Suspected Low-grade Glioma: Is Deferring Treatment Safe?

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Deferring therapeutic intervention may worsen outcome in patients with low-grade glioma. To address this issue, we searched our records and located 26 patients who presented with a transient event (most often seizures), who had radiographic evidence strongly suggestive of a low-grade primary supratentorial neoplasm, and for whom all therapy (except anticonvulsants) was withheld until deemed necessary (WAIT Group). For comparison, 20 patients who presented similarly, but for whom immediate intervention was elected, served as a comparison group (NOWAIT Group). Fifteen patients in the WAIT Group required eventual surgery or radiation therapy at intervals ranging from 4 to 123 months (median, 29 months) between radiographic diagnosis and therapeutic intervention; reasons for such intervention included increasing tumor size, uncontrollable seizures, or malignant transformation of tumor. At surgery, there was an increased number of anaplastic tumors noted in the patients in the WAIT Group ($p < 0.02$); nevertheless, if the rate of malignant transformation was examined from time of diagnosis, no differences were noted between the patients in the two groups. Similarly, no difference in survival or quality of life could be demonstrated from time of radiographic diagnosis. Therefore, we could not demonstrate that deferring therapy worsens outcome for these patients.

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Before the development of computed tomography (CT), the diagnosis of intraparenchymal brain tumors often required the performance of invasive tests with only moderate accuracy. Therefore, when invasive testing was deferred or equivocal, patients were termed "brain tumor suspects" if signs or symptoms suggested the presence of a mass lesion. Current neuroimaging techniques that are safe, accurate, and convenient enable us now to diagnose virtually every brain tumor at a relatively early stage. Nevertheless, enhanced brain imaging has given rise to a new dilemma, that is, how best to approach the patient who presents with a transient neurological event, a normal examination, and whose radiographs demonstrate evidence of a supratentorial unenhancing lesion with little mass effect. The optimal management of these latter day brain tumor suspects remains unclear.

When confronted with such a patient, the physician must first ascertain what the lesion represents; although an astrocytic neoplasm is most likely, it is unclear how often other entities that require different treatments can present with a similar clinicoradiographic picture. Furthermore, even if an astrocytoma can be diagnosed confidently, the degree of anaplasia cannot be accurately predicted from the radiographic appearance of an unenhancing intracerebral lesion [1, 2]. These considerations make it desirable to intervene early to establish a diagnosis at the least. Alternatively, why intervene if a patient will remain stable for many years? For example, as many as 10% of patients with long-term intractable epilepsy harbor low-grade gliomas [3–5], indicating that these lesions can be exceedingly slow growing.

Many recent reviews on low-grade astrocytoma advise immediate histological diagnosis [6, 7], whereas others [8, 9] acknowledge that there is no uniform recommended approach to these patients at the time of their diagnosis. Therefore, we gathered and analyzed a retrospective series in which patients with such lesions were either treated immediately or had intervention delayed. The purpose was to assess both the accuracy of the clinicoradiographic diagnosis and the effects of delaying definitive diagnosis and treatment on outcome.

Materials and Methods

Using a computerized registry that keeps track of neurooncological consultations, 26 patients (WAIT Group) were identified who fit the following criteria: (1) presentation with a seizure or other intermittent neurological complaint, (2) a

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Table 1. Demographic Characteristics of Patient Cohort

	Total Cohort (n = 46)	WAIT Group (n = 26)	NOWAIT Group (n = 20)
Sex (M:F)	1.7:1	1.9:1	1.5:1
Median age (range) (yr)	37 (15–58)	32 (15–56)	38 (24–58)
Location (%)			
Frontal	19 (41)	7 (27)	12 (60)
Temporal	20 (43)	15 (58)	5 (25)
Parietooccipital	6 (13)	4 (15)	2 (10)
Deep	1 (2)		1 (5)
First symptom (%)			
Seizures	41 (89)	23 (88)	18 (90)
Transient events	2 (5)	2 (8)	. . .
Headache	2 (5)	. . .	2 (10)
Focal signs	1 (2)	1 (4)	. . .
Radiographic abnormality (%)			
CT (abnl/perf)	36/45 (80)	17/25 (68)	19/20 (95)
MR (abnl/perf)	20/20 (100)	15/15 (100)	5/5 (100)
Calcified tumors	9 (20)	4 (15)	5 (25)

CT = computed tomography; MR = magnetic resonance; abnl = number of abnormal scans; perf = number of scans performed.

normal interictal neurological examination, (3) CT or magnetic resonance (MR) studies demonstrating a supratentorial unenhancing mass lesion with little or no mass effect, suggestive of a low-grade primary neoplasm and, (4) a decision made to defer intervention and follow the patient without specific therapy other than anticonvulsants. For a comparison group, we identified an additional 20 patients (NOWAIT Group) in whom the first three criteria were met but for whom the decision was made to intervene immediately.

From the original CT and MR reports, the interpretations were graded as being either strongly suggestive or equivocal/negative for the presence of tumor. Tumor location and the presence or absence of calcification were also recorded. The date of the first abnormal radiograph was considered the date of diagnosis for both groups. When available, microscopic slides of the original surgical specimens were reassessed blindly by two of the authors (T.S., L.R.); diagnosis and tumor grade were based on World Health Organization criteria [10].

Malignant transformation of tumor was defined as the radiographic appearance of new contrast enhancement and other characteristics suggestive of glioblastoma multiforme (GBM) in addition to worsened clinical status; because tissue was not obtained for all patients at this point in the course of their disease, histological confirmation was not required. Demographic characteristics, serial radiographs, and eventual outcomes were recorded and analyzed by life-table methods [11]; where comparisons between two groups were made, standard χ^2 analysis was used.

Results

Forty-six patients were found for whom the first three criteria were met; the decision to defer intervention was made in 26 patients (WAIT Group). Demographic characteristics of the entire cohort as well as those in the WAIT and NOWAIT Groups are summarized in Table 1. For the entire cohort, the male:female ratio was 1.7:1 and the median age at the time of diagnosis was 37 years. The interval between the first symptom and the time of tumor diagnosis ranged from 1 day to 13 years; in 61%, this interval was less than 1 month. The most common tumor locations were frontal (41%) and temporal (43%) lobes. Although the two groups were similar in most characteristics, there was an overrepresentation of frontal location in the patients in the NOWAIT Group and temporal location in the patients in the WAIT Group ($p < 0.05$).

Eighty-nine percent of the patients presented with a seizure. CT scanning was performed in 98% of the patients and was strongly suggestive of a low-grade primary neoplasm in 80%. MR imaging, which became available in our area after 1986, was performed in 20 patients and was strongly suggestive in all 20. Tumor calcifications were noted in 9 patients, 5 of whom were in the NOWAIT Group.

Reasons for deferring surgery in the patients in the WAIT Group included lesion inaccessibility (6 patients), equivocal diagnosis (2 patients), and physician/patient preference (17 patients). Of these patients, 15 (58%) subsequently underwent surgical procedures at a median interval of 29 months after initial diagnosis (range, 4–123 months). The reasons for intervention included an enlarging hypodense lesion (4 patients), worsening seizures (4 patients), new neurological symptoms (3 patients), and malignant transformation (3 patients). All the patients who developed malignant transformation before surgery were more than 45 years old at the time of radiographic diagnosis. Eleven patients are still being observed at a median interval of 29 months (range, 15–98 months) from the time of initial radiographic diagnosis.

The nature of the lesions seen radiographically has

Table 2. Tumor Histology at Time of Surgery in Patient Cohort

Histology	Total Cohort (n = 46)	WAIT Group (n = 26)	NOWAIT Group (n = 20)
Glioblastoma	4	4	0
Anaplastic astrocytoma	2	2	0
Anaplastic oligodendroglioma	1	1	0
Fibrillary astrocytoma	7	0	7
Oligodendroglioma/astrocytoma	14	5	9
Oligodendroglioma	1	0	1
Gliosis	1	0	1
Histology not confirmed[a]	5	3	2
Not yet known	11	11	0

[a]These tumors (which were not obtained for secondary review) included one fibrillary astrocytoma and two anaplastic astrocytomas from patients in the WAIT Group and two fibrillary astrocytomas from patients in the NOWAIT Group.

been assessed histologically in 35 patients to date and a second pathological review has been performed in 30 (86%); in all, a primary glial neoplasm was histologically confirmed (Table 2). An increased number of anaplastic tumors (GBM, anaplastic astrocytoma, anaplastic oligodendroglioma) was noted at the time of tissue diagnosis in the patients in the WAIT Group compared with the NOWAIT Group, in which none of the tumors showed anaplastic features (50% vs. 0%, $p < 0.02$). On the other hand, among the entire cohort, malignant transformation (as defined in Materials and Methods) had occurred in 15 (32%) patients at a median interval of 56 months (range, 8–122 months) from the time of initial radiographic diagnosis. When this event was independently assessed, no difference was apparent between the two groups of patients in the occurrence of, or interval to, malignant transformation (Fig 1). When a more restricted definition of malignant transformation that required histological confirmation was used, similar results were obtained. When the rate of this event was analyzed using only those 10 (67%) patients for whom histological specimens were available, no difference in the rate of malignant transformation was noted.

The median follow-up for the entire cohort of patients was 46 months. Twenty-two patients have been followed for at least 5 years after diagnosis; of these, 15 (68%) were able to function independently with minimal or no signs or symptoms at that time. Based on life-table analysis, the median survival after diagnosis for the entire group was 84 months; no difference in terms of quality or quantity of survival was noted between the patients in the WAIT and NOWAIT Groups (Fig 2).

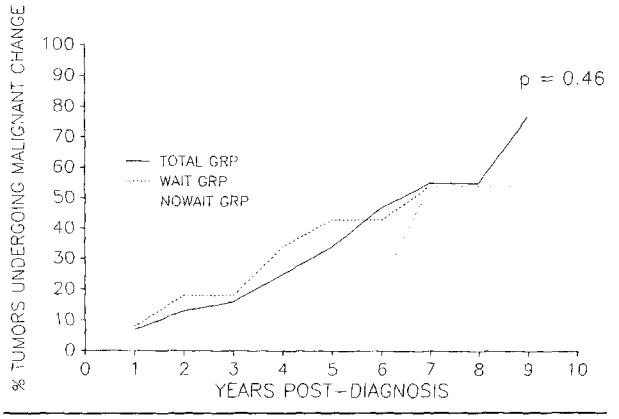

Fig 1. Rate of malignant transformation after date of radiographic diagnosis in patient cohort. No difference in the time to development of this deleterious event was noted between patients in the WAIT Group and patients in the NOWAIT Group ($p = 0.46$). *A significant difference was also not observed if patients are excluded in whom histological verification was not obtained* ($p = 0.18$).

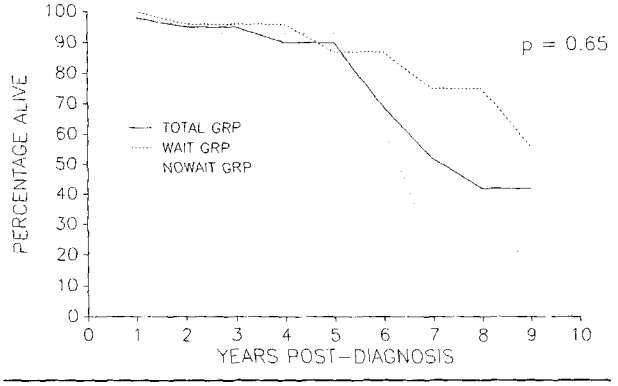

Fig 2. Patient survival as a function of whether immediate intervention was postponed. No statistical difference is noted between the NOWAIT and WAIT Groups of patients in terms of survival ($p = 0.65$).

Discussion

A physician may exercise certain options when encountering a patient whose examination is normal and who has a CT or MR finding consistent with a "low-grade

glioma." He or she may elect to have tissue immediately obtained via craniotomy or biopsy so that the diagnosis can be confirmed and the appropriate treatment administered. Conversely, empirical treatment in the form of radiation therapy may be administered. *Finally, the physician may elect to defer diagnosis* and definitive therapy until symptoms develop. The wisdom of delaying treatment assumes that the diagnosis can be made with great accuracy without tissue documentation and that outcome is independent of the time of intervention. If true, then the decision to defer radiation therapy as long as possible might minimize long-term complications such as neuropsychological impairment [12–14], neuroendocrine dysfunction [15], radiation necrosis [16, 17], and secondary tumors [18, 19]. Furthermore, though even deep-seated tumors can be easily biopsied using stereotactic methods [20, 21], deferring surgical intervention would also be reasonable if the risks, albeit negligible, of surgery outweighed the risk of making a deleterious clinical decision based on the radiographic studies (i.e., if the lesion represented another treatable entity). Whether this is in fact the case remains uncertain.

One reason *not* to defer at least a diagnostic procedure is the chance of overlooking a treatable condition. Especially in recent years with the appearance of acquired immunodeficiency syndrome–related neurological diseases, more emphasis must be placed on diagnosis. *It is therefore important to note that* in all our WAIT patients to date, a glial neoplasm was found at the time of surgery. Furthermore, in no patient was a pathological entity noted that required a different approach. A number of patients are still being followed; it is possible that in some patients, other abnormalities such as hamartoma or scarring might be responsible for the radiographic lesion. Nevertheless, it deserves emphasis that the diagnosis of a low-grade glioma may be made with a reasonable degree of certainty on clinicoradiographic grounds alone.

Little published evidence supports the option of deferring therapy [8, 9]. Therefore, although retrospective, this is the first study that to our knowledge addresses this question. Furthermore, although potential interpretative difficulties are suggested by the significant differences in location between the WAIT and NOWAIT Groups of patients, the following important observations can be derived from our data:

Although interindividual variation exists, the decision to defer therapy is often associated with a stable clinical course lasting years. Improved imaging techniques detect low-grade gliomas at an earlier stage in their natural history. In this series where CT scanning was readily available, the median interval between first symptom and diagnosis was less than 1 month and symptoms were present for more than 1 year in only 19% of the patients before diagnosis. By contrast, in studies which accrued patients from the pre-CT era, Laws and colleagues [6] reported that almost 20% of patients with supratentorial astrocytomas had had symptoms for more than 5 years before diagnosis and Mørk and co-workers [22] noted a median interval of 48 months between the onset of seizure and diagnosis of oligodendroglioma.

Nevertheless, whether earlier intervention is associated with an improved outcome remains unclear; previous retrospective studies have not demonstrated definitively that immediate radiation therapy either prolongs time to progression or improves survival [8, 9, 23]. This study provides evidence that deferring therapy in these patients also does not impact negatively on outcome, either in terms of survival or rate of malignant transformation when compared with a similar group of patients in whom the decision was made to immediately intervene.

When the decision is made to defer therapy, intervention eventually becomes necessary either because of radiographic evidence of tumor growth, intractable seizures, or malignant transformation of the tumor. Our analysis indicates that although long asymptomatic intervals are possible, intervention was eventually required in 58% of the patients in the WAIT Group because (1) the radiographic abnormality increased in size, (2) refractory seizures or new symptoms developed, or (3) there was the abrupt appearance of a lesion indistinguishable from GBM (malignant transformation).

When the decision is made to defer therapy, it is hoped that intervention will occur before malignant transformation occurs. Our experience, however, indicates that even close follow-up cannot guarantee that intervention will be possible before this occurs. Although this could be construed as a reason to immediately intervene, the similar survivals of the two groups of patients suggests that this event plays a minor role in determining outcome. It should be noted though that this event occurred only in patients who were older than 45 years at diagnosis; perhaps in this group of patients, earlier intervention is advisable.

No prognostic factors were significantly associated with an increased interval between diagnosis and intervention. This is no doubt due in part to the small number of patients available for analysis. It has been our impression, however, that the younger the patient, the longer the interval before intervention is necessary.

A difference in the incidence or interval to malignant transformation as a function of deferring therapy was not demonstrable in this series of patients. At the time of surgical intervention, the incidence of histologically confirmed anaplastic gliomas was significantly higher for the patients in the WAIT Group; however, this is difficult to interpret because it probably reflected the fact that long intervals often occurred between time of diagnosis and intervention in this group. A more rele-

vant observation, however, is that the incidence of malignant transformation from time of radiographic diagnosis was similar for both the WAIT and NOWAIT groups of patients. Because malignant transformation was defined on clinicoradiographic criteria, it is possible that the sudden appearance of lesion enhancement may have represented another pathological process such as radiation necrosis; if patients in whom histological verification was not obtained are excluded from the analysis, however, a difference still could not be demonstrated.

Previous studies have noted that increasing anaplasia is a common occurrence with supratentorial low-grade gliomas, a tendency that Muller and co-workers [24, 25] felt was independent of irradiation effects. In our patient population, life-table analysis indicates a relatively high incidence of clinicoradiographic malignant transformation; by 6 years after diagnosis, malignant transformation will have occurred in one-half of the patients. Whether therapy is postponed appears to make no appreciable difference in this rate of transformation. Acknowledging the chance of a beta-type statistical error, these preliminary data suggest therefore that deferring therapy does not place the patient at increased risk for the development of this deleterious occurrence. In contrast, these data also support the observation of Muller and co-workers [24, 25] that irradiation plays a minor, if any, role in malignant transformation of these tumors.

The natural history of these "brain tumor suspects" is not significantly altered by when therapeutic intervention occurs. Numerous studies have addressed the outcome from "benign" or low-grade gliomas, examining mainly prognostic factors and the role of surgery and radiation therapy [6, 7, 22, 23, 26–28]. All these retrospective studies collected patients according to histology; therefore, patient outcome was measured from the time of histological, rather than radiographic, diagnosis.

Although superficially similar, the present study addresses a somewhat different population, that is, patients who are diagnosed based on radiographic, rather than histological, criteria. Furthermore, this study addresses a very specific subset of patients with low-grade gliomas; extrapolation to all patients with such tumors should therefore not be made.

Nevertheless, our findings indicate that patients who present with such a clinical and radiographic picture often do well for long intervals after diagnosis. Furthermore, this outcome is independent of when conventional therapy is administered, although the relatively small numbers and uncontrolled nature of this study do not permit definitive conclusions. It is also important, however, that low-grade glioma is only a relatively benign illness; median survival is still only 84 months from the time of diagnosis and it is expected that all patients eventually die because of their disease. Furthermore, the natural history of these tumors is characterized by a high incidence of eventual malignant transformation.

When is the best time to intervene in low-grade gliomas? Ongoing studies by large cooperative groups [23] will help clarify whether radiation therapy is helpful in treating this neoplasm once diagnosed, although cooperative studies will not answer the more general question of when is the best time to intervene. It is reasonable to recommend, however, that such patients enroll in one of these studies. Because there is no indication that immediate intervention is superior to waiting, however, the decision to intervene at the time of diagnosis remains a clinical one that needs to be made by physicians and their patients on a case-by-case basis.

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