Contemporary management of low grade intracerebral gliomas

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INTRODUCTION

Tumors of neuralglial cells represent nearly 50% of all primary central nervous system tumors. Among them low-grade gliomas (LGGl) comprise about 25 to 35% of these neoplasms (1). This group of tumors is characterized by numerous histological subtypes, which include: ordinary low grade astrocytomas - LGAs (WHO grade II) with its variants (fibrillary, protoplasmic and gemistocytic), pilocytic astrocytoma (WHO grade I), pleomorphic xanthoastrocytoma (WHO grade II), subependymal giant cell astrocytoma (WHO grade I) usually associated with tuberous sclerosis, oligodendroglioma - LGO (WHO grade II), mixed gliomas like oligoastrocytomas - LGOAs (WHO grade II), ependymoma (WHO grade II) with its variants (cellular, papillary, clear cell), subependymoma (WHO grade I), gangliocytoma (WHO grade I), ganglioglioma (WHO grade I or II), dysembryoplastic neuroepithelial tumor (WHO grade I), desmoplastic infantile ganglioglioma (WHO grade I).

Some forms of low-grade gliomas are indolent hamartomatous lesions (especially those of WHO grade I) with a low proliferative activity, small growth potential, and very little ability for malignant transformation. They can often be controlled by radical or subtotal resection alone.

More challenging for management choice is the group of tumors of WHO grade II, especially low grade astrocytomas, oligodendrogliomas and mixed oligoastrocytomas, to which we put our attention. The behavior of ependymomas differs from that of the other gliomas because of their additional potential to spread through cerebrospinal fluid and not only locally, so we will not discuss their management now.

There are several controversies in the management of LGGl: Radical resection vs. stereotactic biopsy sampling? Radiotherapy (Is it effective? Which dose is ideal? Which method should be used? What treatment field?); Radiosurgery (does it have any role in the treatment of these lesions?); Chemotherapy (Is it appropriate? Which drugs are effective? What treatment regimens or combinations are appropriate?); Is metabolic imaging useful in follow up and treatment decisions? (2)

CLINICAL BEHAVIOR OF LGGl

One of the greatest obstacles to treating LGGl is the inability to define accurately their natural history despite of many reported studies. These tumors are frequently quiescent for a long period prior to diagnosis, so it is very difficult to gain a clear picture of their clinical behavior after the establishment of diagnosis. Sometimes, even symptomatic, these tumors can have a prolonged period of latency with little or no growth.

LGGl affect the brain by two main mechanisms - infiltrating the normal brain tissue by tumor cells, and raising intracranial pressure due to space occupying effect. For LGGl epilepsy or seizure is by far the most common presenting symptom or sign at the time of diagnosis in 40%-78% of patients (3). Aside from that, all other symptoms and signs like headaches, motor or speech difficulties, visual impairment, cognitive decline, etc can be present at the time of diagnosis. Patients in the past have been typically presented with a high proportion of compressive symptoms and increased intracranial pressure. Nowadays, patients are generally diagnosed much earlier after having only one episode of altered consciousness (4), so only a minority of them have significant functional limitations at the time of presentation. Thus clinicians (especially neurosurgeons and radiotherapist) bear additional responsibility of causing potential harm to an intact patient.

It is obvious that these tumors will eventually progress to the point where they will require treatment. However, the time needed to reach this symptomatic threshold remains unknown. Some of these tumors will become more malignant over time (Apuzzo, 1995), but again, we do not know how long it will take till they change their biological potentials.

DIAGNOSIS OF LGGl

With introduction of computerized tomography (CT) and magnetic resonance imaging (MRI) the diagnosis of LGGl became more accurate and specific and make it possible to perform expecting observation of these patients especially when tumors are located near or in the eloquent brain zones. LGGs are usually hypodens on CT, and hypointense on T1W images on MRI. Contrast enhancement is usually associated with higher grade of tumor malignancy, or worse prognosis and sooner recurrence. LGO are usually partially calcified on CT, and mixed gliomas may have characteristics of both astrocytomas and oligodendrogliomas.

TREATMENT OPTIONS FOR LGGl

The treatment modality will depend on patient's symptoms. There is in no doubt that there must be some kind of intervention when there are signs of raised intracranial pressure or in cases of rapid development of progressive neurological deficit. Radical surgery in these cases will be the treatment of choice.

However, patients with only seizures and minimum symptoms have more than one treatment options. It depends mostly on the location of the tumor (eloquent cortex, deep structures, and cerebrosplinal fluid obstruction), general condition of the patient, and the potential harm of surgery.

Therapeutic possibilities usually are (1):

1. Expectant observation only based on imaging diagnosis of LG astrocytoma or oligodendroglioma.
2. Biopsy with confirmation of LGGl and then observation only.
3. Biopsy with confirmation of LGGl and then surgical resection only.
4. Biopsy with confirmation of LGGl and then external beam irradiation only.
5. Biopsy followed by surgical resection and irradiation.
6. Primary surgical resection of suspected LGGl only.
7. Primary surgical resection followed by irradiation.
8. Empirical irradiation of suspected LGGl on basis of imaging diagnosis.

Each of these options has been used by different brain tumor centers worldwide with varying degree of success.

Since there is proved possibility for progression of LGGl into higher pathological grades one must be very cautious with expectant observation only. Repeated MRI or CT should be performed on two to three months, thus following and defining any change in tumor presentation. When confirmation of the LGGl is established then observation might be one of the reasonable
options, especially in older patients with unfavorable location of tumor (basal ganglia, deep white matter, primary motor cortex).

Considering stereotactic or open biopsy in certain number of patients the first one has certain advantages. The craniectomy is small one, there is no need for general anesthesia, and procedure is relatively simple. However, one must always be concerned with a sampling error in tumors that contain areas of different degrees of malignancy. To overlook this disadvantage it is necessary to define different trajectories and targets in tumor bed. According to some large series of patients (5), the surgical morbidity with this method is less than 1%, and diagnostic accuracy is as high as 94% (6).

Despite the continuing controversy over its benefits a large proportion of tertiary brain tumor referral centers presently advocate a radical or near-total resection whenever possible for patients with LGgls. As the residual tumor cells are suspected of having an increased propensity to undergo further malignant transformations most surgeons consider it prudent to attempt a "gross total" removal of the lesion to limit further spread and future recurrence. It is also thought that an initial cytoreduction optimizes subsequent adjuvant therapy by removing central ischemic tumor areas that are "protected" from effects of irradiation or chemotherapy (7). Several large retrospective studies that have analyzed the influence of the degree of surgical resection on long term survival proved that radical surgical resection of LGgls correlated with longer survival (1). However, comparing biopsy with irradiation vs. surgical resection and irradiation this correlation becomes less evident.

As with all surgery, cautious preoperative evaluation and management is essential in minimizing operative-related complications. Surgical approaches depend on location of tumor and all attempts should be made to minimize brain retraction. Surgical morbidity usually does not exceed 10%, but for patients who are intact prior to surgery even a 5-8% chance of impairment can be unacceptable. As there is not clear-cut evidence in support of radical debulking conservative resection for lesions that are adjacent to or within eloquent neural parenchyma has been advocated. Even after the most aggressive "gross total" resections it is now widely accepted that there will still be as significant number of LGgls cells left behind. It is not surprising that radiotherapy has widely been employed in the management of LGgls. The goals of external beam irradiation and chemotherapy are local control, decreasing recurrence and preventing malignant transformation. However, the effects of irradiation on the natural history of treated LGgls is even more controversial, although many retrospective series prove higher survival rate in 5 and 10 year periods in irradiated patients (8).

It is now recognized that for some types of LGgls (fibrillary and protoplastic astrocytomas and oligodendrogliomas) after total or subtotal surgical resection radiation therapy can be postponed until disease progression. However, in incompletely resected low grade gliomas the optimal timing of postoperative radiotherapy is an unsettled issue. Several studies indicated an advantage for immediate postoperative radiotherapy (8). Appropriate clinical target volume for irradiation should include the MRI-detected extent of tumor with a 2 to 3 cm margin of surrounding brain tissue with respect to anatomical boundaries. Hyperfractionated radiation may be of some benefit in this indication.

Patients too frail to have surgery should probably undergo irradiation for lack of any other treatment options. High dose greater than 60 Gy should be avoided to prevent secondary complications of the irradiation itself. Modern techniques of radiotherapy may be associated with decreased toxicity to surrounding brain.

Several studies showed different behavior and outcomes of various histological subtypes of LGgls with better overall survival for oligodendrogliomas and mixed oligoastrocytomas than those with ordinary low grade astrocytomas did.

**PROGNOSTIC FACTORS**

There are some proven prognostic factors that influence outcome in patients with LGgls. Favorable ones are: age of less than 40 years, seizures as presenting problem, circumscribed lesion on CT and MRI, non-enhanced or homogenous enhanced images, normal functional status, hypometabolism on positron emission tomography (PET), and microcystic with normal vascular pattern. Unfavorable factors are: age of more than 40 years, signs of increased intracranial pressure, diffuse or multifocal lesions, heterogeneous enhancement with contrast medium, functional status impaired, hypometabolism on PET, gemistocytic variant, and microvascular proliferation (2).

**OUTCOME**

Treatment failure for LGgls is their tendency to recur locally despite different therapeutic regimens, sometimes even at a higher histologic and clinical grade. Tumor recurrences are diagnosed on the basis of radiographic evidences, even before clinical deterioration. Recurrent LGgls have a 45%-88% likelihood of malignant dedifferentiation at second look. With modern therapeutic regimens there is an overall improvement in survival for those patients. Several retrospective studies with patient group from 1970 to 1997 showed median survival of about 100 months and ten year survival rate of 50-70% (1).

**PERSPECTIVES**

In the last decade the majority of oligodendrogliomas have been noted to be chemosensitive, both high- and low-grade (10). Today, this treatment represents an alternative to surgery and radiotherapy for recurrent LGgls. Drugs that have been used are procarbazine, CCNU and vincristin in combination. With further achievements in molecular biology and immunology gene therapy and immunotherapy probably will become one of the alternatives for surgery and irradiation therapy in low-grade gliomas.

**CONCLUSIONS**

Total or subtotal surgical resection is the therapy of choice for most intracerebral LGgls. It should be performed whenever possible. After postoperative MRI and PET, it should be decided about immediate postoperative radiotherapy. If there are the signs of the tumor rest, radiotherapy is essential. Patients in poor clinical grade, or deep seated tumors should undergo stereotactic biopsy followed by stereotactic radiosurgery, or conventional radiation therapy. In recurrent diseases any kind of surgery should be followed by radiation therapy, or/and chemotherapy for chemosensitive oligodendrogliomas. Accurate histopathological diagnosis is essential for treatment choice and prognosis.

**REFERENCES**