Clinical study

Effect of surgery on tumor progression and malignant degeneration in hemispheric diffuse low-grade astrocytomas

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Summary The aim of this study is to determine the impact of surgery on tumor progression and malignant degeneration in hemispheric diffuse astrocytoma WHO grade II. Twenty-eight patients who were operated or underwent stereotactic biopsy for hemispheric diffuse astrocytoma WHO grade II at Marmara University between January 1987 and January 1996, were prospectively reviewed for the presence of recurrence and histopathological dedifferentiation at their fourth years after the initial treatment. Twenty-two patients underwent surgical resection. Of this group, 7 patients had a total, 11 had a subtotal and 4 patients had a partial resection. Six patients underwent stereotactic biopsy. All patients, except for the ones in whom a radiological total surgical removal could be achieved, received postoperative radiotherapy. In the total surgical-removal group only one patient had recurrence, while no upgrade was noted. All of the patients in the partial resection and stereotactic biopsy groups recurred at a higher grade. Our results indicate that both tumor progression and histopathological dedifferentiation were less commonly seen when a total or subtotal resection could be achieved. So, surgery, as radical as possible, should be the choice of treatment in low-grade hemispheric astrocytomas.

Definition: astroctoma, low-grade astrocyoma, surgery, recurrence, radiotherapy

INTRODUCTION

The management of low-grade astrocytoma is one of the major controversies in modern neuro-oncology. Since the recognition of low-grade glioma as a clinical subgroup in the 1930s much has been written on this subject. With the exclusion of distinct pathological entities, such as the pilocytic astrocytoma, oligodendroglioma or optic glioma, diffuse astrocytoma emerges as a group of tumors with a considerable malignant course. Most patients survive more than a decade. But, with many variables affecting survival and the lack of randomized prospective clinical trials we do not have enough data to express the clear advantage of a therapeutic approach over other approaches. To date a consensus regarding the optimal management of low-grade astrocytoma is nonexistent.

Although not supported by all authors there is a tendency in the literature toward a more aggressive management of the low-grade astrocytoma. In this study we tested the hypothesis that extent of surgical resection has an inverse correlation with recurrence and malignant degeneration rates.

PATIENTS AND METHODS

This is a prospective case control study. Twenty eight patients operated at Marmara University Department of Neurosurgery and Marmara University Institute of Neurological Sciences between January 1987 and January 2001 for hemispheric diffuse low-grade astrocytoma with a follow up of four years were analyzed. Twenty-two patients underwent surgery while a stereotactic biopsy was performed in six. Patients were studied by the parameters of age, sex, tumor location, imaging characteristics, histopathology, pre- and postoperative tumor volume, time to recurrence, progression, complications, early and late neurological outcome, time and cause of death.

INCLUSION CRITERIA

Histopathology

The histopathological diagnosis of diffuse astrocytoma grade II was selected. Tumors were classified according to the WHO 2000 classification of CNS tumors. All pathological examination records were reviewed. Diffuse astrocytoma was diagnosed when in a uniform and mature appearing tumor with mild hypercellularity one of the four criteria proposed by Daumas-Duport et al. (nuclear abnormalities/mitoses/endothelial proliferation/necrosis) was found. Most frequently encountered were nuclear abnormalities. Cases of oligoastrocytoma were excluded from the study due to their distinct clinico-pathological characteristics. Other low-grade cases such as pilocytic astrocytoma, oligodendroglioma, DNET, ganglioglioma, pleomorphic xanthoastrocytoma and subependymal giant cell astrocytoma were excluded from the study. Histopathological subtypes were not taken into consideration.

Tumor location

All tumors were supratentorial and located at the cerebral hemispheres. Deep-seated astrocytomas (thalamus, basal ganglia, cerebral ventricles, limbic structures, and pineal region) or infratentorial astrocytomas located at the cerebellar hemispheres were not included in the study.
Imaging

Preoperative, early and late postoperative magnetic resonance imaging (MRI) examinations were required for the study. Early postoperative MRI was accepted when obtained within 24 h of the operation.

Follow-up

Four years of follow up was required for inclusion in the study. In the fourth year surgical or stereotactic biopsy are provided for each patient to determine histological dedifferentiation.
Definitions
‘Total resection’ was defined as the absence of any residual tumor in the early postoperative MRI examination (both T1 and T2 weighted images). ‘Subtotal resection’ was defined as the presence of residual tumor in patients who were operated on with the aim of total radiological resection. The extent of resection was considered ‘partial’ when only cytoreductive surgery was carried out. This group included patients who had tumors preoperatively determined not to be suitable for total resection due to eloquence or any other reason.

The diagnosis of ‘tumor progression’ was established when there was increase in the radiological tumor volume. In cases with total resection this was considered as recurrence. A histological diagnosis was obtained in each case with tumor progression. An increase in the histopathological grade was considered as an ‘upgrade’, ‘malignant degeneration’, or ‘histological dedifferentiation’.

RESULTS
Twenty-eight patients treated for hemispheric low-grade diffuse astrocytoma between January 1987 and January 1996 at Marmara University Hospital and Marmara University Institute of Neurological Sciences fulfilled the inclusion criteria for the study. Seventeen patients were male and 11 were female. The mean age was 30 years ranging from 11 months to 75 years. Tumor location was frontal in 9, temporal in 10, parietal in 7 and occipital in 2 of the cases.

Of the study population 22 patients underwent surgical resection. Of this group 7 patients had a total resection, 11 had a subtotal resection and 4 patients had a partial resection. Six patients underwent stereotactic biopsy.

A radical surgical removal was planned in 18 of the patients at first surgical procedure. Standard microsurgical techniques were used throughout all procedures. Preoperative functional MRI, single photon emitted computed tomography (SPECT), intraoperative awake-speech or motor mapping or ultrasound guidance was used when necessary to facilitate extensive tumor removal.

All patients (except those with total resection) received high dose (minimum 54 Gy) fractionated radiotherapy to the tumor bed. None of the patients received chemotherapy.

Tumor recurrence was seen in 1 of 7 patients with total resection, 6 of 11 patients with subtotal resection, 4 of 4 patients with partial resection and 6 of 6 patients with stereotactic biopsy (Fig. 1).

No histopathological upgrade was noted in the total surgical removal group. All of the patients recurred at a higher grade in the partial resection and stereotactic biopsy groups. Four of 6 patients with subtotal resection who recurred presented at a higher grade (Fig. 2).

DISCUSSION
Low-grade astrocytomas are a diverse group of central nervous system neoplasms. Despite their having been considered ‘benign’ historically, the majority of these tumors behave in an aggressive manner despite surgery, postoperative radiation and/or chemotherapy.2,3 Increasing numbers of translational research, including studies of proliferation, cytogenetics and molecular genetics, have proven that dedifferentiation and tumor progression, after the initial diagnosis and treatment, causing so-called secondary glioblastoma multiforme are the most important prognostic factors.3 Recent advances in our understanding of the tumor biology of these neoplasms are supportive of more aggressive surgical management.

In summary, a majority of the surgical literature suggests a survival benefit with more aggressive surgical resection. Five important series reported in the literature5–8,11 demonstrate a significant survival advantage for gross total or radical subtotal resection compared with subtotal resection or biopsy. In the more aggressively operated patients in these series, the 5 year survival rates range from 51 to 88, whereas comparable survival figures in less aggressively operated patients are between 24 and 64%. However the three other series2,12 did not find a significant difference in median or 5 year survival based on the extent of surgical resection. Although the study was not made in an homogenous patient sample (approximately one-third of cases each were astrocytoma, oligoastrocytoma and oligodendroglioma) Berger et al.4 used the pre and postoperative tumor volume to predict the likelihood of recurrence and found that both preoperative tumor volume and postoperative residual tumor volume are directly related with the increased likelihood of recurrence.

The current study, for the first time in the literature, investigates the histological changes determined at certain periods of time, i.e. 4 years, in 28 low-grade patients, who are alive after their initial treatment. Therefore, this study cannot make any argument about the impact of surgery on patient survival but provides additional support for the hypotheses that surgical cytoreduction decreases the probability of developing malignant histological dedifferentiation.

This clinical finding may be correlative with the molecular biological ‘dedifferentiation hypothesis’ of gliomas.6,13 According to this correlation, surgery decreases the probability of additional mutations (needed for anaplastic transformation) in the low-grade hemispheric glioma, which is morphologically differentiated but has increased growth potential.14

CONCLUSION
Our results indicate that both tumor progression and histopathological dedifferentiation were less commonly seen when a total or subtotal resection could be achieved. In the total surgical removal group only one patient had recurrence while no progression was noted. All of the patients in the partial resection and stereotactic biopsy groups recurred at a higher grade.

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REFERENCES