Our Experience in Brain Oligodendroglioma Management in Adults

Julio César Suárez¹, Enrique José Herrera¹, Alberto Surur², Ricardo Theaux³, Silvia Zunino⁴, Gustavo Jarchum⁵, Daniel Lerda⁶, Martin Arneodo¹, Francisco José Pueyrredon¹, Juan Manuel Ryan¹, Juan Carlos Viano¹.

1 - Neurosurgery Department, Sanatorio Allende - Córdoba / Córdoba / Argentina.
2 - Neuroradiology Department, Sanatorio Allende - Córdoba / Córdoba / Argentina.
3 - Neuropathology Department, Medical School, Universidad Católica de Córdoba - Córdoba / Córdoba / Argentina.
4 - Instituto Privado de Radioterapia Oncológica - Córdoba / Córdoba / Argentina.
5 - Oncology Department, Sanatorio Allende - Córdoba / Córdoba / Argentina.
6 - Department of Molecular Biology and Genetics, Medical School, Universidad Católica de Córdoba - Córdoba / Córdoba / Argentina.

RESUMO

Objetivo: apresentar nossa experiência de 19 anos na abordagem dos oligodendrogliomas cerebrais do adulto.

Material e método: Quinhentos e cinco pacientes portadores de tumor cerebral foram operados em nosso serviço no período de 19 anos: em 30 casos (5,9 %) o diagnóstico histopatológico foi oligodendroglioma; dos quais, só em 26 casos logrou-se fazer um bom acompanhamento pós-operatório. Resultados: Nos 26 doentes estudados, a idade oscilou entre 23 e 72 anos. O diagnóstico histológico mostrou 17 oligodendrogliomas puros e 9 oligoastrocitomas. Em 16 casos Ki67 foi igual ou menor que 5 %, e em 7 era maior que 5 %. Os cromossomos 1p e 19q foram estudados em 12 enfermos, com codeliação positiva em dois pacientes e negativa nos 10 restantes. O tratamento foi a observação clínica em dois casos, cirurgia em 20. Tres deles receberam radioterapia com quimioterapia, e em apenas um enfermo foi realizada a braquiterapia com iodo 125. Atualmente, 19 (73 %) estão vivos e 7 (27 %) faleceram. A sobrevida dos falecidos teve uma média de quatro anos e dois meses, e uma mediana de quatro anos e meio. A sobrevida dos 19 pacientes que ainda vivem está com uma média de sete anos e dois meses, e uma mediana de cinco anos e oito meses. Conclusão: considerando-se a pequena série de casos, entendemos que a melhor alternativa de tratamento é a remoção completa da lesão. Estudos prospectivos randomizados deverão sugerir as alternativas de tratamento.

Palavras-chave: tumor cerebral, gliomas, oligodendrogliomas

ABSTRACT

Objective: to present our 19 years’ experience in the management of oligodendroglioma brain tumors in adults.

Materials and Methods: From a series of 505 adult patients with brain tumors operated on from January 1991 to December 2009, 30 cases (5.9%) were histopathologically diagnosed as oligodendrogliomas. Twenty-six of them achieved a good follow-up. Results: from the 26 patients, the age ranged between 23 and 72 years. Histological diagnosis showed pure oligodendrogliomas in 17 patients and 9 cases of oligoastrocytomas. Ki-67 immunohistochemistry was performed in 23 patients: in 16 positivity was less than or equal to 5% and in 7 it was greater than 5%. Chromosomes 1p and 19q were studied in 12 patients with positive co-deletion in 2 and negative in the other 10. Twenty patients were operated on, 3 received radiation therapy and chemotherapy, and 1 brachytherapy with Iodine-125 and two were not operated on (because the diagnosis was incidental, the tumor was small and was located in the motor area). Currently, 19 patients are alive (73%) and 7 died (27%). Mean survival time of the deceased patients was 7 years and 2 months and a median of 5 years and 8 months. Conclusion: it is not possible to make statistical analysis because small number of cases, although total removal seems to be the best treatment option, due to our small series of cases, we hope randomized double-blinded future studies will clear up the best choice of diagnosis and treatment.

Key words: brain tumours, gliomas, oligodendrogliomas
INTRODUCTION

Oligodendrogliomas predominantly appear in adults, with a peak incidence between the ages of 50 and 60 years, representing 5 to 18% of all gliomas. A significant increase in this incidence has been noted during the last decades due to changes in the criteria for the histopathological diagnosis. Pure oligodendrogliomas have a better prognosis than mixed oligodendrogliomas and astrocytomas. When chromosomes 1p and 19q deletion is associated with, prognosis improves even in anaplastic oligodendrogliomas. According to WHO 2007 classification, they are divided into low-grade oligodendrogliomas (grade II), high-grade oligodendrogliomas (grade III) or anaplastic, low-grade (grade II) oligoastrocytoma, high-grade (grade III) oligoastrocytoma or anaplastic.

Two thirds of these patients have a history of seizures and some of them have been receiving antiepileptic treatment for many years. The most frequent symptoms are generalized epileptic crises followed by simple and complex partial crises.

MRI is the diagnostic method of choice that allows for an early diagnosis by disclosing a well circumscribed brain area with signal increment without gadolinium enhancement in cases of low-grade tumors. Spectroscopy detects metabolic changes related to the levels of choline, myo-inositol and acetylaspartate acid in low-grade tumors, and also the presence of lipids and lactates in high-grade tumors. Immunohistochemistry and molecular biology, with chromosome 1p and 19q evaluation, are currently important predictive and prognostic factors in histopathological diagnosis.

The multidisciplinary treatment of oligodendrogliomas has been redefined over the last 20 years, in order to achieve a better and longer survival. Surgery is still the treatment choice, because it allows an accurate neuropathologic diagnosis, totally removing the tumor (whenever possible) or at least reducing its volume to make adjuvant therapies (radiation therapy and/or chemotherapy) more effective.

The objective of this study was to assess the most frequent symptoms, imaging characteristics, histological type and immunohistochemistry of oligodendroglioma, chromosomes 1p and 19q chromosome studies, extension of surgical resection and the results of the adjuvant treatments (radiation therapy and/or chemotherapy).

Material

Between January 1991 and December 2009, 505 adult patients presenting with brain tumors were surgically treated: 30 cases (5.9%) were histopathologically diagnosed as oligodendrogliomas. Twenty-six of these 30 cases achieved a good follow-up, long enough to constitute the series.

RESULTS

Thirteen were male and 13 female. The age ranged between 23 and 72 years-old, mean age was 39 years and the median age 37 years. In low-grade oligodendrogliomas, the average age was 38 years and in high-grade oligodendrogliomas, the average age was 41 years.

Seizures were the main clinical manifestations, observed in 16 patients: generalized in 6 cases; partial simple in 5; partial complex in 5; polymorphic in 5 and monomorphic in the other 11. Intracranial hypertension syndrome in 8 patients, associated with hemiparesis in 1. Two patients were diagnosed when performing a CT scan following head injury. Duration of symptoms had an average of 22 months, with a range of 1-22 years.

Tumors were located in the right hemisphere in 16 cases and in the left hemisphere in 10 cases. In 9 cases, tumors were found in the frontal lobe, 7 cases in the temporal lobe, 3 cases in the frontotemporal lobe, 3 cases in the frontoparietal lobe and 1 case in the temporoparietal lobe: temporoparietal, temporal occipital and parieto-occipital respectively. In 1 case, the tumor invaded almost the whole hemisphere.

Computed tomography (CT) was performed in 13 cases, magnetic resonance (MRI) in 26, cerebral angiography (CA) in 5, EEG in 16. Eight MRI spectroscopies and 2 functional MRI’s were also performed. Stereotactic brain biopsy was performed in 5 patients presenting with lesions in eloquent areas. EEG performed in 16 patients was normal in 3; 11 had focal abnormalities and 2 diffusely abnormal.

Tumor diameter was less than 10 cm in 22 cases and greater in 4. Intratumoral calcifications were found in 6 cases; tumors were hypointense in 13 cases and hyperintense in the rest; 15
cases showed gadolinium enhancement, corresponding to 14 cases of WHO Grade III tumors and 1 case of WHO Grade II neoplasm; only 5 cases presented with midline shift.

Histological diagnosis showed pure oligodendrogliomas in 17 patients: 8 were WHO Grade II and 9 were WHO Grade III. There were 9 cases of oligoastrocytomas: 4 WHO Grade II and 5 WHO Grade III. Ki-67 immunochemistry was performed in 23 patients: 16 had a positivity of less than or equal to 5% and 7 had a positivity greater than 5%. Chromosomes 1p and 19q were studied in 12 patients with positive co-deletion in 2, and negative in the other 10.

Treatment observation was performed in 2 cases, whose tumors were incidentally diagnosed: histological diagnosis was confirmed by performing stereotactic brain biopsy. Both cases turned out to be WHO Grade II oligodendrogliomas with Ki-67 of 2%. In one of the cases there has been neither tumor progression nor clinical manifestations up to date (follow-up of 3 years and 9 months). This case also presented with positive 1p 19q co-deletion. Regarding the other case, an increment in the volume of the left frontal lesion was detected after 18 months of diagnosis, for which a treatment with Temozolomide was prescribed. After 10 cycles of treatment, lesion continued growing for which surgical treatment was indicated. Pathology showed a WHO Grade III oligodendroglioma, Ki-67 7%, indicating malignization. Chromosome 1p and 19q deletion was negative and 3D conformal intensity modulated radiation therapy was applied. The patient has been followed up for 36 months with good evolution. According to the other 24 patients, 20 were operated on, 3 received radiation therapy with chemotherapy, and 1 brachytherapy with Iodine-125.

Surgery was the only treatment in 3 cases; it was associated to radiation therapy in 8; to radiation therapy with chemotherapy in 6; to chemotherapy in 1; to brachytherapy with chemotherapy in 1; and to radiation therapy with brachytherapy in 1. Intraoperative ultrasound was performed in 4 patients and intraoperative electrocorticography in 2. Total resection was achieved in 14 out of 20 of the surgically treated patients and subtotal resection in 6.

The 3 patients submitted to surgery as the only treatment, in which total resection was achieved, one patient died of a brain abscess 3 months later; in one case, a pure oligodendroglioma evolved from WHO Grade II (first surgery) to WHO Grade III (recurrence 10 years and 8 months later). This patient is alive and has been followed up for 14 years since diagnosis. The other case has been followed up for 3 years since surgery without recurrence. PVC (Procarbazine, Vincristine, CCNU) chemotherapy protocols were applied in three patients, and Temozolomide in 9. From this group of 9 cases, surgery and radiation therapy were associated in 5 cases, radiation therapy in 3 cases and it was the first and only treatment in 1 case until tumor growth was detected. The 3 patients submitted to PVC were operated on. Radiation therapy was associated in 1 case and brachytherapy with Iodine-125 was applied on the residual tumor in the other.

Tumor recurrence was observed in 6 patients, 3 with pure oligodendrogliomas and 3 with oligoastrocytomas. From the group of pure oligodendrogliomas, 2 were WHO Grade II, 1 evolving to WHO Grade III and the other to WHO Grade IV (glioblastoma multiforme), and the third case was a WHO Grade III that remained unchanged. From the group of oligoastrocytomas, 2 were WHO Grade II which evolved to WHO Grade III and the other case was a WHO Grade III that remained unchanged. Treatment was: surgery with total removal in 1 case; brachytherapy with Iodine-125 in 1 case; surgery, brachytherapy (on the residual tumor) and chemotherapy in 1 case; surgery (total removal), radiation therapy and chemotherapy in 1 case; radiation therapy and chemotherapy in 1 case; and total removal surgery and radiation therapy in 1 case.

Tumor recurrence was observed twice in 2 cases. One of these cases, who had an oligoastrocytoma, was also operated, between the first and second recurrence, for a cauda equina extramedullary intraspinal anaplastic astrocytoma. The first recurrence was a WHO Grade III oligoastrocytoma and the second recurrence was a glioblastoma multiforme. This patient died 12 years after the initial diagnosis and 27 years and 4 months after the first partial complex seizure. In the other case, the initial diagnosis was a WHO Grade III oligodendroglioma and the patient was alive 9 years and 2 months since the first operation.

Out of the 16 patients who presented with seizures on admission, 10 cases were seizure-free thereafter, whereas persisting after subtotal removal in 6 cases. Sporadic seizures appeared in 4 cases after surgery. In 2 cases, seizure relapse coincided with tumor recurrence.

Mean survival of patients with WHO Grade II oligodendroglioma was 6 years and 9 months, whereas for WHO Grade III patients was 6 years.

Seven patients (27%) died and 19 (73%) are alive. Causes of death were recurrence and malignization in 4 cases and brain abscess, myocardial infarction and pulmonary embolism in the other 3, respectively. Four patients died of recurrence: 3 of
them had Ki-67 greater than 5% in the first surgery and 1 had a WHO Grade II oligoastrocytoma with Ki-67 of 2%, but MRI showed a small gadolinium-enhancing area; an Iodine-125 seed was surgically implanted.

Survival of the 7 deceased patients ranged between 3 months and 12 years, an average of 4 years and 2 months and a median of 4 years and 6 months. Survival of the 19 alive patients has a range between 29 months and 16 years, a mean of 7 years and 2 months and a median of 5 years and 8 months. A 12-year survival probability of 56.5% was estimated with Medcalc 11.4.4.0 (2010). Standard error: 15.2%. Confidence interval: 95% (Fig. 1).

**Figure 1.** Survival Kaplan-Meier Curve.

**Discussion**

We found no sex predominance in our series, like other authors. However, some other authors presented male-predominant series.

As shown in other publications, the main clinical manifestations in our patients were seizures 16/26 (61.5%), since they are considered to be the first symptoms in astroglial tumors in 50% of the cases. Seizures are factors that indicate a good prognosis in low-grade oligodendrogliomas and low-grade gliomas in general.

MRI is an important prognostic factor because when tumor volume is less than 10 cm, images are hypointense, without gadolinium enhancement and spectroscopy does not show the presence of lipids and lactate, anticipating a low-grade oligodendroglioma.

Currently, and even with the advances in molecular biology, histopathology is still the main diagnostic instrument of this type of central nervous system neoplasm.

Neuropathological studies include microscopy and immunohistochemistry; histological characteristics that are associated with patient's survival are high cellularity, mytosis, endothelial proliferation and necrosis. Immunohistochemical study of these tumors shows a prognostic value for Ki-67 (MIB-1) greater than 5%. In 23 out of our 26 patients’ case series, Ki-67 was measured, with the following results: 16 cases less than or equal to 5% and 7 cases greater than 5%.

In 5 patients, the first diagnosis was made by a stereotactic biopsy; one case of a WHO Grade III oligodendroglioma and four WHO Grade II cases. Out of the 4 cases, tumor regrew in 3 patients: after reoperation, new histology showed an anaplastic tumor. One patient incidentally diagnosed has been under observation for 45 months, without tumor growth or MRI changes: hypodense lesion, no gadolinium enhancement and no lactates or lipids in spectroscopy.

In our series, only 2 out of the 12 studied cases presented with combined allelic co-deletion in chromosomes 1p and 19q, in which chromogenic in situ hybridization was used (CISH). These results differ from other publications where deletion is detected in 40 to 66% of the cases: they may be false negative results, for which it does not rule out the diagnosis of oligodendroglioma.

Some international publications show that 1p and 19q chromosome deletions in oligodendrogliomas are correlated with a better prognosis and a greater sensitivity to chemotherapy. In our experience, in the 2 patients who presented with positive co-deletion in chromosomes 1p and 19q, one was incidentally diagnosed and has been under observation for 45 months without tumor changes: the other is a totally resected WHO Grade II oligodendroglioma with Ki-67 smaller than 5%. The tumor recurred 128 months later: the patient was reoperated on, 3D conformal intensity modulated radiation therapy was applied and Temozolomide was prescribed. This case has been followed up for 40 months since the second surgery.
Total tumor removal is the ideal option because it offers a longer survival and a better anatomopathological diagnosis than stereotactic biopsy. This goal is sometimes hard to achieve because the lesion may be located in an eloquent area or due to its infiltrative characteristics. Total removal was achieved in 16 out of 20 operated cases.

Surgery should be complemented with radiation therapy associated to chemotherapy. In this way, better results can be achieved comparing to using only radiation therapy, especially in pure or mixed anaplastic oligodendrogliomas, taking into account that these are indolent but progressive tumors.

### Conclusion

Due to our small series of cases, it is not adequate to make an statistical analysis, although total removal seems to be the best treatment option, because it offers a good histopathological diagnosis, a longer survival and it also helps epilepsy treatment of epilepsy, as the presence of tumour behaves like a irritative focus to the brain. Pure or mixed oligodendrogliomas very frequently become clinically apparent with seizures; generalized tonic-clonic and complex partial crises are the most common. MRI has an important role as a prognostic factor as a low grade tumor usually presents with no gadolinium enhancement and spectroscopy does not reveal the presence of lipids and lactate. Microscopic studies, Ki-67 immunohistochemistry and chromosome 1p and 19q evaluations have a great diagnostic and prognostic value in these tumors also. Finally, adjuvant treatment with 3D conformal intensity modulated radiation therapy associated to chemotherapy offers a better and longer survival, taking into account that oligodendrogliomas are indolent but progressive tumors.

### References


CORRESPONDING AUTHOR

Julio César Suárez
Address: Nazaret 3273 - 3 F - CP5009 - Córdoba, Argentina
E-mail: totoralar@yahoo.com