Oligodendroglioma: incidence and biological behavior in a defined population

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Oligodendrogliaomas comprise about 5% of all primary brain tumors. Neoplastic proliferation of oligodendrocytes and growth of oligodendrogliaomas are considered to be slow, and associated with a long natural history. These tumors are characterized by a uniformity of the neoplastic cells, but their biological behavior seems unpredictable. Several investigators have come to different conclusions when clinical, morphological, and cytological characteristics have been correlated with survival of the individual patient.

The purpose of this work was to establish the incidence and to study the biological behavior of oligodendrogliaomas in a homogeneous and defined population. In particular, the findings were analyzed with regard to the total duration of survival from the first symptom and to the postoperative survival period.

Clinical Material and Methods

Source of Patients

The Cancer Registry of Norway covers the entire population of the country. In the 25-year period from January 1, 1953, to December 31, 1977, a total of 288
patients were recorded by the Cancer Registry as having a histologically verified diagnosis of oligodendroglioma or anaplastic (malignant) oligodendroglioma. In the same 25-year period, the population of Norway increased from 3.3 to 4.0 million.

**Histological Evaluation**

Histological sections from all 288 patients were reexamined by two pathologists (T.B.H. and S.J.M.) independently and without knowledge of the clinical data. The definition of oligodendroglioma of the World Health Organization (WHO) was adopted, that is: “a tumor composed predominantly of oligodendroglial cells.” After exclusion of these mixed gliomas and of some cases where the material was too scanty for a certain diagnosis, 208 patients remained in the study. In 11 cases the diagnosis was first made at autopsy.

**Therapy**

The surgical treatment consisted of craniotomy with biopsy and removal of as much tumor tissue as possible. Forty-seven tumors were considered as totally removed, and 142 were subtotally resected. Biopsy alone was performed in eight cases. Thirty-seven patients had more than one craniotomy; 87 patients had surgery only, and 107 received surgery plus radiotherapy.

**Follow-Up Review**

Operative deaths included all deaths within 1 month after the primary operation, regardless of cause. These cases were excluded from the analyses of survival. Maximum follow-up and survival time for a single patient was 33.1 years. The follow-up period was discontinued on December 31, 1982. The shortest observation time was 5.1 years.

**Statistical Analysis**

The hospital records were analyzed with respect to patients’ sex and age at diagnosis, presenting symptoms, duration of the earliest symptoms before diagnosis, pre- and postoperative clinical status (based on the performance status defined by the WHO), medical treatment, radiological findings, location of the neoplasm, gross intraoperative findings, surgical treatment, and postoperative treatment. Place of residence, history of head trauma, presence of any other neoplastic disease, ABO blood group, psychiatric examination/treatment, and cerebrospinal fluid (CSF) examination were also recorded.

The Central Bureau of Statistics of Norway was the source of data concerning death certificates. Survival times were recorded and compared with the clinical, radiological, and pathological findings. Survival curves were produced by the life-table method. All variables were evaluated individually with paired comparisons (the Lee-Desu statistic). Differences with \( p < 0.05 \) were considered statistically significant. The course of the disease was calculated as the survival time from the presentation of tumor-related symptoms and as the survival time after the first operation (postoperative survival).

**Results**

At the end of the observation period, 25 patients were still alive. Death certificates were available in all other cases in the series. An autopsy was performed in 36 cases. All variables in each patient’s data file were evaluated individually and a paired comparison was made for survival and prognostic data.

**Incidence**

Of the 6180 primary intracranial tumors recorded in the Cancer Registry of Norway from January 1, 1953, through December 31, 1977, 4902 patients had a primary intracerebral neoplasm (craniopharyngiomas, pituitary adenomas, pinealomas, and tumors of cranial nerves and meninges not included), and, of these, 208 are confirmed as oligodendrogliomas. During the same period, no oligodendroglioma occurred among the 180 primary intramedullary tumors. This gives an incidence of approximately 240 new cases per year of primary central nervous system neoplasms in Norway’s population of 4 million; of these, 10 (4.2%) are oligodendrogliomas.

**Localization**

All of the oligodendrogliomas were supratentorial. About one-half of the tumors affected the frontal lobe, one-third the parietal lobe, one-quarter the temporal lobe, and one-sixteenth the occipital lobe. There was a slight preponderance of lesions on the right side, and 20% were bilateral or at the midline. There were only six predominantly intraventricular lesions. The most frequent site was in the white matter of the frontal lobe (111 cases or 53%).

**Natural Course**

In 11 cases no operation was performed. However, two of these patients were given radiation therapy. The median survival from the first symptom of the nine untreated oligodendroglioma cases was 14 months.

**Postoperative Survival**

Twenty-two patients died during the 1st month after craniotomy, giving an operative mortality rate of 11.2% for the total time period of this study (1953 to 1977). The operative mortality rate after 1969 was six of 71 patients (8.4%).

Figure 1 shows the survival curve of the 175 patients who lived longer than 1 month after the initial craniotomy. About 80% of the patients lived for more than
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**TABLE 1**

<table>
<thead>
<tr>
<th>Presenting symptom in patients with cerebral oligodendroglioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>seizures</td>
</tr>
<tr>
<td>headache</td>
</tr>
<tr>
<td>mental changes</td>
</tr>
<tr>
<td>vertigo/nausea</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Duration of symptoms before diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Symptoms</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>&lt; 1 yr</td>
</tr>
<tr>
<td>1 to 6 yrs</td>
</tr>
<tr>
<td>&gt; 6 yrs</td>
</tr>
</tbody>
</table>

* Median time after onset of first symptoms: 20.5 months (mean 43 months).

1 year after their initial surgery. The 5-year survival rate was 34.2% (60 of 175 patients). Seventy-four (42%) of the 175 patients died between the 2nd and 6th year after surgery. The median postoperative survival time was 35 months (mean 52 months).

**Symptoms**

A seizure was the most frequent first symptom, occurring in 57% of the patients. Other presenting symptoms are shown in Table 1. Table 2 lists the duration of symptoms before the tumor was detected. In 26 patients the oligodendroglioma was diagnosed 10 years or more after the first symptom. The longest preoperative duration of symptoms was 16.5 years.

The median duration of seizures before diagnosis was 48 months in 119 patients (mean 64 months), as opposed to 4.4 months (mean 13.3 months) in 87 patients with other presenting symptoms. In two cases the time of onset of symptoms could not be assessed. There was no difference in preoperative symptoms or total duration of oligodendroglioma-related symptoms in two arbitrary groups created by splitting the series into patients entered in the Cancer Registry from 1953 through 1969 and those entered from 1970 through 1977.

The median actuarial survival time from onset of symptoms was 74 months (mean 85 months). The longest duration of disease was 397 months (33.1 years), in a patient who was still living when the follow-up survey was discontinued. Patients with seizures as their first symptom had a median total duration of disease of 99 months as opposed to 32.5 months in the others (p < 0.0001). Patients presenting with headache and mental changes (changes in mentality, personality, memory, or behavior) survived for 31 and 23 months, respectively, after onset of symptoms.

There were no statistically significant differences in postoperative survival of patients with different presenting symptoms. The 103 patients with seizures survived for 39 months (median) after operation as opposed to 31 months in the 70 other patients (p = 0.1106).

**Clinical Signs**

On admission, 43% of the patients had paresis, 46% had papilledema, only 11% had visual field defects, and 4% had sensory loss. In 28% of cases, seizures were the reason for admission. Patients with paresis on admission had a median survival period of 53.5 months from onset of symptoms as opposed to 86 months in those without this symptom. Patients with seizures as the only clinical tumor manifestation on admission had a median duration of disease of 98 months as opposed to 48 months in patients with other symptoms. Table 3 lists admission signs that proved of significance for postoperative survival.

The preoperative functional status was defined by...
TABLE 4
Preoperative clinical status and postoperative survival

<table>
<thead>
<tr>
<th>WHO Status*</th>
<th>No. of Cases</th>
<th>Postoperative Survival</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22</td>
<td>93 (mos)</td>
<td>p = 0.0016</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>42 (mos)</td>
<td>p = 0.0359</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>29 (mos)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>30 (mos)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>27 (mos)</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>16</td>
<td>84 (mos)</td>
<td></td>
</tr>
</tbody>
</table>

* World Health Organization (WHO) classification: 0 = normal; 1 = some signs/symptoms of disease, normal activity with effort; 2 = able to care for most personal needs, unable to work; 3 = disabled, independent less than half the daytime; 4 = completely disabled. The relationship of the patients’ functional status to their postoperative survival is listed in Table 4. Patients with slow preoperative clinical progression of their disease had a postoperative median survival time of 54.5 months, as compared with 31 months (p < 0.0063) in patients with a more rapid progress.

Radiological Findings

Plain skull x-ray films showed calcification in 54 (28%) of 192 tumors. Arteriography revealed that 42 (20%) of 181 tumors so studied were hypervascular. Computerized tomodraphy was introduced too late to be of interest for the present series. Forty-two patients with arteriographically hyper vascular lesions had a median survival time of 42 months from the onset of symptoms, as opposed to 80 months in the 138 who did not display this feature.

Tumor calcification, seen on plain skull x-ray films in a total of 53 patients, was associated with a median disease duration of 108 months as opposed to 57.5 months in the 137 patients without calcification. The 45 surgical patients with calcification visualized in the plain skull x-ray film lived for a median of 61 months after craniotomy as opposed to 32.5 months (p = 0.0312) in 118 surgical patients whose brain lesions showed no calcification.

Surgical Findings

The shortest median postoperative survival, 27.5 months, was recorded in patients with oligodendrogliomas located in the temporal lobe, as opposed to 37 months in patients with the lesion in the frontal lobe. Any differences were not of statistical significance.

At surgery, 155 of the oligodendrogliomas were macroscopically poorly defined, as opposed to 22 cases that were well demarcated. The tumor consistency was soft in 84 cases and firm in 81. Grossly, 57 lesions were partly cystic, and 45 hypervascular; hematoma of varying age and mostly small was noted in 31, necrosis in 31, and calcification in 25 tumors. Infiltration of the leptomeninges was noted in 70 cases. Signs of seeding via the CSF were seen in two patients, and adherence to the dura was present in 16 cases. In summary, on gross examination most oligodendrogliomas in this series were not demarcated, not cystic, not related to hematoma, not necrotic, not calcified, and had not spread into the leptomeninges or along CSF pathways.

The presence of gross necrosis was related to a shorter total duration of disease, as was hypervascularity and soft tumor consistency. Lesions considered by the surgeon as being well demarcated were associated with a longer total duration of disease. Grossly visible cysts, calcification, and local leptomeningeal infiltration did not correlate with the duration of disease. Table 5 lists various features noted grossly at operation with corresponding survival data.

Patients with total tumor excision had a median postoperative survival period of 45.5 months. The difference in survival times between patients treated with surgical extirpation and those treated with the other

TABLE 5
Surgical findings and postoperative survival in oligodendroglioma patients

<table>
<thead>
<tr>
<th>Feature of Tumor</th>
<th>No. of Cases</th>
<th>Postoperative Survival</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>well demarcated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>20</td>
<td>62 (mos)</td>
<td>p = 0.0039</td>
</tr>
<tr>
<td>present</td>
<td>134</td>
<td>32 (mos)</td>
<td></td>
</tr>
<tr>
<td>necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>26</td>
<td>17 (mos)</td>
<td>p = 0.0039</td>
</tr>
<tr>
<td>present</td>
<td>113</td>
<td>39 (mos)</td>
<td></td>
</tr>
<tr>
<td>color</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gray-white</td>
<td>30</td>
<td>59 (mos)</td>
<td>p = 0.0345</td>
</tr>
<tr>
<td>brownish</td>
<td>18</td>
<td>16 (mos)</td>
<td>p = 0.0059</td>
</tr>
<tr>
<td>calcification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>21</td>
<td>40 (mos)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>75</td>
<td>32 (mos)</td>
<td></td>
</tr>
<tr>
<td>hypervascularity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>38</td>
<td>32.5 (mos)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>105</td>
<td>38 (mos)</td>
<td></td>
</tr>
<tr>
<td>hematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>24</td>
<td>26 (mos)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>122</td>
<td>36 (mos)</td>
<td></td>
</tr>
<tr>
<td>leptomeningeal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>63</td>
<td>35 (mos)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>89</td>
<td>38 (mos)</td>
<td></td>
</tr>
<tr>
<td>gross cysts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>52</td>
<td>32 (mos)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>109</td>
<td>35 (mos)</td>
<td></td>
</tr>
</tbody>
</table>

* Difference compared with "not gray-white."
† Difference compared with "not brownish."
‡ NS: p > 0.05.
surgical modalities combined (32 months) had a p value of 0.0510.

Age and Sex Distribution

Figure 2 shows the age at diagnosis and the sex distribution in the complete series. The age range was from 3 to 76 years, the median age at diagnosis was 47 years (mean 44 years). Diagnosis was made in females at ages from 3 to 76 years, with a median age of 49 years (mean 46 years). Diagnosis was made in males at 4 to 76 years of age, with a median age of 46 years (mean 43 years). Males were afflicted in 127 cases (61%). For comparison, during the same 25-year period in Norway, 58% of all primary intracerebral tumors occurred in males.

Twelve (6%) of the oligodendrogliomas occurred in children aged under 16 years of age, and five in adolescents (16 to 19 years). The 17 patients below 20 years of age had a median duration of disease from first symptom of 125 months, as opposed to 67 months in patients between 20 and 39 years and 81 months in the 40- to 60-year-old group. The 18 patients older than 60 years at the time of diagnosis lived for a median of 30 months after onset of symptoms. In paired comparison, none of these differences was statistically significant.

The 14 patients under 20 years of age who survived for more than 1 month after initial surgery had a median survival time of 61 months as opposed to 37.5, 34.5, and 32.5 months in the age groups 20 to 39, 40 to 60, and over 60 years, respectively. These differences were not statistically significant.

There was no difference in survival relating to gender.

There was no difference in survival relating to gender.

Radiation Therapy and Postoperative Survival

Preliminary evaluation showed that irradiated oligodendroglioma patients lived 11 months (median) longer than those without radiation therapy (p = 0.0092).

Metastases

No systemic metastases (outside the central nervous system) were demonstrated in this series.

ABO Blood Groups and Survival

Table 6 lists the blood group distribution in the 181 patients where this information could be retrieved. Of these, 158 patients were followed for more than 4 weeks after operation. The longest median postoperative survival was found in patients in B and O blood groups. The A group (76 patients) had a median postoperative survival of only 30 months.

Head Trauma and Other Tumors

Thirty-seven patients (18%) gave a history of head trauma. No effort was made to establish the site or magnitude of this.

Three of the oligodendroglioma patients were registered in the Cancer Registry of Norway as having a second primary neoplasm. One patient had a basal cell carcinoma of the lip, one a lymphoid hyperplasia of unknown neoplastic potential, and the third patient was treated for cancer of the cervix uteri.

Discussion

Incidence

The incidence of primary brain tumors varies in different series. This may be attributed to variations in the origin of patients. Comparisons are unreliable when the number of individuals at risk is unknown and when the source of patients is not stated. Most reports are from highly specialized centers and the geographic region is unspecified. The present series
comprises the total number of cases in Norway as registered by the Cancer Registry of Norway. All cancers and established precancerous lesions are reported by Norway's 18 pathological laboratories and also by all hospitals.

**Age and Sex**

The mean age of the patients in this series is about the same as in other reports, and the clustering of oligodendrogliomas between the ages of 40 and 60 years is consistent with reports from other countries (see Fig. 2 and Table 7).

The number of childhood oligodendrogliomas varies in different series.\(^{13,14,19,28,33,35}\) Jellinger and Machacek\(^{23}\) found 13 (2%) oligodendrogliomas among 616 neuroectodermal tumors in a series of 810 intracranial neoplasms in children under 16 years of age in Vienna, from 1940 to 1980. It has been suggested that oligodendroglioma is a rare pediatric brain tumor; however, our series (which probably includes all cases that occurred in a known population over a period of 25 years) points to a higher incidence (Fig. 2). The somewhat longer survival that we found in younger subjects is in line with results from other studies of primary brain tumors,\(^{8,16,37}\) but the difference was not statistically significant. The reported male predominance in oligodendrogliomas\(^{20,29,33,34}\) was confirmed in our study.

**Localization**

Oligodendrogliomas are supratentorial in the overwhelming majority of published cases. In a large series of primary intramedullary tumors of the spinal cord and filum terminale, only eight (2.6%) of 301 tumors were oligodendrogliomas.\(^{40}\) The proportion of cerebral oligodendrogliomas affecting the frontal lobes varies from about 50% to 75% in different studies\(^{11,14,20,33,39}\) (see also Table 7). In the present series, the tumor localization in any particular lobe did not influence survival significantly, as pointed out by others.\(^{33}\)

**Symptoms**

Table 8 lists the fate of oligodendroglioma patients from different series. Almost half of our patients had...
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had symptoms for less than 1 year before diagnosis. It is noteworthy that the median duration in our series was 20.5 months but the mean duration was 43 months. This point may have been obscured in reports that only give the mean duration of preoperative symptoms. A few patients with extremely long duration can have a disproportionate effect on the mean figure.

Patients with seizures as the first symptom had a significantly longer total survival time (p < 0.0001). Yet the postoperative survival period was not significantly different (p = 0.1106). On the other hand, those patients with seizures as the only symptom at preoperative hospital admission had significantly longer postoperative survival (Table 3) than the other oligodendroglioma patients. This may be related to the clinical status. Patients who have seizures as the first symptom are likely to have a better admission status and probably also a slower clinical progression than patients with multiple or other symptoms.

Calcification

Plain skull x-ray films revealed calcified deposits in 28% of oligodendrogliomas. In other studies this varies from 28% to 77% (Table 7). Calcification had a significant relationship to a longer preoperative clinical history and to a longer postoperative survival and therefore may reflect the biological behavior of the neoplastic tissue. On the other hand, histological evaluation and statistical analysis of the present series established microscopic calcification as having no prognostic value (in preparation).

Gross Appearance

As opposed to well demarcated and gray-white lesions, presence of necrosis and a soft tumor consistency had a significant relationship to a shorter postoperative survival (Table 5). The prognostic value of the gross tumor appearance has to our knowledge not been described previously.

Growth and Spread

Single case reports and small series of oligodendrogliomas with subarachnoid seeding40,41,44 probably have contributed to the idea that these tumors are prone to disseminate through the CSF pathways. In the present series, subarachnoid growth was frequently encountered at the tumor site. In spite of this, seeding via the CSF was seen in only two of our 208 cases. Extranuclear metastases after surgical treatment, as reported in exceptional cases,42,43 were not found.

Trauma

A history of head trauma is frequent in both healthy and diseased people,31 and the figures in the present study are well within expected limits.

ABO Blood Groups

The blood group distribution in this series did not deviate substantially from that found in the general population of Norway.18 Our findings thus confirm those of Pearce and Yates from England.32 The statistically significant difference in postoperative survival between oligodendroglioma patients of blood group A and those of B is intriguing (Table 6). Statistical association does not necessarily imply causation, but the ABO system may be related to the biological behavior of cancer, since some cancers have a higher incidence in subsets of the ABO system46 (for instance, the increased incidence of gastric carcinoma in subjects with blood group A). Further studies in defined and relatively homogeneous populations would be of interest to elucidate whether blood group A can be established as an adverse prognostic factor in patients with oligodendrogliomas.

Combined with other cerebral gliomas,26,30 oligodendrogliomas have a distinct biological behavior. Patients with oligodendroglioma generally do better than those with most other gliomas, at least for the first year or two after treatment.28 In a recent study of 461 patients with low-grade astrocytomas, the postoperative 5-year survival (operative deaths excluded) amounted to 36.5%,26 compared to 34% in our series of oligodendrogliomas. There is no justification for using the phrase "benign brain tumor" where oligodendrogliomas are concerned. Patients with oligodendrogliomas are rarely, if ever, cancer-free, even after prolonged survival. In the present series, all deaths were ascribed to the patient's brain tumor. A tendency toward anaplastic change in oligodendroglioma is difficult to assess from the clinical development alone. A change in symptoms or the rapid development of new or recurrent symptoms may be related to an intracranial pressure-volume decompensation secondary to the neoplastic mass effect, and does not necessarily imply a change in tumor growth per se. Nevertheless, an assessment of the preoperative clinical development seems to be of prognostic value.

Combined treatment by surgery and irradiation may give a distinctly longer median survival time than treatment by surgery alone, but does not influence the fatal outcome.

Summary

The present study indicates that clinical, radiological and gross surgical findings give statistically significant clues as to the prognosis in patients with oligodendroglioma. It is remarkable that the pattern persists independently of the type of treatment regimen. The results thus speak in favor of a pre-set biological clock behavior. It is reported for the first time that the ABO blood group may be of high prognostic value in cases with cerebral oligodendroglioma.

The survival data from our unselected series also
indicate that the prognosis in cerebral oligodendrogliomas is less favorable than has generally been stated.\textsuperscript{38}

Acknowledgments

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