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Letter to the Editor

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To the editor: Peter Burger *et al*[1] have published a provocative paper on the correlation of 1p-19q-defects in human gliomas with the light microscopic appearance of oligodendroglioma.[1] Our interest in this subject is derived from our own recent experience with a large cohort of 142 gliomas including 45 oligodendrogliomas and 97 astrocytomas of all grades. (The patients were chosen without regard to participation in drug trials.) We became interested after our own experience suggested that the diagnostic criteria that we use to define an oligodendroglioma may have become too stringent, thus resulting in the false diagnosis of astrocytoma or mixed glioma (oligoastrocytoma). Parenthetically, we rarely use the diagnosis of mixed glioma or oligoastrocytoma preferring to classify the tumor according to the predominate glial morphology. We derived from the concept that if the oligodendroglioma has intrinsically a better chemotherapeutic sensitivity,[2] we feared that our diagnostic criteria may become overly rigid resulting in certain patients not becoming eligible for oligodendroglioma-type therapeutic protocols. Alternatively, the inclusion of oligodendrogliomas in an astrocytoma drug trial may falsely inflate the response rate. If, as Burger suggests, routine testing, of 1p19q status may not be economically feasible, we sought to determine which group of patients, whose tumors exhibited morphologic features that indicated molecular testing, would be beneficial. The molecular analysis of the 45 oligodendrogliomas has been published elsewhere.[3] All 142 tumors were originally classified and graded according to WHO standards existing at the time of original diagnosis. For this study, we re-reviewed the material using the criteria for oligodendrogliomas and astrocytoma defined in Burger's report. Molecular data were obtained for all tumors using the methods described previously[3] including loss of heterozygosity (LOH) analysis for chromosomes 1 and 19, and comparative genomic hybridization (CGH). We defined 1p- and/or 19q- as complete loss of the affected arm on the respective chromosome by loss of all informative markers for that allele by LOH (FGR, MYCL1, AMY2B for 1p and D19S216, D19S221, D19S226 for 19q), and by complete centromeric to telomeric loss as identified by CGH. Among the 97 astrocytomas, no tumor exhibited simultaneous, complete loss of both 1p and 19q. Partial losses of genetic material could be found on either chromosome, but the combination of 1p-19q- was not identified. Among the 45 tumors originally identified as oligodendrogliomas, 1p-19q- was found in 31 (69%). Using the criteria of Burger *et al*, the tumors were subdivided by light microscopy into the following groups: (a) unequivocal oligodendrogliomas (WHO Grade II and III) with round regular nuclei, and thread-like chromatin often associated with hematoxylinophilic chromocenters. (b) unequivocal astrocytoma (WHO Grades II, II and IV) with pleomorphic nuclei and eosinophilic cytoplasm; (c) a mixed glioma group with distinctive regions of oligodendroglioma and astrocytoma; (d) were distinct regions of oligodendroglioma and astrocytoma. (c) we were then left with a small group of cases that we called 'favor oligodendroglioma' that were characterized by cells with mildly pleomorphic nuclei, clumped chromatin, and perinuclear haloes. The results of this morphologic analysis are shown in Table 1.

The results indicate that 1p-19q- analysis need not be performed on tumors identified as unequivocal oligodendroglioma or unequivocal astrocytoma by the strict criteria of Burger. Unequivocal oligodendrogliomas will have this abnormality in 28/30 (93%) cases. Similarly, among tumors diagnosed as unequivocal astrocytomas using the criteria of Burger, only 1/6 will have the 1p-19q- marker (or including the much larger cohort, 1/104 tumors). The data clearly indicate that 'questionable' cases and mixed gliomas provide a rich population of tumors in which 1p-19q- analysis may provide diagnostically useful information.

In order to further define the prognostic utility of the 1p-19q- marker, the survivals of the 45 patients with light microscopically diagnosed (LMD) oligodendrogliomas were subdivided according to 1p;19q status and compared against a group of LMD well-differentiated astrocytomas from the astrocytoma cohort of the study. The 31 patients with 1p-19q- LMD oligodendrogliomas (all grades) were compared against the 14 patients whose LMD oligodendrogliomas (all grades) did not show this marker as well as against the nine patients with LMD well-differentiated fibrillary astrocytomas taken from the astrocytic cohort. A logrank test was used to compare the distribution of survival among the three patient groups. This comparison was not statistically significant ($P=0.252$). Interestingly, even after 5 years follow-up, the power to detect clinically important survival differences was low or almost nonexistent in these three populations due to the small number of deaths. We conclude: (a) that 1p19q status may assist in a stricter classification of gliomas; (b) that 1p19q status does not provide prognostic data that are independent of histologic grading; and (c) further studies are needed to

Table 1 Reclassification of 45 tumors originally diagnosed by light microscopy as oligodendroglioma using the criteria of Burger *et al*

	Oligodendroglioma	*Astrocytoma*	*Favor oligodendroglioma*	*Mixed glioma*
1p only	2	0	0	0
1p-19q-	26	1	3	1
All other	2	5	4	1

determine those molecular factors that make oligodendrogliomas as a group more intrinsically sensitive to therapeutic interventions.

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