Is Necrosis Helpful in the Grading of Gliomas?  
Editorial Opinion  
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Abstract. The major function of a classification of neoplasms is to correlate with prognosis. During the 1980s two trends developed in the classification of gliomas: 1) the presence of necrosis in astrocytomas defines a subset with the worst prognosis (glioblastoma multiforme) and 2) no comparable subset of oligodendrogliomas appears to exist, either histologically or prognostically. Even the worst of the oligodendrogliomas has a better prognosis than glioblastomas. These asymmetries must be kept in mind when one is considering the diagnosis of glioblastoma. The absence of a specific stain for oligodendrogliomas, the difficulty in differentiating small anaplastic cells from oligodendrogliial cells and the common occurrence of mixtures of normal and/or reactive oligodendrogliii and astrocytic gliomas combine to create potentially confusing misclassification of many gliomas.

Key Words: Astrocytoma; Glioblastoma multiforme; Oligodendroglioma; Mixed gliomas; Necrosis.

The question whether necrosis is helpful in the grading of gliomas can only be answered after one has identified the type of glioma and a past history of necrosis-inducing treatment(s), such as radiotherapy or chemotherapy. Clearly, in untreated astrocytomas the presence of necrosis indicates a high degree of malignancy, namely glioblastoma multiforme, with a very poor prognosis. Almost equally clearly, in untreated oligodendrogliomas the presence of necrosis does not separate the rapidly progressive from the very slowly progressive lesions, and this fact is all the more important because even the most malignant-appearing oligodendrogliomas do not have so bad a prognosis as glioblastomas. In other gliomas, such as ependymomas and mixed gliomas, the evidence has not been presented adequately to permit a conclusion one way or the other.

The conclusion having been stated up front, what is the evidence?

One of the major reasons that neuropathologists classify brain tumors is to define the prognosis for guidance of the care of future patients with "the same tumor" (1–14). Many investigators during the past 80 years have been content to define prognosis only in general terms, such as rapidly or slowly growing tumors, or as malignant, semi-malignant, semi-benign or benign tumors (7, 8), but with the development of life-table analytic methods (15–17) more precision has become possible. Indeed, one of the ironies surrounding the classic revolution introduced by Kernohan et al (3) and Kernohan and Sayre (6) is that they did not take advantage of the presence of Berkson and Gage (15) at the same institution at the same time to present their results in modern terms rather than the simple averages of olden times.

Among the more obvious factors that must be considered in defining the prognosis are the histologic features ("the diagnosis," including the cell type and grade or degree of malignancy) and the usual statistical considerations of adequacy of numbers of patients and duration and completeness of follow-up. Other, less obvious perhaps, but still important factors are the anatomic site involved, the patient's age, the number and extent of surgical excisions, and the type and amount of radio- and/or chemotherapies used.

To the best of my knowledge there is no report that has defined the effect of all of these factors, but there are enough recent reports that have attempted to define the prognosis of patients with astrocytomas (5, 6, 13, 14, 18–42) or oligodendrogliomas (5, 6, 43–50) of various grades of malignancy (including glioblastoma multiforme either as a separate tumor or as the most malignant grade of astrocytoma) to serve as the basis for this review of the recent literature concerning the follow-up of patients with astrocytomas, glioblastomas or oligodendrogliomas. I have transcribed the reported results to graphic representations with identical coordinates to facilitate direct comparison. No report was excluded if it met the following two criteria: 1) adequacy of histologic diagnosis (see below) and 2) adequacy of follow-up data providing or permitting life-table analysis (15–17).

Many of the reports concerned large numbers of patients with "malignant gliomas," which I tentatively accepted as equivalent to "glioblastoma" even though only 80–90% of the patients were actually said to have had "glioblastoma multiforme" (see below), the other 10–20% having various other gliomas with more or less malignant features. Most of these large series concerned cooperative studies pooled from many medical institutions related to comparisons of different treatments of patients with "malignant gliomas." All of the reports concerning oligodendrogliomas, however, concerned patients from single institutions.

All histologic diagnoses were based on sections stained.

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nized that it was only a three-tiered scheme in which “astrocytoma grades 3 and 4” were both “glioblastoma multiforme,” characterized by high degrees of cellular and nuclear pleomorphism and mitoses, usually but not always with accompanying endothelial proliferation and necrosis. However, as Daumas-Duport et al (13) have recently pointed out, the classification is really only two-tiered, overlapping actuarially-defined prognoses collapsing the scheme into grades 1–2 with relatively good prognosis and grades 3–4 with relatively bad prognosis. With the advent of necrosis as the determining factor (19, 34), a truly three-tiered scheme developed: astrocytoma (ordinary or low-grade), anaplastic astrocytoma (with atypical features but not necrosis) and “true” glioblastoma multiforme (or anaplastic astrocytoma with necrosis).

The diagnosis of oligodendroglioma was generally along classical lines (3, 5–12), emphasizing the “fried egg” appearance of the cells with perinuclear halos, with additional investigative consideration given to many other histologic features: degrees of cellular density, pleomorphism, mitosis, microcysts, necrosis, etc.

For the purpose of the present analysis the primary division was between astrocytomas (including glioblastoma multiforme) and oligodendrogliomas. The secondary division was the presence or absence of necrosis, when stated, or the acceptance of the diagnosis of “glioblastoma multiforme” or “malignant glioma” as a first approximation to “true” glioblastomas as anaplastic astrocytomas with necrosis.” If this particular histologic ambiguity had turned out to have any significant effect on the analysis, these reports would have been separately compared, probably using meta-analytic techniques (31–55), but such proved not to be necessary.

As shown in Figure 1, patients with astrocytomas have a very wide range of survival rates, from pilocytic ones with 100% of patients surviving ten years (Fig. 1B) down to “glioblastomas” with not over 30% of the most favorable patients (those under 45 years of age) surviving two years and the median of all the reports indicating that only about 10% of patients with “glioblastomas” or “malignant gliomas” survive two years (Fig. 1A).

It should be noted that Figure 1A includes reports of survival rates of patients with “malignant gliomas,” only about 80–90% of whom actually had “glioblastomas,” and that these were frequently classified as equivalent to astrocytomas of grades 3 and 4 of Kernohan and Sayre (6), in which necrosis was not necessarily the critical criterion. However, there is now abundant evidence that the presence of necrosis clearly separates the “true” glioblastomas from most of the other anaplastic astrocytomas (13, 19, 20, 34, 35). The slight overlap of survival rates of “true” glioblastomas with some of the anaplastic astrocytomas shown in Figure 1 is due to the effects of differences in age, DNA and S-phase analyses, biological factors that can supplement the purely histologic in pro-

Fig. 1. Survival rates reported by various investigators (13, 14, 18–42) for patients with “glioblastomas,” “malignant gliomas” or astrocytomas with necrosis (A) or all other astrocytomas without necrosis (B). The best survival rates in (A) are those reported for patients with “true” glioblastomas under age 45 years (19, 20) or receiving interstitial implants of 131I (26). The worst survival rates in (B) are those reported for patients with anaplastic astrocytomas over age 65 years (19) or having evidence of abnormal DNA (21).

with hematoxylin and eosin. No special stains were used routinely. Most of the specimens were reviewed by one or more neuropathologists acting for the institution or for the cooperative study group.

The diagnosis of “glioblastoma multiforme” was, in the days before necrosis became of differential diagnostic importance, usually based on the supposedly four-tiered criteria of Kernohan and Sayre (6), who already recog-
viding a better prognostic index, as reviewed elsewhere (56). As will become apparent below, this overlap among the astrocytomas becomes irrelevant when the best survival rates of patients with glioblastomas are compared with the worst of the oligodendrogliomas.

As shown in Figure 2, patients with oligodendrogliomas have almost as broad a range of survival rates, from about 60% surviving ten years to 0% surviving three years. The patients in group "D" of Ludwig et al (46) and Smith et al (49) have the worst prognosis, and these most malignant oligodendrogliomas are characterized histologically by pleomorphism, high cell density, high nuclear/cytoplasmic ratio and endothelial proliferation as well as necrosis (Fig. 2A). By contrast, patients with oligodendrogliomas having microcysts and low to medium cellularity, with or without necrosis (43-50), as shown in Figures 2A and 2B, have the best prognosis. There is, however, no consistency in the intermediate patterns attempting to correlate prognosis with various histologic characteristics as reported by different investigators (43-50). Such differences suggest that each institution attracts patients with different clinical presentations (e.g. epileptic seizures evaluated by computerized tomography and magnetic resonance imaging which can reveal small tumors) and with different prognoses related to the duration or stage in the evolution of their tumors.

As emphasized in Figure 3, in which the extremes of Figures 1A and 2A are indicated, there is essentially no overlap between the survival rates for patients with "glioblastomas" (c.f. Fig. 1A) and those with oligodendrogliomas (c.f. Fig. 2A). Indeed, the worst prognosis reported for patients with even the most malignant-appearing oligodendrogliomas, group "D" (46, 49), is almost identical during the first two years of follow-up with the best prognosis reported for patients with "glioblastomas" or "malignant gliomas" included in Figure 1A. The overlap after two years suggests that the "glioblastoma" series with the best long-term results may have been contaminated with 5-15% of patients with oligodendrogliomas, anaplastic astrocytomas or other "malignant gliomas" having an inherently better prognosis than "true" glioblastomas, as already suggested by the definition of "malignant gliomas" in many of the reports as permitting the inclusion of 10-15% of non-glioblastomas in their prospective therapeutic trials.

The most common cerebral tumors are gliomas and the most common of these are astrocytomas, but the most common differential diagnosis in my experience involves cases with mixtures of astrocytomas with oligodendrogliomas (57, 58). Where to draw the line, how to define neoplastic and reactive astrocytes and how to classify these "mixed gliomas" is not yet clear to me. My impression is that most neuropathologists (7-12) prefer to classify such tumors one way or the other as either astrocytomas or oligodendrogliomas, thereby decreasing or eliminating the group of "mixed gliomas," or to suggest that it is the astrocytic component that will become most malignant and will define the prognosis of a "mixed glioma."

The existence of "mixed gliomas," even if only reluctantly admitted (7-11), raises the question of how pure the groups that I have analyzed above really are. The difficulty was already bad enough before the prognostic importance of necrosis in astrocytomas was realized; but if any oligodendrogliomas or mixed gliomas are misdiagnosed as "glioblastomas" or "malignant gliomas" because of the presence of necrosis and various numbers of...
astrocytes, the situation becomes even more difficult. This is true because there are important asymmetries in the grading scheme such that 1) necrosis in astrocytomas carries a very bad prognosis (Fig. 1) whereas necrosis in oligodendrogliomas does not necessarily imply a bad prognosis (Fig. 2) and 2) even the worst of the oligodendrogliomas has a better prognosis than the best of the "glioblastomas," "malignant gliomas" or "true" glioblastomas diagnosed as "anaplastic astrocytomas with necrosis" (Fig. 3).

The temptation to resolve the issue by saying that glioblastoma multiforme is a mixture of tumors, including not only the highest grade of astrocytomas but also the highest grade of oligodendrogliomas (which is so pleomorphic as to be no longer recognizable as an oligodendrogloma), leads immediately to an impasse since the major criterion of necrosis does not separate the various grades of oligodendroglioma from each other (Fig. 2) whereas it does separate the highest grade of astrocytoma (glioblastoma multiforme) from the intermediate grade or anaplastic astrocytoma (13, 19, 20, 34, 35). The importance of being able first to separate astrocytomas and oligodendrogliomas should, therefore, be obvious if the classification and grading of gliomas is to be of real service in evaluating the results of different treatments of patients.

This difficulty of asymmetry in the classification criteria is compounded by certain practical problems:

1) The frequency of "mixed gliomas," variously defined as composed of different proportions, patterns and types of astrocytes and oligodendroglia (57, 58), is not known, nor have the prognoses yet been adequately defined. "Mixed gliomas" have presented difficulties in definition from the earliest days of classification of brain tumors (57). Hart et al (57) recognized mixtures of oligodendroglia with either ependymomas (16 cases) or astrocytomas (86 cases) and described them as compact (75 cases) or diffuse (27 cases). However, they found no difference in survival rates related either to different percentages of mixtures between 25% and 75% of astrocytes or to their compact or diffuse pattern. Their results were expressed only as medians, means and ranges of survival times and could not be translated adequately for inclusion in Figures 1 or 2. It may be noted that their grade II median survival of eight months would fall within the range for glioblastomas and that their grade I median survival of 24 months would fall within the range for oligodendroglia or anaplastic astrocytomas. It is interesting that they specifically excluded cases of grades III and IV malignancy since they expected these to behave like glioblastomas. Mork et al (47) referred to this study as the basis for their rejecting oligodendroglia containing more than 25% astrocytes, although Smith et al (49) accepted mixtures up to 49% astrocytes. Neither of these groups of investigators (47, 49) reported median survivals even approaching the eight months reported by Hart et al (57). Nor have others (41, 50) approached this short a survival.

Wallner et al (50), apparently using the criteria of Davis, as reported by Levin et al (31, 32), found that their 11 patients with "mixed" tumors (containing at least one focus of another histological type) appeared usually "a minor astrocytic component") had essentially the same survival rates as their 29 patients with oligodendroglia (i.e. 57–61% at five years and 33–38% at ten years).

Winger et al (41), using the histologic criteria of Burger et al (19) and Burger and Vogel (9), reported survival rates of their 11 patients with "anaplastic mixed gliomas" to be almost identical with their 76 patients with anaplastic astrocytomas (50–55% survival at one year or 57–63 weeks median survival), quite in contrast with either their 188 patients with glioblastomas (median survival of 32 weeks) or their 10 patients with anaplastic oligodendroglia (278 weeks median survival).

2) Normal or reactive astrocytes and oligodendroglia are routinely incorporated in gliomas. Their differentiation from low-grade malignant cells of either series is notoriously difficult, as shown by most classifications attempting to define "grade I" neoplasms (5, 6, 9).

3) There is evidence of interconvertibility of immature forms of astrocytes and oligodendroglia (59, 60). Whether "mixed tumors" recapitulate these transitional forms is still not known, but Heperes and Buka (58), analyzing
oligodendrogliomas (50 cases) and mixed oligodendrocytomas (16 cases), concluded that "glioblastoma oligodendroglioma" and "transitional oligoastrocytoma" should be recognized as glial fibrillary acidic protein-containing subtypes of oligodendroglioma, whereas "mixed oligoastrocytoma" should be differentiated by having "two distinct and non-transitional cell populations."

4) It is difficult to differentiate small anaplastic cells presumably of astrocytic origin from oligodendroglia or even lymphocytes (61). Yet it is just these small anaplastic cells that are the most malignant and the most likely to be responsible for the recurrence (61, 62).

5) There is no specific stain for normal or abnormal oligodendroglia in paraffin-embedded tumor tissue. Although normal oligodendrocytes contain S-100 protein, myelin basic protein, myelin-associated glycoprotein and carbonic anhydrase C, their presence in oligodendroglia has not been confirmed and the reactivity with anti-leu 7 (HNK-1) monoclonal antibody is "far from specific" (12). With these statements by the late master of neuroimmunohistochemistry, but admittedly on the basis of much more limited personal observations, I wholeheartedly agree.

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REFERENCES


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