Neurosurgical treatment of oligodendrogial tumors in children and adolescents: a single-institution series of 35 consecutive patients

Clinical article

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Object. The object of this study was to delineate long-term results of the surgical treatment of pediatric CNS tumors classified as oligodendroglioma (OD) or oligoastrocytoma (OA) WHO Grade II or III.

Methods. A cohort of 45 consecutive patients 19 years or younger who had undergone primary resection of CNS tumors originally described as oligodendroglial during the years 1970–2009 at a single institution were reviewed in this retrospective study of surgical morbidity, mortality, and academic achievement and/or work participation. Gross motor function and activities of daily living were scored using the Barthel Index (BI).

Results. Patient records for 35 consecutive children and adolescents who had undergone resection for an OA (17 patients) or OD (18 patients) were included in this study. Of the 35 patients, 12 were in the 1st decade of life at the first surgery, whereas 23 were in the 2nd decade. The male/female ratio was 1.19 (19/16). No patient was lost to follow-up. The tumor was localized to the supratentorial compartment in 33 patients, the posterior fossa in 1 patient, and the cervical medulla in 1 patient. Twenty-four tumors were considered to be WHO Grade II, and 11 were classified as WHO Grade III. Among these latter lesions were 2 tumors initially classified as WHO Grade II and later reclassified as WHO Grade III following repeat surgery.

Fifty-four tumor resections were performed. Two patients underwent repeat tumor resection within 5 days of the initial procedure, after MRI confirmed residual tumor. Another 10 patients underwent a second resection because of clinical deterioration and progressive disease at time points ranging from 1 month to 10 years after the initial operation. Six patients underwent a third resection, and 1 patient underwent a fourth excision following tumor dissemination to the spinal canal. Sixteen (46%) of the 35 children received adjuvant therapy: 7, fractionated radiotherapy; 4, chemotherapy; and 5, both fractionated radiotherapy and chemotherapy. One patient with primary supratentorial disease experienced clinically malignant development with widespread intraspinal dissemination 9 years after initial treatment. Only 2 patients needed treatment for persistent hydrocephalus.

In this series there was no surgical mortality, which was defined as death within 30 days of resection. However, 12 patients in the study, with follow-up times from 1 month to 33 years, died. Twenty-three patients, with follow-up times from 4 to 31 years, remained alive. Among these survivors, the BI was 100 (normal) in 22 patients and 80 in 1 patient. Nineteen patients had full- or part-time work or were in normal school programs.

Conclusions. Pediatric oligodendrogial tumors are mainly localized to the supratentorial compartment and more often occur in the 2nd decade of life rather than the 1st. Two-thirds of the patients remained alive after follow-ups from 4 to 31 years. Twelve children succumbed to their disease, 9 of them within 3 years of resection despite combined treatment with radio- and chemotherapy. Three of them remained alive from 9 to 33 years after primary resection. Among the 23 survivors, a stable, very long-term result was attainable in at least 20. Five-, 10-, 20-, and 30-year overall survival in patients with Grade II tumors was 92%, 92%, 92%, and 88%, respectively.

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Key Words • pediatric oligodendroglioma • oligoastrocytoma • long-term results • pediatric neurosurgery • oncology

OLIGODENDRGLIOMAS and oligoastrocytomas, localized mainly in the cerebral hemispheres, represent a minor proportion of gliomas in childhood and adolescence. They are usually classified as WHO Grade II or III. No large study of consecutive pediatric patients harboring such neoplasms with long-term outcome data has been published. In this report we summarize our experience with resection and adjuvant oncological therapy in 35 consecutive cases of OD and OA in patients 0–19 years of age during the period from 1970 to 2009.
Methods

We retrospectively analyzed a cohort of 45 consecutive patients 19 years or younger who had undergone primary resection of CNS tumors originally described as oligodendrogial during the years 1970–2009 in the Department of Neurosurgery at The National Hospital, Oslo, Norway. Cases were collected from surgical protocols of the given time period in which initial histological evaluation revealed an OD or OA.

Recorded data included patient sex, age at the time of primary tumor resection, and management of hydrocephalus. We also noted scholastic outcome, which was simplified into normal versus special schooling, and employment, which was categorized as open (in the competitive labor market), sheltered (for handicapped individuals, often reduced time and financed by the social security system), or no work.

Computed tomography scans were used for tumor diagnosis and follow-up since 1976. Since 1987, when MRI became available, the tumor was visualized on preoperative MR images, and repeat MRI was introduced in the follow-up. The aim of the surgical procedure was GTR or at least substantial tumor volume reduction. The degree of resection was evaluated on postoperative MRI, often while the patient remained under the anesthesia from the primary resection.

The BI is a well established and validated scale using 10 variables to measure performance in basic ADLs primarily related to personal care and mobility. Scores range from 0 to 100, with a higher score denoting greater independence. We intended to assess functional status and illustrate eventual differences among subgroups within our cohort.

Data were analyzed using SPSS software (version 16.0, SPSS Inc.).

Results

After a critical pathological review, 35 of the 45 tumors met updated and extended diagnostic criteria (18 ODs and 17 OAs). Some tumors were more difficult to classify than most, and international expert neuropathologists evaluated a couple of them. Nevertheless, this study includes all cases of oligodendrogial pediatric gliomas surgically treated in this period, which represent 3.3% of all pediatric CNS tumors surgically treated at our institution in the same time period.

Clinical Presentation

Five patients (14%) presented with clinical symptoms of increased intracranial pressure (headache). In 2 of them, acute symptoms occurred after hemorrhage in the tumor. Twenty patients (57%) experienced one or more epileptic seizures. At initial presentation, the tumor was localized to the supratentorial compartment in 33 patients, posterior fossa in 1 patient, and cervical medulla in 1 patient. Neurofibromatosis Type 1 was also diagnosed in 1 patient, and Duchenne muscular dystrophy had been diagnosed in another patient in advance of the tumor disease.

The ages of the children at the primary surgery are graphically presented in Fig. 1. Twelve patients were in the 1st decade of life at the primary operation and 23 were in the 2nd decade. The median patient age on primary diagnosis was 13 years. The male/female ratio was 1.19 (19/16).

Tumor Location and Extent of Resection

According to radiological and preoperative findings, most tumors were unilateral and localized to the cerebral hemispheres: 7 frontal, 15 temporal, 4 parietal, and 3 occipital. Four supratentorial tumors had mainly an intraventricular presentation. One tumor was localized to the posterior fossa and one to the cervical medulla.

All 35 patients underwent an open procedure with tumor resection whose aim was gross-total removal. In the early period of the study, the degree of resection achieved was based on the surgeon’s description and/or CT scans. After its introduction in 1987, MRI better documented the extent of resection on immediate postoperative imaging. Gross-total resection was accomplished in 25 patients. A more restricted resection was performed in a 15-year-old girl with WHO Grade III OD in the cervical medulla. After postoperative radiotherapy, she finished school and was fully employed, but she needed a second resection after 10 years because of clinical deterioration and tumor growth. The histology was again WHO Grade III OD. After another year of follow-up, the BI was still 100; however, the prognosis appears dubious because of tumor dissemination.

In total, 12 patients underwent a second resection. In 2 patients, this was an early secondary procedure occurring within 5 days of the initial resection because of residual tumor confirmed on MRI. In 10 patients, repeat resection was performed because of clinical deterioration and progressive disease from 1 month to 10 years after the initial procedure. Six patients underwent a third resection, and 1 patient underwent a fourth excision after tumor dissemination to the spinal canal.

Nonsurgical Antitumor Therapy

Sixteen (46%) of the 35 children received adjuvant therapy. In the postoperative period 12 patients underwent fractionated radiotherapy to the initially involved anatomical regions of the brain. Fractionation was 1.8 Gy × 30 fractions for 9 patients and was similar but slightly different for the other 3 patients. Five of these 12 patients also had chemotherapy.

Four children were given chemotherapy as the only adjuvant treatment. A mesencephalic/diencephalic tumor was diagnosed in a 10-month-old boy with left-sided hemiplegia. After partial tumor resection of what was classified as a Grade II/III OA, he underwent 15 months of chemotherapy according to the International Society of Pediatric Oncology/United Kingdom Children’s Cancer Study Group (SIOP/UKCCSG) protocol for children younger than 3 years of age. He responded favorably to treatment, as indicated by follow-up MRI. He still has left-sided hemiparesis, and reduced hearing developed during his chemotherapy; otherwise, the clinical course has been uneventful for 10 years, and there have been no signs of residual tumor.

In the first half of the study period (20 years), 6 of 14 patients received radiotherapy. We believe this reflects...
our belief that tumors in these patients had a dismal prognosis. Only 1 of these 10 patients received chemotherapy (first temozolomide; later vincristine, lomustine, and Natulan), which was administered 20 years after surgery, when residual tumor progressed.

In the second half of the study period, only 6 of 21 patients were given radiotherapy. These 6 all had Grade III tumors and were given intravenous chemotherapy (vincristine, cyclophosphamide, etoposide, or methotrexate, depending on age and so forth). One patient in the 1st year of life received intravenous chemotherapy without radiation. Five patients were given oral temozolomide in a late stage, when disease was out of control.

**Pathological Analysis**

The histological diagnosis was WHO Grade II OD in 12 patients and WHO Grade III OD in 6 patients. Among these latter 6 cases were 2 lesions categorized as Grade II at the first surgery, although malignant development over time led to a repeated resection along with upgrading to Grade III. Seventeen lesions were diagnosed as OA: WHO Grade II in 15 cases and WHO Grade III in 2.

Since 2000, routine examination for the loss of chromosome arms 1p and 19q was performed in patients with oligodendrogial tumors. Of the 16 patients in whom this analysis was undertaken, none showed combined 1p and 19q loss. One patient demonstrated a 1p deletion without a 19q deletion, a finding considered to be unrelated to 1p/19q loss. We attempted to analyze for 1p/19q loss in some older cases, but these attempts were unsuccessful because of no or limited tumor material and/or poor sample quality.

**Mortality and Survival**

There was no operative mortality, which was defined as death within 30 days from surgery. However, 12 patients in the study died, and the distribution of their follow-up times is shown in Fig. 2. Three patients died within a year of treatment as a result of progressive disease. Ten patients died despite combined treatment, 9 of them within 5 years and 1 patient at 9 years after primary resection. Two patients survived for 23 and 33 years after primary resection but ultimately succumbed to progressive disease.

Twenty-three patients (66%) survived, having follow-up times ranging from 4 to 31 years (Fig. 3). The median follow-up period was 14 years, and 8 patients had more than 23 years of follow-up. Accumulated survival for the entire series showed 5-, 10-, and 20-year OS of 74%, 71%, and 71%, respectively. There was a marked discrepancy between the patients with Grade II lesions and those with Grade III lesions (Fig. 4): 5-, 10-, and 20-year OS of 92% each and 30-year OS of 88% in the patients with low-grade tumors, compared with 5- and 10-year OS of 27% and 18%, respectively, in the patients with anaplastic tumor.

**Postoperative Function**

Overall, gross motor function and management of ADLs was good. In terms of the BI, the score was 100 in 22 patients and 80 in 1 patient.

Of the 23 survivors, only 2 had focal neurological deficits: homonymous hemianopia after occipital tumor resection in 1 patient and residual hemiparesis in 1 child with hemiplegia preoperatively. Three patients still have moderate or mild epilepsy and use antiepileptic medication.

Currently, 6 of the 23 survivors have an age below 20 years (11–19 years), and they all follow regular school programs. The remaining 17 patients are ages 20–46 years. Two are students, 14 have regular work, and 1 is unemployed.

**Discussion**

Oligodendrogial tumors represent only a small proportion of gliomas in children and teenagers.1,2,6 The present consecutive series covers a period of 40 years, in which remarkable diagnostic and operative progress has been made. In a large Norwegian, population-based consecutive series of 208 ODs in patients of all ages, 19 patients were younger than 20 years, and an operative mortality of 26% (5 of 19) was found.12 That historical study included patients treated in the 25 years between 1953 and 1977, all patients had supratentorial tumors, and not a single OD in the medulla spinalis was diagnosed in Norway during this time period.

The present series of 35 consecutive cases diagnosed in children and adolescents between 1970 and 2009 confirms that oligodendrogial tumors are mainly localized in the supratentorial compartment, most often in the cerebral hemispheres. There was a slight male preponderance, but in contrast to data in other pediatric glioma series, tumors in the present study were twice as common in the 2nd decade of life than in the 1st.3,12 These oligodendrogial cases represented 3.3% of all CNS tumor cases surgically treated in this age group during the same 40-year period at our institution.

Two cases had spinal involvement. There was 1 case of primary anaplastic OD in the cervical medulla and 1 supratentorial case with repeated recurrences and, after 9 years, tumor dissemination to the spinal canal. Although rare, such dissemination has been described by several authors.6,17 One child had a tumor in the posterior fossa, a location that has been considered to imply a severe prognosis.11,13 The patient died as a result of late tumor progression after 23 years, despite adjuvant treatment.

Oligodendrogial tumors have generally been consid-
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Considered to have a dismal prognosis, although prolonged survival has been observed in some cases. In a recent study in adults at our institution, a better prognosis was encountered in patients with a female sex, frontal lobe tumor location, epilepsy as an initial symptom, WHO Grade II tumor, and young age. The 95 patients in that study were treated between 1998 and 2007. A male preponderance among the study cohort was found (1.6), and two-thirds of the tumors were Grade II. The follow-up period was relatively short, however. The combined 1p/19q deletion was also found to indicate a better prognosis.

In our pediatric study, 1p/19q analysis was performed in 16 cases diagnosed during the last 10 years of the study period, and codeletion was found in none of these cases. Only 1 case of 1p deletion without 19q deletion was found. These findings are in accordance with previous reports stating that 1p/19q deletions are rare in patients younger than 15 years of age.

Only 9 of 35 cases in our study were originally classified as Grade III. Two of the 26 patients with an initial Grade II tumor had progressive disease over time and demonstrated, when they underwent repeat resection, Grade III tumors. Both of these patients died of their disease from 2 to 9 years after initial treatment.

Some authors have found that GTR improves outcome in terms of prolonged disease-free survival but not necessarily OS. Our surgical intention was GTR, and we performed early repeat resection in 2 cases in which unexpected residual tumor was found on immediate postoperative MR images. We also performed repeat surgery later in several other patients based on individual clinical decisions. Partial resection was performed in those cases in which more aggressive resection was considered to be too hazardous, that is, in cases with a tumor location in the cervical medulla or the brainstem and in 4 supratentorial cases with an intraventricular presentation and tumor extension into the axial midline structures. Based on these findings, we believe that a hemispheric tumor location, and therefore often concomitant epilepsy as a presenting symptom, usually indicates a good prognosis, not only because the disease is more suitable for radical surgery, but also because of early clinical symptoms.

Furthermore, some authors have found that prognosis is related to the age of the patient, even within the group of children and teenagers with oligodendrogial tumors. Razack and coworkers described a better prognosis for children younger than 12 years of age in a study of 19 cases. In our study 14 patients were younger than 12 years of age, and 10 (71%) of them survived. In contrast, there were 13 survivors (62%) among the 21 patients in the age group of 12–19 years. Creach and coworkers analyzed 37 pediatric cases and found an improved prognosis in patients younger than 12 years of age but not in those younger than 3 years. In our study, only 3 of the 35 patients were younger than 3 years at the initial surgery, and they all remained alive with follow-up periods of 11, 20, and 31 years. Note that although some clinical studies with children and teenagers surgically treated for oligodendrogial tumors have been published during recent years, they did not report on very long-term prognosis.

Our clinical results clearly indicate that long-term survival is more common in children and teenagers than in adults with such tumors. Two-thirds of the patients remained alive after treatment, with follow-up periods from 4 to 31 years and a clinical condition rated as 100 on the BI. The only exception was a 12-year-old boy in whom Duchenne muscular dystrophy had been diagnosed at an early age and who underwent resection for an OD at the age of 5 years. He had a BI of 80 and his condition was deteriorating, most probably because of his neuromuscular disease.

Even in the 12 patients who died, OS was heterogeneous. One patient with a Grade II tumor died within a few months after surgery, which was the early part of the study period before the introduction of CT scanning and MRI. Six of the 8 patients who died within 5 years of primary resection had Grade III tumors, and they succumbed to their disease despite repeat resections and/or combined therapy when indicated. Note, however, that there were also 2 long-time survivors among those who died. Grade II tumors were diagnosed in both of these patients, but they
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More than one-third of the patients received radiotherapy. Half of these patients had high-grade tumors, and all patients with Grade III tumors received radiotherapy unless they were very young. The other half of the patients who underwent radiotherapy harbored Grade II tumors. This decision to administer radiotherapy may appear arbitrary but probably reflects prevailing opinion at the time of the decision. As discussed above, 2 of the patients died 23 and 33 years after initial treatment. They both experienced cerebral stroke some years before they died at the ages of 35 and 39 years. We believe that their strokes could have been related to late effects from radiotherapy.

Conclusions

Clinical results in this series of pediatric oligodendroglial tumors demonstrated that about one-third of the patients proved to have a tumor problem with a dismal prognosis despite aggressive combined treatment. The outcome appears to be related to the histological grading. Only 3 of 11 patients with high-grade tumors remain alive, one of them with progressive disease. A minor proportion of the patients with low-grade tumors also demonstrated progressive disease, despite their low tumor grading and aggressive combined treatment.

On the other hand, most of the children and teenagers included in the present series had a very good result in terms of survival, ADLs, education, and working capacity. Among the 23 survivors, a rewarding very long-term result appears to have been obtainable in at least 20.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Lundar, Scheie, Brandal. Analysis and interpretation of data: Lundar, Due-Tønnessen, Egge, Scheie, Brandal. Drafting the article: Lundar, Due-Tønnessen, Stensvold, Brandal. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lundar. Statistical analysis: Lundar.

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