

Low-grade glial tumors in basal ganglia and thalamus: natural history and biological reappraisal.

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ABSTRACT[^]

THE NATURAL HISTORY of 70 patients affected by low-grade astrocytomas was recorded after the histological diagnosis was obtained by serial stereotactic biopsy. Forty-three percent of these patients died within 3 years. The value of cell kinetics assessment at the time of stereotactic biopsy was investigated, and the labeling index percent may be considered the most accurate prognostic factor in these histologically homogeneous astrocytomas. It has been confirmed that the young age of patients predicts a more favorable course, but the value of this also seems to be linked to and dependent on cell kinetics. These data are discussed in view of the opportunity to perform more aggressive "cytoreductive" treatments in deep brain tumors when these indices support an expected poor prognosis.

Low-grade glial tumors within the basal ganglia and thalamus are considered biologically similar to hemispheric slow-growing gliomas, but the surgical removal of these tumors cannot be proposed as first-choice treatment, even though stereotactically guided microsurgery was attempted in selected cases (18). Moreover, there are few data regarding the natural history and prognosis of these tumors in critical areas, first, because of difficulties encountered in the past in obtaining the correct histological diagnosis and, second, because of the unreliability of "blind" treatments attempted in these patients without histological diagnosis (25). The current use of serial stereotactic biopsy assesses the histological diagnosis (3,11) and investigates the spatial growth modalities of these tumors (10); however, it is well known that subgroups of tumors masked under the same histological diagnosis may be characterized by different behavior and prognosis (24).

The aim of this report is to analyze the cell kinetics and natural history in a series of 70 patients harboring solid, slow-growing glial tumors located within the basal ganglia and thalamus. All patients had serial stereotactic biopsy with no further antineoplastic treatment. The "wait and see" strategy was chosen because of the diagnosis of mature astrocytoma in all patients. Patients who later developed highly malignant tumors (30 patients) did not undergo any further palliative treatment because of the rapid deterioration of their neurological conditions and unfavorable geographical and familial reasons. The evolution of these "untreated" tumors was carefully recorded by clinical and computed tomographic (CT) serial examinations during a 3-year follow-up period. This series may be considered "historical" with regard to survival.

The prognostic value of the patient's age at the time of the onset of the disease (7,21), as well as other well-known prognostic factors (29), was retrospectively investigated in this series and compared with cell kinetic data determined at the time of the histological diagnosis. The results are discussed in view of the indications to apply more aggressive treatments in those tumors showing sudden growth, even in spite of the histological findings of mature astrocytoma provided by serial stereotactic biopsy.

PATIENTS AND METHODS[^]

Seventy patients observed between 1984 and 1988 were retrospectively selected following these criteria: 1) histological diagnosis of slow-growing, solid glial tumors (Grades I and II, World Health Organization) (30) obtained by serial stereotactic biopsy and supported by low or moderate cellular density, nuclear monomorphism, slightly increased capillary density with absence of loops of proliferative vessels, scattered mitosis, and no necrosis. Patients were withdrawn from the series if they had subependymal giant cell astrocytomas (2), oligodendrogliomas (21), astrocytomas with gemistocytic cells (19), and pilocytic astrocytoma (23) because of the peculiar behavior of these neoplasms; 2) absence of any treatment after the histological diagnosis and cell kinetic assessment; 3) clinical and neuroradiological follow-up available 3 years after the stereotactic biopsy.

In this series, the age ranged between 11 and 68 years (mean, 47 yr). Thirty-six were males. All the lesions were supratentorial; 32 were seated in the thalamus and 38 in the basal ganglia. The heralding symptomatology included epileptic seizures (35%), intracranial hypertension (25%), and focal deficits (40%). The Karnofsky index score at the time of admission was always over 70 (15).

The serial stereotactic biopsies were performed with Riechert, Brown-Roberts-Wells, Cosman-Roberts-Wells, Zeppelin, and Leksell frames (3,11). The target point was determined by the mathematical transposition of the CT images in the stereotactic plane (14) and, after 1987, by tridimensional computerized reconstruction of the lesion (13). The Sedan or Nashold bioptic instrument was used to obtain tissue specimens from multiple different targets (mean, three sites of tissue samplings) within the tumoral area along a single biopsy trajectory (20,26). The stereotactic procedure was performed through a precoronaric approach, and in hypodense, poorly defined lesions, the choice of sampling sites was guided by impedance transtumoral monitoring (3); the areas adjacent to the internal capsula were necessarily avoided.

The samples of tissue used in determining the labeling index (LI) were incubated in 2 ml of complete medium with [³H]thymidine at 37°C for 1 hour in a shaking water bath. After incubation, the biopsy specimens were fixed in Bouin's solution for 1 hour, embedded in paraffin, and sectioned at 4 μm for autoradiographic procedure. Deparaffined slides were harvested by the use of a stripping film technique and exposed at 4°C for 10 days. The slides were developed in Kodak D 19b (Eastman Kodak, Rochester, NY) for 5 minutes at 18°C, fixed, and stained with hematoxylin and eosin at 4°C. Last, the slides were examined by optical microscopy, and 1,000 to 10,000 cells were scored to count the total number of labeled cells, which represent the pool in the S phase of the cell cycle incorporating [³H]thymidine in deoxyribonucleic acid. The LI was calculated as the ratio percent between labeled cells and total cells. The highest value of LI percent among those from serial samples within the same lesion was taken as the representative LI percent value of the tumor (12,27).

Each patient was followed up for a 3-year period after histological diagnosis by serial CT scan and periodical clinical reappraisal. In conclusion, an analysis was carried out to assess the predictive accuracy of LI percent versus well-identified prognostic factors, such as the age of the patient at the time of the onset of the disease, the heralding symptomatology, the CT pattern, and the volume and the size of the tumor at the time of stereotactic biopsy. The survival rate at the 3-year follow-up was accepted as an independent variable against five LI percent cutoff values according to literature data and previous reported series of glial tumors investigated by cell kinetics methodology (2,12).

RESULTS[^]

The mean LI percent value in our series was 4.8%, and LI percent values ranged between 0.3 and 17.5%. Mortality and permanent morbidity from stereotactic biopsy were nil. Thirty of 70 patients affected by so-called "low-grade astrocytomas" died within 3 years of stereotactic biopsy (43% of the whole series). The mortality rate was 100% in patients characterized by an LI percent higher than 5, and it was 20% in patients with an LI percent lower than 5 (Fig. 1).

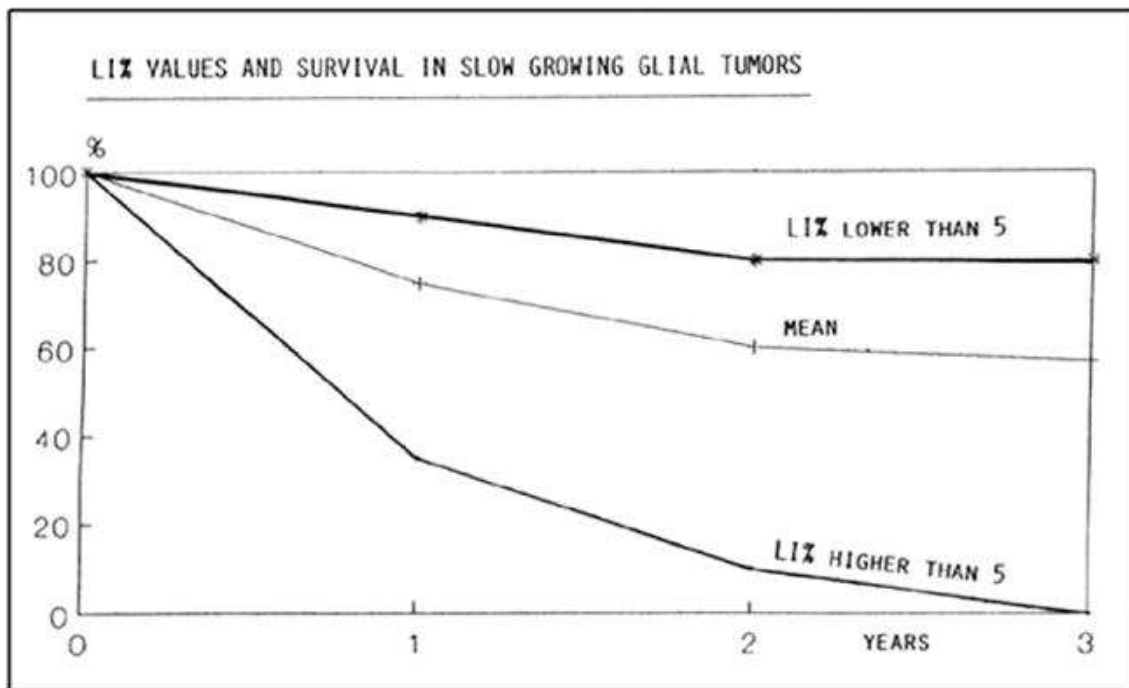


Figure 1. Survival since stereotactic biopsy in slow-growing glial tumors. One hundred percent mortality rate at 3-year follow-up resulted in an LI percent higher than five series versus 20% mortality rate in an LI percent lower than five series. The overall mortality rate in the whole series was 43%.

The range of well-known prognostic factors, as well as age, was reviewed in the two groups of patients with LI percent scores at the cutoff value of 5 (6). The age of the patient at the time of the onset of the disease was lower than 40 in 77% of the patients belonging to the series of lower LI percent astrocytomas, whereas an age at the time of onset of lower than 40 was present only in 25% of patients belonging to the higher LI percent series. The volume of the lesions, as detected by CT and/or magnetic resonance imaging examinations, and the contrast enhancement of the lesions did not correlate with the survival of different LI percent populations in those series when homogeneous enhancement or homogeneous ipodensity was found.

As in previously reported studies (4), in our series, the occurrence of epileptic seizures as the first symptom of the disease was a favorable prognostic factor at $P < 0.001$ ([chi]² test); signs of intracranial hypertension were predictive of poor prognosis at $P < 0.001$ ([chi]² test, Fisher's exact test). No significant indications may be derived when the heralding symptomatology includes just focal deficits. The age at the time of the onset of the disease and cell kinetics data were significantly related to the prognosis at $P < 0.02$ and at $P < 0.001$, respectively (Table 1). The spatial reconstruction of gliomas as proposed by Daumas-Duport et al. (10) was attempted, considering as "nodular" the tumors in which the stereotactic transtumoral trajectory reached sound tissue or reactive gliosis at the deepest target. Conversely, the tumors in which the so-called "brain adjacent tumor" presented neoplastic cells labeled by [³H]thymidine at the deepest estimated boundaries of the lesion were considered to be "diffuse." The nodular and diffuse growth modalities proved independent from tumor evolution and tumor proliferative activity.

Parameter	No. of Subjects		P Value
	Alive	Dead	
Age (yr)			
<40	17 (24)	5 (7)	0.02
>40	23 (33)	25 (36)	
Heralding symptoms			
Focal deficits	18 (26)	20 (29)	0.07
No focal deficits	22 (31)	10 (14)	
Epilepsy	22 (31)	2 (3)	<0.001
No epilepsy	18 (26)	28 (40)	
Intracranial hypertension	1 (1)	9 (13)	<0.001 ^b
No intracranial hypertension	39 (56)	21 (30)	
Labeling index %			
<5	40 (57)	10 (14)	<0.001
>5		20 (29)	

^a A statistical level of $P < 0.05$ was considered significant. The χ^2 test was used.

^b By Fisher's exact test.

Table 1. Age, Heralding Symptoms, and Labeling Index Percent Among 70 Patients, According to Survival at 3 Years from Stereotactic Biopsy^a

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CONCLUSION AND DISCUSSION[^]

From these data in histologically homogeneous series of slow-growing glial tumors, the following points must be stressed: 1) 43% of the so-called "slow-growing" glial tumor patients died within 3 years of stereotactic biopsy. No clear-cut biological index predicts malignant evolution, but the LI percent determination represents the most accurate prognostic factor dividing patients with a 100% expected mortality at a 3-year follow-up from patients with 20% expected mortality during the same time. The prognostic accuracy of stereotactic biopsy was improved by LI percent determination; the bias as the result of glioma heterogeneity was significantly lowered, and the risk of astrocytoma undergrading by morphological evaluation of small size samples is stressed (2). The age of patients at the time of diagnosis is proved to be related to survival, but it must be noted that age is irrelevant with respect to the prognosis when the LI percent is higher than 5. On the contrary, age seems to play a dramatic role in patients with low LI percent values (Fig. 2); in fact, all survivors from the whole series were younger than 40 years and belonged to the group with the LI percent lower than 5. The relevant favorable prognostic value of young age in the homogeneous low LI percent group suggests the presence of a host-related mechanism fighting tumor-related mechanisms expressed by the LI percent. In fact, among those tumors characterized by an LI percent lower than 5, patients who developed malignant evolution belonged only to the older series, whereas, in younger patients, there was 100% survival. Moreover, it must be noted that younger patients had more of a possibility of harboring a tumor with a low LI percent value.

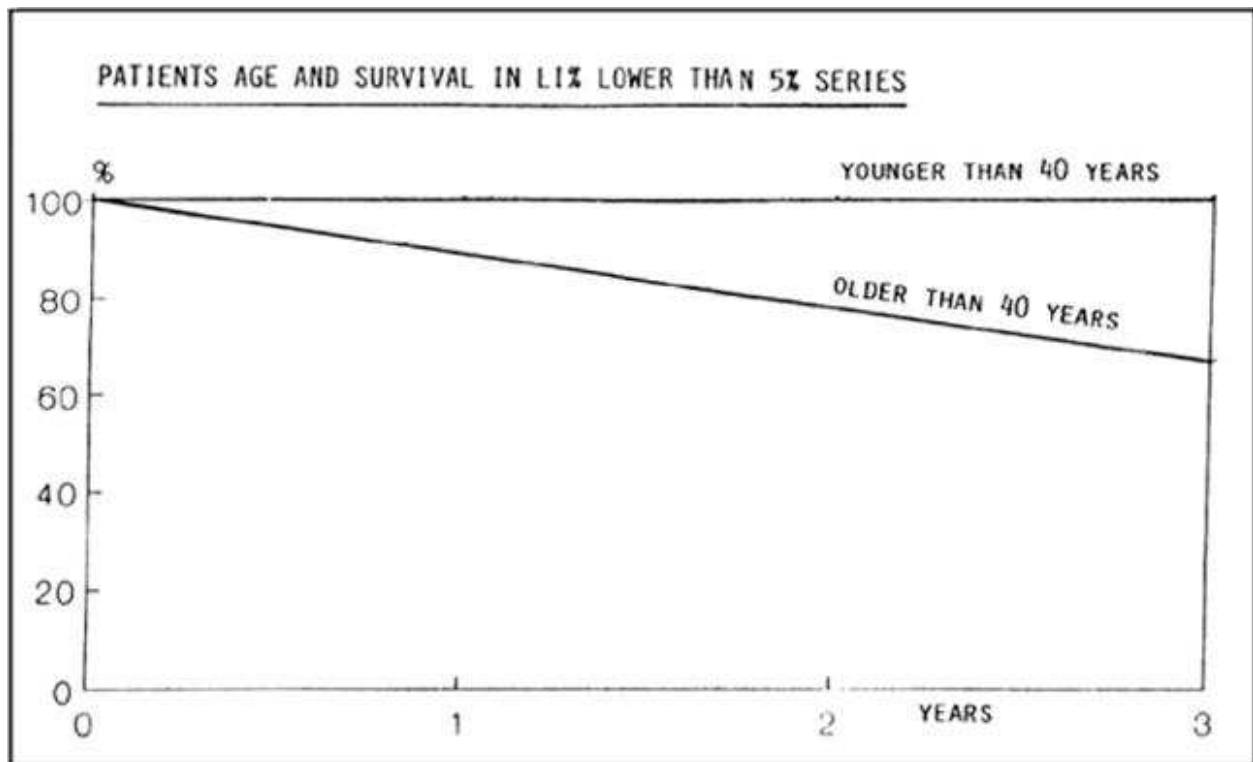


Figure 2. Survival in patients harboring slow-growing glial tumors characterized by LI percent values lower than 5. One hundred percent of patients younger than 40 years were still living at a 3-year follow-up, whereas 30% of patients older than 40 years of age died, in spite of the favorable indications of an LI percent lower than 5.

This study provides suggestions on how to understand the potential evolution of so-called slow-growing glial tumors. The histological findings derived from stereotactic biopsy may lead to the “wait-and-see” strategy, which is affected by a 43% mortality rate at 3 years after diagnosis. Furthermore, these data offer guidelines to establish indications and to evaluate the results of potentially therapeutic treatments such as radiosurgery (1,9), interstitial irradiation (28), and guided microsurgical removal (18).

In fact, literature data indicate that conventional radiation therapy in hemispheric low-grade astrocytomas is less effective than are cytoreductive procedures (24). In our opinion, the long-term evaluation of different treatments performed in low-grade glial tumors must be strongly linked to the preoperative cell kinetics assessment obtained by [³H]thymidine, as in this series, or by different methods that aim to measure the ratio between proliferating and resting cell pools in glial tumors, such as Ki-67 (6) or bromodeoxyuridine (16).

In conclusion, it seems that more aggressive cytoreductive treatments are recommended in these tumors, but long-term results must be evaluated in neoplasms with expected malignant evolution, in which the wait-and-see strategy leads to the so-called “secondary glioblastoma” (5). At present, the cell kinetics investigation seems to be the most helpful guide in these fields.

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COMMENTS[^]

Virtually all reports of patients with supratentorial low-grade astrocytomas have noted findings that are similar to the conclusions in this report. Most notably, the inability to predict the natural history of a tumor on the basis of routine histological examination has

been reported in other series of patients with similar pathology. In addition, the influence of patient age on prognosis is again confirmed. It is unlikely that another series of this size where no treatment was provided will be available in the foreseeable future, so this report is as close as we can get to examining the natural history of these lesions.

The authors report a strong correlation between the labeling index (LI) and prognosis. However, the high LIs of some of these lesions (as high as 17.5%) are compatible with highly malignant tumors and are incompatible with the histological findings of a low-grade lesion. The rapid progression of these tumors, resulting in death, is not surprising and supports the conclusion that histology can be misleading. A glial tumor with an LI of 17.5% is an aggressive tumor, regardless of the histological grade. Unfortunately, the authors did not perform a multivariate analysis of their findings, so it is not possible to determine the relative importance of the significant variables such as age, epilepsy, intracranial hypertension, or LI. This would have been helpful in interpreting their findings.

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COMMENTS[^]

Franzini et al. report a series of 70 patients with deep-seated “low-grade” gliomas. Thirty-two of these lesions were in the thalamus, and 38 were in the basal ganglia. There appear to be two groups of patients, young and “old.” As with most gliomas, young patients do better than older patients. Even more powerful than age, the malignant potential of the tumor appears to affect long-term survival. Most of us have now come to the conclusion that histology alone does not necessarily correlate with malignant potential and prognosis in patients with low-grade gliomas.

These authors have attempted to assess malignant potential by means of a simple and straightforward method of determining the thymidine labeling index. A simple labeling index can give us another parameter to look at when attempting to predict survival for patients and families and to help in therapeutic decision making.

The findings of their study are not surprising. A low labeling index is good (3-yr survival, 80%), and a high labeling index is bad (3-yr survival, 0%). In addition, more young patients had low labeling index values than did older patients. Certainly, the prognosis of patients with low-grade gliomas seems better in comparison with that of patients with malignant gliomas, but a 57% 3-year survival is not very good for a so-called “benign” tumor.

I think that the important message in this article is that these tumors kill patients. They cannot be observed; they won't go away. They grow. We need to assess the role of radiation therapy in light of these biological parameters. I have not been impressed with the results of radiation therapy on these lesions. I think that many of these deep-seated tumors can and should be removed. Five-year survival with stereotactically resected thalamic pilocytic astrocytomas is 100%. Stereotactic volumetric resection, as proposed by our group (1–3), provides a method for achieving gross total removal of many of these lesions with low morbidity.

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