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CORRESPONDENCE

A suggestion to introduce the diagnosis of "diffuse midline glioma of the pons, H3 K27 wildtype (WHO grade IV)"

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We have read with great interest the publication regarding clarification of criteria for *diffuse midline glioma, H3 K27M-mutant* by Louis et al. [5] and would like to contribute to the discussion the following point.

It has been common sense now for nearly 20 years among pediatric neurooncologists that neuroradiologically defined diffuse intrinsic pontine gliomas (DIPG) display a very poor prognosis independent of histological grade (when biopsied). Thus, biopsies had been usually omitted until recent identification of potential drug targets for individualized therapy has led to reevaluation of this approach [8]. Nevertheless, biopsies are only performed in the (admittedly growing!) minority of DIPG patients; in the majority of cases, diagnosis is still established by typical MRI features [T1-hypo (or iso) intense and T2-hyperintense tumor involving at least 50% of the pons] together with a very short clinical history (usually < 6 months), and at least one typical brainstem symptom (cranial nerve deficits, ataxia and/or long tract signs) [1].

With the introduction of the new brain tumor entity "*diffuse midline glioma, H3 K27M-mutant*" (DMG IV), most DIPG are now subsumed together with other diffuse midline gliomas carrying a H3 K27M mutation. This seems to be reasonable as thalamic, spinal, and other non-pontine diffuse brainstem gliomas with H3 K27M mutations confer similarly unfavorable prognosis as typical DIPG [3]. However, at least in thalamic gliomas, there is a significant prognostic difference between thalamic DMG IV with H3 K27M-mutations and thalamic WHO grade II-IV astrocytomas [7] with wildtype H3 K27 [3, 7]. In DIPG this seems to be different: H3 K27 wildtype DIPG (approximately 15% of the biopsied population) share the same unfavorable prognosis as H3 K27M mutant DIPG [2], and this is independent of their underlying histological tumor grading. We would like to draw the attention to the fact that some (probably up to 3–5%; Table 1) of these very poor prognostic H3 K27 wildtype DIPG show WHO grade II histology [2], and according to the revised 4th edition of the *WHO classifica*tion [6] these DIPG might be considered as astrocytoma WHO grade II, thus as a pediatric low grade glioma (pedLGG), although the prognosis of pedLGG is much better compared to DIPG. Moreover, there would be

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Table 1 Survival comparison of patients with known histological grading and H3 K27M mutation status ($n=128$) of a large cohort reported as a collaborative effort recently [2]

Variable	No. of patients (%)	Median overall survival (months)
Grade IV, H3WT	$n=13$ (10)	11
Grade IV, H3K27M	$n=41$ (40)	12
Grade III, H3WT	$n=2$ (2)	16
Grade III, H3K27M	$n=37$ (39)	11
Grade II, H3WT	$n=4$ (3)	10.5
Grade II, H3K27M	$n=21$ (16)	12

the possibility that the well acknowledged pedLGG "chemotherapy only" approach [4] might be considered as adequate treatment although radiotherapy remains the only established standard of care for DIPG (National Cancer Institute; https://www.cancer.gov/types/brain/hp/child-glioma-treatment-pdq#section/_40).

Although based on Kaplan–Meier analysis histological grade II suggested a slightly longer survival in DIPG patients [2], the median overall survival is generally very poor in all DIPG patients (Table 1), and interestingly the outcome is also very unfavorable in patients characterized by histological grade II with or without H3 mutant tumors (Table 1). This is in contrast to thalamic gliomas, where Ryall and colleagues defined a patient group (H3 wildtype tumors with histological grade I or II) with a comparatively excellent survival [7]. Furthermore, DIPG with histological grade II and H3 K27M mutation showed even a slightly better median overall survival than their H3 wildtype counterparts (of note small patient numbers). However, we may conclude that the survival of neuroradiologically confirmed DIPG seems overall very poor, independently of their histological grade AND their H3 mutational status. And this observation seems to be unique, at least markedly different from their thalamic counterparts. At least within the High Grade Glioma (HIT-HGG) study group of the Gesellschaft für Pädiatrische Onkologie and Hämatologie (GPOH) in Germany, Austria, and Switzerland and the European SIOPE DIPG Registry, we temporarily have solved this issue of adequate classification for H3 K27 wildtype pontine gliomas by still using the term DIPG to describe the pontine subgroup of diffuse midline gliomas with a very poor prognosis and typical clinical and MRI features. Since this approach is not sufficiently exact within the new WHO classification and usually appears very confusing for interdisciplinary daily practice, we suggest introducing an additional provisory variant of pediatric diffuse midline gliomas WHO IV with the possible designation as "diffuse midline glioma of the pons, H3 K27 wildtype". This subgroup would then define tumors that are (1) gliomas with histological grade II–IV, and (2) diffuse, and (3) do NOT carry a H3 K27M mutation, and (4) exhibit typical neuroradiological and clinical features of a DIPG, preferentially confirmed by central neuroradiological review.

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