did (*P*, 0.000), and the median survival was 32 versus 64 months (Breslow and Mantel-Cox *P*, 0.000). Cox's multivariate analysis applied to patients of the whole series with Clinical Syndrome non-A and to those with Clinical Syndrome A; it confirmed the prognostic significance of the histological findings in both groups ($P \leq 0.001$) and demostrated the effectiveness of radiation therapy in the former (*P*, 0.002) and its ineffectiveness in the latter, in which age younger than 40 years was more significant (*Table 3A*).

Even after exclusion of the malignant tumors, both the response to radiation therapy (*Fig. 1*) and the survival of the nonirradiated patients (*Fig. 2*) remained significantly different in the two syndromes. In fact, in patients operated on for benign oligodendrogliomas, Cox's univariate and multivariate analyses demonstrated different prognostic variables according to the clinical syndrome: radiation therapy (*P*, 0.000) and preoperative history less than 12 months (*P*, 0.006) in the 47 patients with Syndrome non-A, and subtotal or total surgical tumor resection (*P*, 0.005) and second operations (*P*, 0.027) in the 32 with Syndrome A (*Table 3B*). Furthermore, a check of the histological features of benign tumors did not show significant differences between those with A and those with non-A clinical syndromes, (respectively, moderate nuclear pleomorphism, 50 versus 68%; *P*, NS; minimal endothelial proliferation, 15.8 versus 29.7%; *P*, NS; and no mitosis per 10 high-power fields, 37.5 versus 23.4%; *P*, NS).

DISCUSSION

Clinical features

The clinical features of patients who have undergone surgery for cerebral oligodendroglioma differ widely from one published series to the next. The figures for seizure as the symptom of onset range from 32 to 79%, intracranial hypertension from 1.3 to 64%, and focal neurological deficits, less common, from 3 to 17% (4, 7, 11, 39, 43, 46, 47, 53, 56, 58, 67, 72, 77, 79, 81). At admission, papilledema or, at any rate, intracranial hypertension was present in 28 to 88% (7, 29, 38, 39, 43, 47, 53, 56, 68, 72, 73, 77, 79, 81), and motor deficits were present in 16 to 54% of patients (7, 10, 38, 39, 43, 53, 72, 79, 80).

TABLE 3. Univariate and Multivariate Cox Proportional Hazards Survival Analyses (*P* Values)

Factor	Variables	A (Patients of the Whole Series)						B (Patients with Benign Tumors)					
		All 105 (84)[a]		Syndrome A 40 (29)[a]		Syndrome non-A 65 (55)[a]		All 79 (59)[a]		Syndrome A 32 (21)[a]		Syndrome non-A 47 (38)[a]	
		One-variable models	Best model	One-variable models	Best model	One-variable models	Best model	One-variable models	Best model	One-variable models	Best model	One-variable models	Best model
Period of surgery	1977–1986 versus 1953–1976	0.0204	0.0438	0.1937		0.4695		0.0086	0.0002	0.4272		0.0826	
Age	≤40 yr versus >40 yr	0.0180		0.0428	0.0046	0.3533		0.0325		0.3052		0.2082	
Sex	Female versus male	0.1253		0.0300		0.6263		0.1578		0.1640		0.4770	
Preoperative history	>12 mo versus ≤12 mo	0.5967		0.4957		0.3044		0.0618		0.4094		0.0266	0.0064
Location	T versus all other sites	0.0252		0.0200		0.9105		0.0614		0.0147		0.7294	
Side	Right versus left versus median	0.5199		0.5962		0.5632		0.5924		0.4800		0.7496	
Intracranial hypertension	No versus yes	0.2422				0.8284		0.5434				0.7902	
Seizures	Yes versus no	0.7030				0.5545		0.4207				0.1468	
Neurological deficit	No versus yes	0.0523				0.3597		0.1472				0.3645	
Mental changes	No versus yes	0.1175		0.2630		0.2870		0.1310		0.3288		0.2248	
Clinical syndrome	A versus Non-A	0.0261						0.1143					
Surgical removal	Subtotal-total versus biopsy-partial	0.0103		0.0194		0.5324		0.0030	0.0014	0.0023	0.0051	0.2490	
Histological findings	Benign versus malignant	0.0000	0.0000	0.0001	0.0012	0.0000	0.0004						
Karnofsky score on discharge	80–100 versus 50–70	0.3107				0.5231		0.4377				0.4513	
Radiation therapy	Yes versus no	0.0259	0.0043	0.4673		0.0001	0.0020	0.0211	0.0049	0.9017		0.0001	0.0000
Second operation	Yes versus no	0.2200		0.4693		0.1126		0.6171		0.2562	0.0273	0.4979	

For abbreviations, see *Table 1*. The first is the variable correlated positively with survival.
[a] Number of patients analyzed; in parentheses, number of deaths from tumor recurrence.

Table 1 groups the patients of our series by clinical syndrome defined by onset, evolution of the clinical history, and signs present at admission. Intracranial hypertension was the onset symptom in about one third of our patients and seizure in the other two thirds (87 of 137 patients). Of the latter, only half reached the operating table without other symptoms, with a median preoperative history of 36 months and a mean of 48 months, whereas the other half, presenting with intracranial hypertension or neurological deficits, usually motor, had longer preoperative histories (median, 60 months; mean, 75 months). Seizures may remain the only symptoms for 20 or more years, as in two of our patients and as reported in other studies (1, 25, 39, 56). Even in 1975, Mansuy et al. (40) noted that when onset of the disease was marked by seizures, diagnosis and surgery were often late, after the onset of deficits or intracranial hypertension. In recent years, however, CT scanning has made for ever earlier diagnosis with a consequent change in the frequency of the clinical patterns seen at admission. Paillas et al. (47) found a decrease in the length of the preoperative history from 4 to 5 to 2 years after the introduction of CT scanning, and Lee and Van Tassel (36) reported that 51% of patients diagnosed by CT had histories of no more than 6 months. In our 37 patients diagnosed after 1977, the year in which we started to use CT, the duration of the preoperative history was, on overage, 2.5 years less than in patients diagnosed before that date. Furthermore, on comparing the patients admitted before and after that date, we found that the frequency of those reaching diagnosis with a history of seizures and negative neurological status at admission had risen from 25 to 51% (*P*, 0.003), and that the frequency of an epileptic onset followed by neurological deficits and/or intracranial hypertension had fallen from 38 to 13.5% (*P*, 0.004) whereas the frequency of intracranial hypertension at onset of the disease had changed little, from 35 to 24% (*P*, NS). It is therefore clear that right from the earliest years of its use, the CT scan shortened the preoperative history of tumors with epileptic onset, bringing forward the time of diagnosis to the initial stage of the disease, thereby increasing the number of patients who have been neurologically healthy at the time of operation.

Series survival

In our 105 patients treated surgically for cerebral oligodendroglioma and followed up, the cumulative 5-year survival

rate was 52.4% and the 10-year rate 24%; mean survival was 90.2 months (SE, 9) and median survival 64 months (SE, 9.6). In the literature, the survival varies widely according to series; the mean ranges from 21 to 122.6 months and the median from 35 to 85.2 months, the 5-year survival rate from 23 to 97% and the 10-year survival rate from 13.3 to 34% (2, 7, 10, 16, 17, 19, 22, 29, 38, 39, 43, 46, 47, 53, 54, 56, 58, 63, 65, 67, 70, 72, 76, 77, 79, 81). In the 105 patients of our series, the univariate analyses (*Tables 2 and 3A*) show numerous variables correlating positively with survival, but on Cox's multivariate best-fitting model (*Table 3A*), only three retain prognostic significance: 1) benign histology, 2) postoperative radiation therapy, and 3) the more recent period of operation from 1977 to 1986, the era of the CT scan. On the other hand, in the subgroup of 79 patients operated on for benign tumors, Cox's univariate and multivariate analyses (*Table 3B*) attested to the prognostic significance of period of surgery from 1977 to 1986, subtotal or total surgical resection of the tumor, and radiation therapy.

Histological findings and survival

The histological status of this glioma used to be rated an unreliable predictor (16, 22, 56, 67, 77). Mansuy et al. (39) observed that for the majority of oligodendrogliomas, malignancy is meaningful when several signs of anaplasia are found together, whereas according to Russel and Rubinstein (59), it is not possible in individual cases to attach any prognostic value to any particular histological feature. In recent years, significant prognostic correlations have been found with single histological features (but the results of the various studies are not always concordant; 8, 44, 68, 70, 79), or with four-tiered grading systems based on progressive malingnancy (but in the main without significant differences in survival for the majority of patients in the intermediate grades; 34, 38, 41, 70). More recently, Shaw et al. (63) have proposed a two-grade prognostic system: low, grades 1 and 2, and high, grades 3 and 4, of the St Anne-Mayo method (15). According to the World Health Organization classification (82), and adopting the above-mentioned criteria, we have separated tumors with definite or pronounced histological malignancy from the great majority with modest or no evidence of anaplasia, in which "the life history of the tumor may be altered by factors foreign to the histologic picture" (22). The patients with malignant tumors in our series had unquestionably worse survival values than those with benign tumors both on univariate analysis (5-year survival, 19 versus 63%; *P*, 0.000; median survival, 35 versus 84 months; Breslow and Mantel-Cox, *P*, 0.000) and on multivariate analysis (*P*, 0.000) (*Tables 2 and 3A*). Among the benign tumors, we found no significant survival difference between pure and mixed oligodendrogliomas (*Table 2*).

Radiation therapy and factors responsive to irradiation

The role of postoperative radiation therapy in oligodendrogliomas is much debated, although there is no lack of anecdotal examples of its efficacy in securing the remission of intracranial hypertension symptoms for years (66, 81) and in inducing a reduction of tumor volume or the loss of abnormal vascularity on angiography and contrast enhancement on the CT scan in ventricular and midline tumors (20, 32). In 1964, Sheline et al. (65), in one of the first statistical comparisons between two small groups of matched patients, one irradiated and the other not, found a significantly higher 5-year survival rate (85 versus 31%), longer median survival (8 versus 2.8 years), and a nonsignificant increase in 10-year survival (55 versus 25%) in the irradiated patients. Other workers reported good survival values in irradiated patients (6, 12, 55, 78), or values that were at least better than in nonirradiated patients (2, 16, 37, 43, 47, 48, 56, 66, 68, 81), but also not significantly different survival rates (7, 10, 19, 45, 53, 63, 77). In the whole of our series, the irradiated patients fared better than the nonirradiated patients both in terms of 5-year survival rate (57 versus 36%; *P*, 0.042; medians on the survival curves, 76 versus 37 months; Breslow and Mantel-Cox $P \leq 0.018$; *Table 2; Fig. 3*) and on multivariate analysis (*P*, 0.004; *Table 3A*). Radiation therapy clearly improved the survival of both patients with malignant tumors and those with benign tumors (*Fig. 3*). Of patients with benign tumors, those who were irradiated fared significantly better than the nonirradiated patients, with a 5-year survival rate of 70 versus 45% ($P = 0.041$) median on the survival curves, 86 versus 48 months (Breslow and Mantel-Cox $P < 0.014$). Whitton and Bloom (78) reported a similar 5-year survival rate, i.e., 64%, in irradiated low-grade oligodendrogliomas. In our patients who had malignant oligodendrogliomas, survival, although better after radiation therapy, remained poor; in the patients followed up, 20 irradiated versus 6 nonirradiated, the 5-year survival rates were different, 25 versus 0%, and the survival curves quite separate, with medians of 38 versus 27 months, but statistical significance was not attained in this small sample. The radiation dose did not correlate with survival time in our series (*Table 2*) or in those of others (7, 37, 78); however, Shaw et al. (63) found longer survival after irradiation with doses of more than 50 Gy in patients with incomplete tumor resection.

On analyzing the effect of radiation therapy in subgroups of patients (*Table 4*), we recognized two variables of the clinical syndrome present at admission, A and non-A, as factors influencing the prognosis of nonirradiated patients and the relevance of radiation therapy to the prognosis. The 5-year survival rate of the 40 patients with Clinical Syndrome A, that is, with seizures but no neurological deficits or intracranial hypertension at admission, did not differ significantly whether they were irradiated, 67 versus 80% (*P*, NS), and the same applies to their median survival time, 85 versus 122 months (Breslow and Mantel-Cox *P*, NS). In contrast, the 5-year survival rate of the other 65 patients, those who had Clinical Syndrome non-A, that is, with neurological deficits and/or intracranial hypertension at admission, was significantly higher with radiation therapy than without, 53 versus 11% (*P*, 0.002), and their median survival was longer, 64 versus 32 months (Breslow and Mantel-Cox *P*, 0.000) (*Table 4*). It is worth noting that the 5-year survival rate and median survival times in the two syndromes, A and non-A, were substantially similar when irradiated patients only are compared (67 versus 53% [*P*, NS] and 85 versus 64 months [Breslow and Mantel-Cox *P*, NS]) but considerably higher in patients with Clinical Syndrome A when nonirradiated patients are compared (80 versus 11%; *P*,

TABLE 4. Influence of Radiation Therapy on Survival According to Main Variables

Factor (Variables)	Radiation Therapy	No. Patients	Five-Year Survival Rate		Survival Curves Based on the Kaplan-Meier Method		
			%	*P* value	Median survival time (mo)	*P* values	
						Breslow	Mantel-Cox
Period of surgery							
1953–1976	no	19	16	0.004	36	0.000	0.000
	yes	56	54		66		
1977–1986	no	9	78	NS	122	NS	NS
	yes	21	71		85		
Age							
≤40yr	no	12	42	NS	37	NS	NS
	yes	40	70		84		
>40yr	no	16	31	NS	37	0.030	0.047
	yes	37	46		51		
Preoperative history							
≤12mo	no	13	15	0.005	35	0.002	0.001
	yes	38	61		66		
>12mo	no	15	53	NS	62	NS	NS
	yes	39	56		76		
Location							
Temporal	no	5	80	NS	92	NS	NS
	yes	9	78		110		
All other sites	no	23	26	0.013	37	0.001	0.004
	yes	68	56		66		
Intracranial hypertension							
Present	no	11	9	0.017	27	0.000	0.000
	yes	32	50		57		
Absent	no	17	53	NS	62	NS	NS
	yes	45	64		81		
Seizures							
Present	no	21	43	NS	48	NS	NS
	yes	58	59		78		
Absent	no	7	14	NS	32	0.026	0.011
	yes	19	58		66		
Neurological deficit							
Present	no	11	9	0.030	33	0.002	0.001
	yes	23	48		51		
Absent	no	17	53	NS	73	NS	NS
	yes	54	63		84		
Mental changes							
Present	no	5	20	NS	38	NS	NS
	yes	9	55		64		
Absent	no	23	39	NS	37	0.037	NS
	yes	68	59		78		
Clinical syndrome							
A	no	10	80	NS	122	NS	NS
	yes	30	67		85		
B+C	no	9	11	NS	36	0.016	0.008
	yes	22	45		49		
D	no	9	11	0.014	30	0.002	0.001
	yes	21	60		78		
Non-A (B+C+D+E)	no	18	11	0.002	32	0.000	0.000
	yes	47	53		64		

For abbreviations, see *Table 1*. NS, not significant.

TABLE 4. Influence of Radiation Therapy on Survival According to Main Variables—*Continued*

Factor (Variables)	Radiation Therapy	No. Patients	Five-Year Survival Rate		Survival Curves Based on the Kaplan-Meier Method		
			%	*P* value	Median survival time (mo)	*P* values	
						Breslow	Mantel-Cox
Surgical removal							
Biopsy-partial	no	21	43	NS	38	NS	NS
	yes	55	51		64		
Subtotal-total	no	8	37	NS	32	0.031	NS
	yes	21	76		111		
Histological findings							
Anaplastic	no	6	0	NS	27	NS	NS
	yes	20	25		38		
Benign	no	22	45	0.041	48	0.008	0.014
	yes	57	70		86		
Karnofsky score on discharge							
50–70	no	9	0	0.014	37	NS	NS
	yes	14	50		49		
80–100	no	19	47	NS	59	NS	NS
	yes	63	60		78		

0.000; median survival, 122 versus 32 months; Breslow and Mantel-Cox *P*, 0.000). Thus, the prognostic value of the clinical syndrome, A versus non-A, correlates inversely with the frequency of postoperative radiation therapy in patients with Syndrome non-A. Cox's multivariate study confirmed that radiation therapy was effective for patients with Syndrome non-A but useless for those with Syndrome A (*Table 3A*).

The exclusion of anaplastic tumors does not affect the outcome of the survival comparison either between the two syndromes in patients irradiated and in those nonirradiated (*Fig. 2*) or between irradiated and nonirradiated patients in each clinical syndrome (*Fig. 1*). As seen, we did not find the histological features of benign tumors significantly different in the Clinical Syndromes A and non-A; on the other hand, comparing the frequencies of the other variables considered (excluding, obviously, those related to seizures, neurological deficits, intracranial hypertension and KPS scores at discharge) in benign tumors of the two syndromes, we found time of operation from 1977 to 1986 ($P \leq 0.003$), temporal site ($P \leq 0.047$), and subtotal or total removal of the tumor ($P \leq 0.001$) not uniformly distributed, being more frequent in patients with Clinical Syndrome A, whether the comparison covered all patients or only those who were not irradiated. In the patients who had seizures only, the higher frequency of patients treated in the more recent period and the higher frequency of the temporal site of the tumor can be explained by the easier and earlier diagnosis

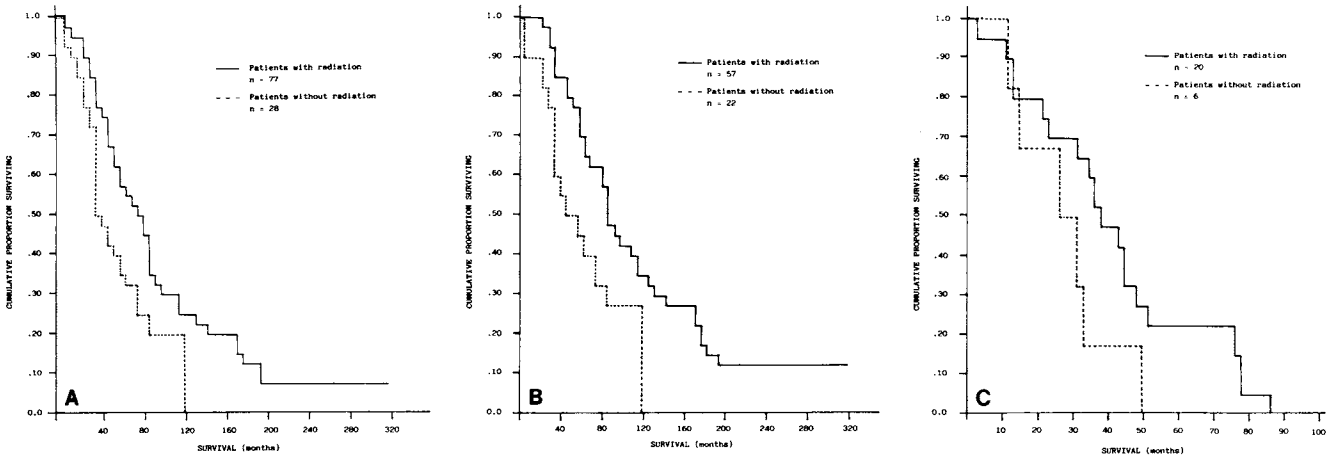
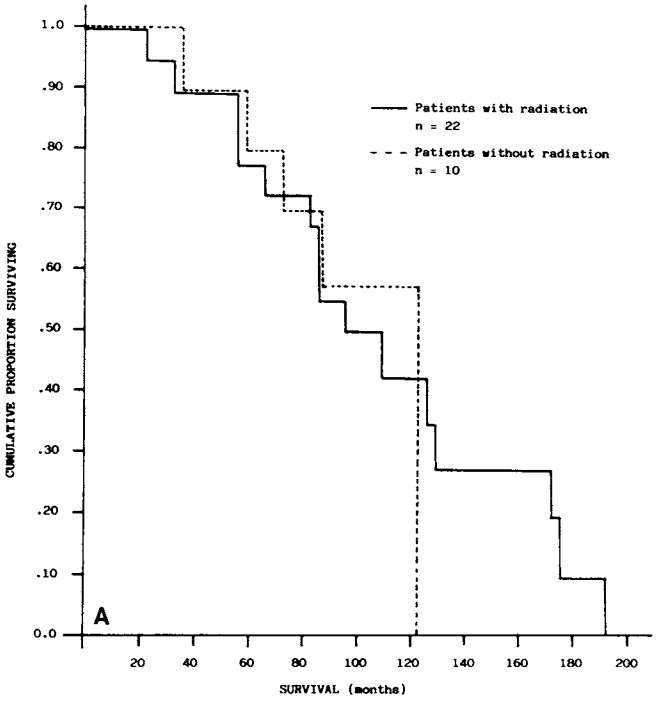


FIGURE 1. Survival curves for all patients and for those with different histological features by radiation therapy. *A*, whole series, irradiated versus nonirradiated. Median, 76 versus 37 months; Breslow *P*, 0.009; Mantel-Cox *P*, 0.018; 5-year survival rate, 57 versus 36%; *P*, 0.042. *B*, benign tumors, irradiated versus nonirradiated. Median, 86 versus 48 months; Breslow *P*, 0.008; Mantel-Cox *P*, 0.014; 5-year survival rate, 70 versus 45%; *P*, 0.041. *C*, anaplastic tumors, irradiated versus nonirradiated. Median, 38 versus 27 months; Breslow *P*, 0.239; Mantel-Cox *P*, 0.134; 5-year survival rate, 25 versus 0%; *P*, 0.236.



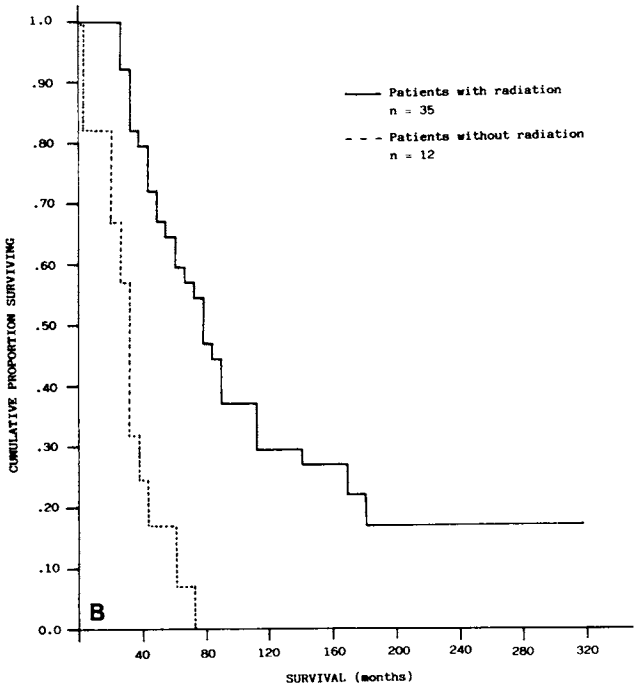
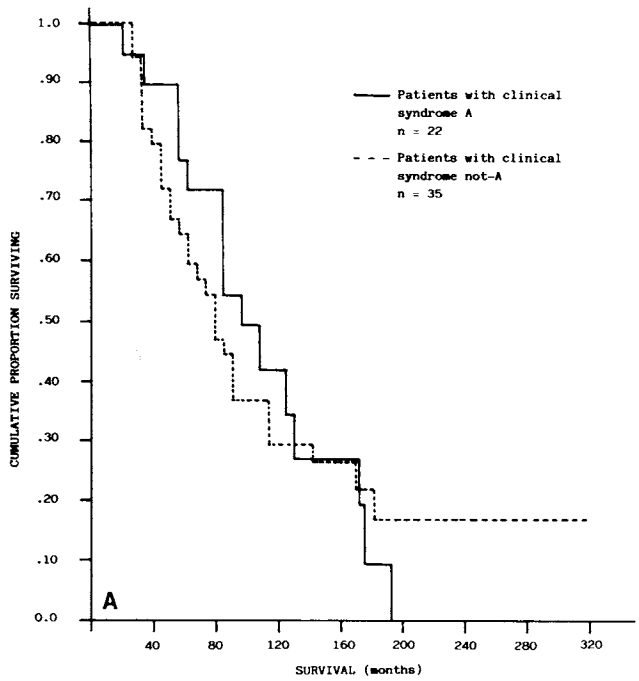


FIGURE 2. Survival curves for patients with benign tumors and different clinical syndromes by radiation therapy. *A*, clinical Syndrome A, irradiated versus nonirradiated. Median, 95 versus 122 months; Breslow *P*, 0.851; Mantel-Cox *P*, 0.901; 5-year survival rate, 77 versus 80%; *P*, 0.624. *B*, clinical Syndrome non-A, irradiated versus nonirradiated. Median, 81 versus 36 months; Breslow and Mantel-Cox *P*, 0.000; 5-year survival rate, 66 versus 17%; *P*, 0.004.



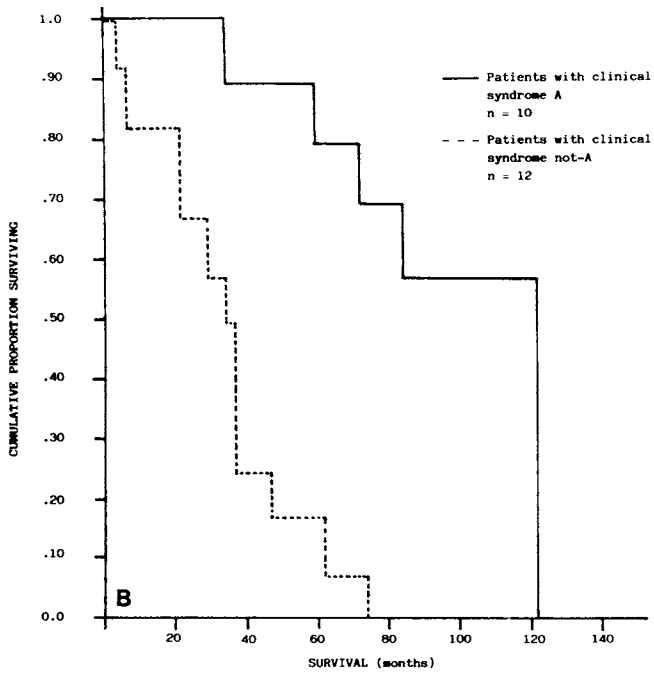


FIGURE 3. Survival curves for patients with benign tumors irradiated and nonirradiated by clinical syndrome. *A*, benign tumors irradiated, A versus non-A clinical syndrome. Median, 95 versus 81 months; Breslow *P*, 0.274; Mantel-Cox *P*, 0.833; 5-year survival rate, 77 versus 66%; *P*, 0.266. *B*, benign tumors nonirradiated, A versus non-A clinical syndrome. Median, 122 versus 36 months; Breslow and Mantel-Cox *P*, 0.000; 5-year survival rate, 80 versus 17%; *P*, 0.005.

in the CT era, whereas the higher frequency of subtotal or total tumor removal may well have been because the tumor tissue was more often confined to the hemispheres, although midline or deep main sites were uncommon in both syndromes (5 of 47 in Syndrome non-A and 1 of 32 in Syndrome A). In no case, at all events, was the higher frequency of these variables in any way related to the longer survival and unresponsiveness to radiation therapy of the patients with Clinical Syndrome A (because the 5-year survival rate and the median survival of patients who had seizures only were equally good with and without radiation therapy, even when they were treated in the period from 1953–1976, namely, 69 versus 67%; *P*, NS; and 105 versus 65 months, Breslow and Mantel-Cox *P*, NS; when the tumor site was nontemporal, namely, 72 versus 67%; *P*, NS; and 80 versus 76 months, Breslow and Mantel-Cox *P*, NS; and when only biopsy or partial removal of the tumor was performed, namely 70 versus 71%; *P*, NS; and 84 versus 86 months, Breslow and Mantel-Cox *P*, NS). Last, in the subgroup of patients with benign tumors and Clinical Syndrome non-A, in whom those who received radiation therapy fared better (*Fig. 1*), none of the other variables (included the histological features) was distributed in a significantly nonhomogeneous manner between irradiated and nonirradiated patients.

Cox's univariate and, especially, multivariate best-model analyses of the subgroup of patients operated on for benign tumors (*Table 3B*) confirmed the prognostic relevance of radiation therapy (*P*, 0.000), in addition to preoperative history less than 12 months (*P*, 0.006), in those with Syndrome non-A, and of surgical treatment, subtotal or total resection of the tumors (*P*, 0.005) and second operations (*P*, 0.027) in those with Syndrome A.

It is surprising to note at the end of this analysis that the patients with histologically benign tumors and Clinical Syndrome non-A who did not receive radiation therapy (*Fig. 1*) had practically the same survival values as patients with malignant tumors (most of whom were irradiated) (*Table 2*), that is, 5-year survival rates of 17 versus 19% and median survival times of 36 versus 35 months.

The influence on survival attributed to individual clinical features in patients treated surgically for oligodendroglioma is controversial (7, 43, 63, 68, 72, 79). However, our experience proves that the prognosis of intracranial hypertension, like that of neurological deficits, is modified by radiation therapy (*Table 4*), and the prognosis of seizures is distinctly different when the neurological status is normal from when other signs are present (*Table 2*). A normal preoperative clinical status, compared with other clinical conditions, has been correlated with significantly longer postoperative survival (37, 43). This is true even when the tumors have similar histological features, as in the group of our patients with benign tumors, or when the variable, normal preoperative clinical status, has been adjusted for histological features previously found to be of prognostic value (37).

The results that emerge from our series lead us to speculate that the different composition of clinical patterns of patients at admission, like the different frequency of radiation therapy in patients with intracranial hypertension and/or neurological deficits or the different frequency of patients with seizures only among those who are not irradiated, might help explain the discordance of survival results and of the effectiveness of radiation therapy reported in the published oligodendroglioma series. In the series of Chin et al. (10) and Reedy et al. (53), in which the postoperative survival values are good and not affected by radiation therapy, more than 50% of the patients were epileptic and neurologically healthy. In the series of Mork et al. (43), postoperative radiation therapy was relevant to survival, as in our series, but a large majority of the patients had intracranial hypertension and/or neurological deficits. The different median survival times in the last two series, 35 months in the Norwegian study (43) versus 64 months in ours, can be explained by the different frequency of patients with seizures and negative neurological status among those who were followed up, 13 and 38%, respectively. Actually, the median survival time of the patients without neurological signs is high and almost equal, 93 months in the series of Mork et al. (43) and 86 months in ours, despite the fact that the therapeutic procedures in the two series were probably not homogeneous. A relation of this kind among survival, effectiveness of postoperative radiation therapy, and preoperative clinical syndrome seems to apply to low-grade astrocytomas, too. Hirsch et al. (28), in a group of children treated surgically for astrocytomas, oligodendrogliomas, and mixed glial tumors, 62% of whom presented with only sezures before surgery, observed a 95% probability of nonrecurrence within 5 years, almost all of whom received no radiation therapy. Other workers (42, 51, 75) report a very high survival rate unaffected by radiation therapy in patients with low-grade astrocytomas treated surgically in the CT era, of whom 80% (51, 75) had seizures and were neurologically healthy; furthermore, in 80% of the patients in the series of Vertosik et al. (75), biopsies of tumors were performed only by a closed stereotactic needle procedure or, in a few cases, by open craniotomy. Last, in a retrospective study of survival of patients presenting with epilepsy, mostly without neurological signs, and with lesions on CT scans suggesting low-grade gliomas, Smith et al. (69) failed to demonstrate beneficial effects of radiation therapy.

Some authors (11, 37, 63) have observed that radiation therapy is relevant to survival only after partial or incomplete but not after radical surgical removal of the tumor. In our patients with benign tumors, the extent of surgery does not account for the different prognostic effects of radiation therapy (*Table 5*). In fact, within each clinical syndrome, the response to radiation therapy bore no relation to the extent of tumor resection, being always negative in patients with Syndrome A and highly positive (beyond the statistical significance level dependent on small numbers) in those with Syndrome non-A. Survival values of our nonirradiated patients depended on the clinical syndrome rather than on the extent of surgery.

After all, if it is legitimate to assume that almost all so-called total removals are actually only extensive removals of diseased tissue, because oligodendroglioma is an infiltrative tumor (61), and because to date, our experience and that of others (40, 43, 81) demonstrates that nearly all surgically treated patients die in the end of tumor recurrence, it is hard to explain why radiation therapy should be effective after a very limited, partial or incomplete, removal and be ineffective after a simply

TABLE 5. Quality of Surgery and Survival in Benign Oligodendrogliomas According to Clinical Syndrome and Radiation Therapy

Clinical Syndrome	Radiation Therapy	No. Patients	Five-Year Survival Rate		Survival Curves Based on the Kaplan-Meier Method		
			%	*P* value	Median survival time (mo)	*P* values	
						Breslow	Mantel-Cox
Biopsy and partial removal							
A and non-A	yes	41	63	NS	81	0.024	0.035
	no	17	41		38		
A	yes	10	70	NS	84	NS	NS
	no	7	71		86		
Non-A	yes	31	61	0.027	78	0.000	0.000
	no	10	20		36		
Subtotal and total removal							
A and non-A	yes	16	87	NS	172	NS	NS
	no	5	60		*		
A	yes	12	83	NS	131	NS	NS
	no	3	100		*		
Non-A	yes	4	100	NS	115	0.020	0.017
	no	2	0		30		

For abbreviations, see *Table 1*. NS, not significant. *, three patients alive (after 78 months).

more extensive, total or radical, removal of the tumor tissue, unless it is accepted, as suggested (37), that oligodendrogliomas that permit total removal have relatively less aggressive biological behavior. In effect, our study shows that good survival, no response to radiation therapy, and a frequency of more radical surgical removal are characteristics of oligodendrogliomas that produce epilepsy only (Syndrome A). Thus, the better survival and unresponsiveness to radiation therapy attributed to total removal might be attributable less to the completeness of tumor resection and more to the higher frequency of this clinical syndrome, in which tumor removal is more frequently reported as total or complete.

In low-grade cerebral astrocytomas, the response to irradiation has been related to the age of patients (26, 62), especially after incomplete removal of the tumors (35, 50); the beneficial effects of radiation therapy were observed in patients older than but not in patients younger than 30 or 40 years. In our series of benign oligodendrogliomas, the survival difference between patients irradiated and nonirradiated was greater in those older than in those 40 years or younger (*Table 6*). However, in each category of age, the clinical status regulated the result of radiation therapy; therefore, the response to irradiation should not be related to age per se, but to the frequencies of the two clinical syndromes. In the older age group, Syndrome non-A was almost twice as frequent as Syndrome A (66 versus 34%).

Quality of surgery and survival

The relevance to survival of the most complete removal of the tumor possible is often asserted (16, 22, 29, 47, 56, 58, 77) but not always backed by statistical analysis (37, 43, 63, 72, 78, 79, 81). In our 105 patients of the whole series, the longer survival rates after subtotal or total resection versus after biopsy or partial removal of tumors on univariate studies (*Tables 2 and 3A*) did not attain significance on Cox's multivariate best-model analysis (*Table 3A*).

In contrast, in the subgroup of 79 patients who had benign tumors, the better survival after more radical resection of the tumors was statistically significant on the multivariate study, too (*Table 3B*). Within this group, we found that patients with seizures who were neurologically healthy had survival rates after biopsy or partial removal that were shorter than after subtotal or total tumor removal (5-year rate, 71 versus 87%; *P*, NS; median, 85 versus 172 months; Breslow and Mantel-Cox $P \leq 0.013$), but these survival times were longer anyway than those of patients with Syndrome non-A, whose survival rates were not different after biopsy or partial removal and subtotal or total tumor resection (5-year rate, 51 versus 67%; *P*, NS; median, 62 versus 61 months; Breslow and Mantel-Cox *P*, NS). On multivariate analyses of patients with the two different clinical syndromes, the quality of surgery retained its prognostic significance only in those with Syndrome A (*Table 3B*).

Period of surgery and survival

The better survival rate for the time of operation from 1977 to 1986, coinciding with the CT era, versus the period from 1953 to 1976, on univariate and multivariate analyses both of patients of the whole series and of those with benign tumors (*Tables 2 and 3*) agrees with the better prognosis of low-grade astrocytomas treated in the CT era (42, 51, 75). However, in our 30 patients with adequate follow-up who were operated on in the more recent period, the better prognosis and the unresponsiveness to radiation therapy as well have a reasonable explanation on the basis of the relationship we found between survival time, effectiveness of radiation therapy, and clinical syndrome. In these patients, several factors combined to favor the prognosis and the unresponsiveness to radiation therapy, such as the higher frequency of patients who had epilepsy with

TABLE 6. Age of Patients at Surgery and Survival in Benign Oligodendrogliomas According to Clinical Syndrome and Radiation Therapy

Clinical Syndrome	Radiation Therapy	No. Patients	Five-Year Survival Rate		Survival Curves Based on the Kaplan-Meier Method		
			%	*P* value	Median survival time (mo)	P values	
						Breslow	Mantel-Cox
40 yr or younger							
A and non-A	yes	31	77	NS	86	NS	NS
	no	10	50		48		
A	yes	14	86	NS	86	NS	NS
	no	5	100		*		
Non-A	yes	17	71	0.010	81	0.002	0.000
	no	5	0		36		
Older than 40 yr							
A and non-A	yes	26	61	NS	86	0.037	0.038
	no	12	42		38		
A	yes	8	62	NS	95	NS	NS
	no	5	60		72		
Non-A	yes	18	61	NS	72	0.002	0.002
	no	7	28		37		

For abbreviations, see *Table 1*. NS, not significant. *, four patients alive (after 89 mo).

normal neurological status (60 versus 29% in patients treated in the period from 1953–1976; *P*, 0.003), a high frequency of postoperative radiation therapy in patients with Clinical Syndrome non-A (83 versus 70% of those treated in the period from 1953–1976; *P*, NS), and, above all, a high frequency of Clinical Syndrome A in nonirradiated patients (78 versus 16% in those treated in the period from 1953–1976; *P*, 0.003).

Suggestions for the treatment of low-grade oligodendrogliomas

According to our experience, benign oligodendrogliomas that produce seizures as the only clinical tumor manifestation, Clinical Syndrome A, differ from those that produce neurological deficits and/or intracranial hypertension, Clinical Syndrome non-A, in prognosis when nonirradiated, in response to postoperative radiation therapy, in frequency of subtotal or total surgical removal, and in their occurrence in patients older than 40 years. Furthermore, in the few cases examined, the frequency of vascularization on angiography and of enhancement of the CT scan after contrast administration was different, too (namely, 1 of 7 and 0 of 4 in those with Syndrome A versus 7 of 22 versus 7 of 8 in those with Syndrome non-A). Blush or abnormal vascularity on angiography and contrast enhancement on CT are considered specific characteristics of benign intraventricular or midline oligodendrogliomas (20, 60), usually presenting with signs of intracranial hypertension.

Our long-term follow-up study is a retrospective one; therefore, the indication that adjunctive radiation therapy should be decided in relation to preoperative clinical syndrome remains to be confirmed by other studies. However, it seems no longer appropriate to lump all cerebral oligodendrogliomas together, and after all, in benign tumors, it is reasonably advisable that the preoperative clinical syndrome be considered in deciding treatment and in assessing outcome. In patients with seizures only and nonenhancing lesions imaged early by magnetic resonance, the aim of surgery, beyond removal to the extent consistent with preservation of neurological function, should be the complete eradication of the diseased tissue, possible, perhaps, when the tumor is still small and, therefore, with a narrow area of peripheral infiltration. Moreover, in these patients, we found that survival time was significantly longer after subtotal or total resection than after biopsy or partial removal of tumors on univariate and multivariate analyses (*Table 3B*); this questions the suggestion (52, 69) that, for neurologically healthy epileptic patients with low-grade gliomas diagnosed on CT scans, deferring surgery until signs develop does not worsen outcome. On the other hand, the value of postoperative radiation therapy should be carefully considered and balanced against the risk of radionecrosis and, especially when the diagnosis is made in childhood (74), of the long-term harmful effects of x-rays (21). On this account, irradiation should be kept in reserve for later use, after the appearance of neurological signs.

On the contrary, in patients with intracranial hypertension and/or neurological deficits at surgery, our results definitely justify radiation therapy but do not support aggressive surgery. "Nonanaplastic, CT-enhanced tumors with increasing symptoms" responsive to chemotherapy (9, 27, 33) seem to belong to this second group of patients.

Life history of tumors

In patients treated surgically for cerebral oligodendroglioma, postoperative survivals of more than 20 years are uncommon (6, 17, 22, 29, 38, 43, 56, 57, 64, 71) and mainly occur in patients who undergo second operations or die of recurrences. Roberts and German (57) report perhaps the longest survival, 39 years after surgery in a patient who was appar-

ently cured. On the other hand, Pelc et al. (49) demonstrated in a patient without complaints except occasional seizures CT evidence of persisting tumor tissue 14 years after surgery (and 24 years after the onset of symptoms). Of our patients who were alive after more than 10 years' follow-up, only three, 2.2% of 137 who received surgical treatment, had CT findings considered negative after 13.7, 17.8, and 26.6 years, respectively. The average life span of the disease (from first symptom to death of recurrence) in patients treated surgically for cerebral oligodendroglioma was estimated at between 8 and 14 years by Earnest et al. (22) and was 8.5 years in Cushing's patients (56). In our 84 patients who died of the tumors (at surgery, histologically benign in 59 and malignant in 25), the median duration of the disease was 85 months and the mean 8.4 years.

A check on 18 of our patients who died of recurrences of tumors that were histologically benign at surgery and who had never received radiation therapy led to some considerations regarding the disease duration and its relation to survival. In the patients with seizures at clinical onset, the duration of the disease did not differ significantly between the 6 patients who were neurologically healthy and the 6 patients who had deficits and/or intracranial hypertension at the time of surgery (median, 105 versus 82 months), but survival was inversely related to the duration of the preoperative history (72 and 24 months in the former, 36 and 54 months in the latter, respectively). An inverse correlation of this kind between preoperative history and survival has been attributed to oligodendrogliomas in the past (23, 67, 77). Of patients with intracranial hypertension and/or neurological deficits at the time of surgery, the 6 in whom these disorders followed histories of seizures had longer duration of the disease than the 6 in whom the disease started with intracranial hypertension (median, 82 versus 39 months; P, 0.002) because of the longer preoperative history (median, 54 versus 6 months; P, 0.000), the postoperative survival times being almost the same (median, 36 versus 34 months). It looks as if in patients with intracranial hypertension at clinical onset, an asymptomatic phase of the tumor is equivalent to the seizure phase in the other patients, a reasonable inference, considering the often extensive calcifications and the frequently large size on diagnosis of the tumors producing intracranial hypertension at onset.

Our findings on survival and duration of the disease raise a related question regarding the natural history of the tumor. In short, we think there may well be two, probably successive, periods in the life history of histologically benign oligodendrogliomas. In the first phase, that of onset, in which no symptoms or only epileptic ones are produced, the tumor is consistent with long survival, does not respond to radiation therapy, and in the main shows no vascularization on radiological examinations. In the second phase, in which intracranial hypertension and/or neurological deficits are produced, the tumor correlates with short survival in nonirradiated patients, is highly responsive to radiation therapy, and is often faintly vascularized on the angiogram and mildly enhanced after contrast on the CT scan. The two phases might express a different capacity for vasogenesis or proliferation of the tumor, despite the similar picture of benign histology. Hoshino et al. (30), using the bromodeoxyuridine labeling index in low-grade astrocytomas of comparable histological appearance, found two groups with different proliferative indexes and different prognoses. They suggested that the different responses to adjuvant therapies, radiation therapy or chemotherapy, reported in the treatment of these low-grade gliomas might be explained in terms of their different proliferative capacities.

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COMMENTS

Cerebral oligodendroglioma is seen infrequently. Therefore, most clinical series are small, and considerable uncertainly remains regarding factors that affect prognosis. One of the largest series to date is this study by Celli et al., who report 137 patients (of which 105 were considered suitable for analysis) with supratentorial oligodendrogliomas treated surgically from 1953 to 1986. Multivariate analysis demonstrates that three variables (only) correlate positively with survival: benign histological findings, more recent period of operation (1977–1986), and postoperative radiation therapy. Subgroup analysis, however, demonstrates that postoperative radiation therapy correlates positively with survival in patients who present with intracranial hypertension and/or neurological deficits but not in patients who present with seizures and negative neurological status. If confirmed, this is an important finding and could lend support to the hypothesis that different clinical presentations correspond to different stages in the natural history of oligodendroglioma. Unfortunately, because radiation therapy dose information was unavailable in 35 of the 77 irradiated patients, the authors chose to analyze radiation therapy as a dichotomous rather than a continuous variable. Therefore, the possibility that patients in the subgroup that did not respond to radiation therapy received, on average, a lower (inadequate) dose than patients in the subgroup who did respond has not been excluded. For most tumors, including oligodendrogliomas, the absolute dose level, not simply whether radiation therapy was delivered, is related to outcome (survival, local control, and complications). Therefore, the questions of whether or when radiation therapy should be delivered to patients in either subgroup, and what dose should be delivered, remains open. By the same token, the conclusion that the two subgroups represent different stages in the natural history of oligodendroglioma must be considered tenuous.

Today, of course, if radiation therapy is used, it should be planned with modern three-dimensional software, which integrates magnetic resonance imaging into the planning process, and possibly performed with multiple noncoplanar beams, with appropriate wedges, compensators, and custom blocking. The risk of radionecrosis or other serious complication after an adequate radiation dose—probably about 54 Gy for a benign oligodendroglioma—delivered with such techniques must be considered extremely low.

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Oligodendrogliomas remain intriguing tumors. Although relatively rare, their potential for significant economic and human impact, because of their location and the age group they affect, have made them the subject of multiple studies. As much as any other primary intracranial tumor, they remain enigmas. The roles of gross surgical resection, radiation therapy, and chemotherapy are all controversial. The authors have reviewed the records on 137 patients treated surgically between 1953 and 1986. One hundred five patients had a minimum observation time of five years. Extensive statistical evaluation of this population showed that several factors were associated with improved survival. These included benign histological findings, postoperative irradiation, and time of operation. Intriguingly, subtotal surgical resection and radiation therapy seemed to play more major statistical roles in the subgroup of patients operated on for benign rather than malignant tumors. As the authors have noted, however, their most interesting point was that the clinical response to radiation therapy seemed to be least pronounced or absent in those patients presenting with seizures and normal neurological status. The authors categorized them as Clinical Syndrome A. This is an especially intriguing point, because the role of radiation therapy has not been consistently shown in other studies, and the question always arises about whether the effectiveness of radiation therapy is limited to a certain subgroup, which is either represented or not in the observer's study. In this logical paradigm, those studies that do not show the role of radiation therapy have not evaluated the groups appropriately.

Everyone who has dealt with oligodendrogliomas has had a series of patients who have had marked clinical and radiographic improvement after radiation therapy. However, the absence of a consistent improvement in survival or disease-free interval continues to make radiation therapy a problematic general recommendation for patients with oligodendrogliomas.

This is an important article, in that it raises again the issue of subgroups of patients who may benefit from radiation therapy. In doing this, it should stimulate other investigators to look at their data again to see if a similar pattern can be found. Until a prospective national or international study can be organized, repeated careful review of retrospective data is the only weapon available to those who wish to optimize the treatment of this challenging tumor.

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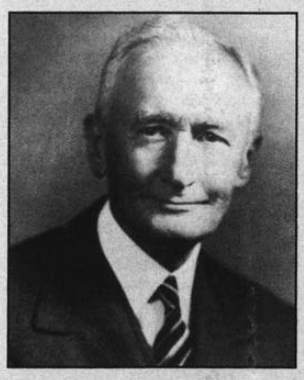
LEGACY

MEDICINE AND NEUROSURGERY:
PEOPLE, THE ARTS, AND LETTERS



This principle figure of neurosurgery at the Massachusetts General Hospital is credited with the delineation between the herniated intervertebral disc and enchondroma. This soft-spoken and gentle man was different from other neurosurgeons of his day. At the dinner of the founding meeting of the Society of Neurological Surgeons, after soup was served, Cushing rose and stated, "We will now leave for case presentations at the Brigham." Our neurosurgeon protested that dinner had just begun. Cushing responded "Those of you who want to learn something, come with me; those who want to eat, stay here with him!"

See answer on page 1120.