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IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO

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Abstract

The WHO 2007 classification of tumors of the CNS distinguishes between diffuse astrocytoma WHO grade II (A II_{WHO2007}) and anaplastic astrocytoma WHO grade III (AA III_{WHO2007}). Patients with A II_{WHO2007} are significantly younger and survive significantly longer than those with AA III_{WHO2007}. So far, classification and grading relies on morphological grounds only and does not yet take into account *IDH* status, a molecular marker of prognostic relevance. We here demonstrate that WHO 2007 grading performs poorly in predicting prognosis when applied to

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astrocytoma carrying *IDH* mutations. Three independent series including a total of 1360 adult diffuse astrocytic gliomas with *IDH* mutation containing 683 A II *IDH*mut, 562 AA III *IDH*mut and 115 GBM *IDH*mut have been examined for age distribution and survival. In all three series patients with A II *IDH*mut and AA III *IDH*mut were of identical age at presentation of disease (36–37 years) and the difference in survival between grades was much less (10.9 years for A II *IDH*mut, 9.3 years for AA III *IDH*mut) than that reported for A II WHO2007 versus AA III WHO2007. Our analyses imply that the differences in age and survival between A II WHO2007 and AA III WHO2007 predominantly depend on the fraction of *IDH*-non-mutant astrocytomas in the cohort. This data poses a substantial challenge for the current practice of astrocytoma grading and risk stratification and is likely to have far-reaching consequences on the management of patients with *IDH*-mutant astrocytoma.

Introduction

Grading of adult diffuse astrocytomas and anaplastic astrocytomas according to WHO grades II (A II WHO2007) and III (AA III WHO2007) has been well established over the last 20 years. While the numbers for age and survival given by different studies vary, there is consensus that patients with A II WHO2007 are significantly younger and survive significantly longer than patients with AA III WHO2007. According to WHO 2007 patients with A II WHO2007 average 34 years and have a survival of 6–8 years, those with AA III WHO2007 average 45 years and survive approximately 2 years [10]. In an extensive population-based series patients with A II WHO2007 of the fibrillary subtype averaged 40 years and patients with AA III WHO2007 averaged 46 years and followed a markedly worse clinical course with an average survival of 1.6 years as opposed to 5.6 years in A II WHO2007 [13].

The current parameters for the discrimination between WHO grades II and III are cellular differentiation, presence or absence of early vascular changes and proliferation. Proliferation is of superior impact as otherwise well-differentiated astrocytomas with inconspicuous vessels but more than only very few mitoses are considered as WHO grade III with all clinical consequences attached to this diagnostic decision.

The identification of *IDH* mutations in the majority of astrocytomas [2, 7, 21, 25] and concurrent analyses revealed that among AA III WHO2007 the presence of these mutations was associated with a significant better clinical course [6, 17, 23], an observation not observed for A II WHO2007 [1, 20]. Numerous studies indicate the possibility that worse outcome of AA III WHO2007 compared to A II WHO2007 is strongly influenced by the inclusion of cases that indeed molecularly represent glioblastoma (GBM). Consequently, the inclusion of *IDH* mutational status into future astrocytoma classifications is discussed and has been proposed by the Haarlem international consensus meeting [11].

A point so far not sufficiently addressed is the feasibility of the current WHO criteria for grading *IDH*-mutated astrocytoma. We here provide evidence that application of the WHO2007 grading criteria on *IDH*-mutant astrocytoma lacks the power it had in distinguishing A II and AA III before exclusion of *IDH* wild-type tumors. We here present evidence that *IDH*-mutant diffuse astrocytoma graded according to the WHO2007 criteria

(A II) and their anaplastic counterparts (AA III_{IDHmut}) represent closely related groups which are virtually identical in patient age and that show only little difference in overall survival.

Materials and methods

Data collection

Data were derived from the files of the Department of Neuropathology Heidelberg ($n = 866$), a recently published series originating from the Department of Pathology MD Anderson Cancer Center and from the VU University Medical Center/The Netherlands ($n = 263$) [14], and a recently published series by the TCGA ($n = 231$) [3]. Therefore, the results here are in part based upon data generated by the TCGA Research Network: <http://cancergenome.nih.gov/>. Level 1 450k methylation data and sequence data were downloaded from the open-source TCGA pages (<https://tcga-data.nci.nih.gov/tcga/>). Inclusion criteria were the diagnosis of a diffuse astrocytic glioma including diffuse astrocytoma, anaplastic astrocytoma, presence of an *IDH* mutation, absence of 1p/19q codeletion (1p/19q code), information on age and gender available and patient age of 18 or older. TCGA and Heidelberg patients with GBM and *IDH* mutation were also included. For the TCGA series the presence of 450k methylation data were required. Cases included are listed in Table 1.

IDH and 1p/19q status

IDH and 1p/19q status in the MD Anderson series had been analyzed by *IDH1*-R132H immunohistochemistry, Sanger sequencing for *IDH1* and *IDH2* and by fluorescence in situ hybridization or microsatellite analysis for chromosomal arms 1p and 19q. A subset of samples was analyzed using low-pass whole genome sequencing for 1p/19q analysis [14]. The TCGA series was reanalyzed on basis of the Illumina Infinium HumanMethylation450 BeadChip (450k) array (Illumina, San Diego, USA). The array data were used to calculate a low-resolution copy number profile (CNP) as previously described [18]. The data were analyzed as previously described to allot the tumors to either a G-CIMP or a non-G-CIMP cluster [12, 24]. Furthermore, the TCGA exome sequencing data allowed to directly score *IDH* mutations. The cases of the Heidelberg series have been sequenced for *IDH1* and *IDH2* and the majority of the cases were analyzed by fluorescence in situ hybridization or microsatellite analysis for chromosomal arms 1p and 19q. In more recent cases the 1p/19q status has been determined by calculating a copy number profile on basis of 450k methylation data.

Classification and grading

An integrated diagnosis following the preliminary suggestions of the Haarlem consensus meeting [11, 16] was established with tumor classification as *IDH*-mutated astrocytoma depending on the absence of 1p/19q code. Tumor grading was performed using the WHO 2007 grading parameters differentiation, cellularity, proliferation and extent of microvascular proliferation. *IDH*-mutated GBM exhibited additional necrosis in the absence of 1p/19q code.

Statistics

Boxplots were generated using the statistical software R. Kaplan–Meier plots and log-rank tests were conducted by Partek GenomicsSuite software (Partek, St. Louis USA) and MedCalc software (Ostende, Belgium).

Results and discussion

Age distribution

The present analysis includes a total of 1360 adult diffuse astrocytic tumors with *IDH* mutation from three independent series (Table 1). Age distribution for *IDH*-mutant tumors with an integrated diagnosis that included both histological interpretation and molecular analysis [16] varied from those published for tumors classified according to WHO. Most notably, there was no significant difference in patient age between A II *IDH*mut and AA III *IDH*mut both averaging 38 years as opposed to an approximate 6–12 years difference between A II WHO2007 and AA III WHO2007 [10, 13]. Also, the age of GBM *IDH*mut averaging 42 years was only 4 years higher than that of A II *IDH*mut and AA III *IDH*mut. It is likely that the difference in age between patients with integrated diagnoses versus morphology-based WHO2007 diagnoses is due to the confounding by *IDH* wild-type tumors with morphologic characteristics of AA, which from a biologic point of view predominantly represent underdiagnosed GBM, since they generally exhibit classic molecular hallmarks of GBM, including loss of chromosome 10, gain of chromosome 7 and frequently amplification of EGFR [3]. The strong age effect of eliminating “*IDH* wild type anaplastic astrocytoma WHO grade III” raises the question on the effect of eliminating “*IDH* wild type diffuse astrocytoma WHO grade II”. A recent study found an age difference of 4 years between *IDH*-mutated and wild-type diffuse astrocytomas [1]. These tumors are presumed to represent a mixture of different tumor types [3]. We assume that this mixed bag likely contains patients with tumors having an higher average age (i.e., GBM) and others with a younger average age (i.e., DNT, pilocytic astrocytoma, ganglioglioma) than that of diffuse astrocytomas thus exerting less influence on the average age of WHO grade II astrocytomas.

Box plots of patient ages with integrated diagnoses for the three studies are shown in the left panels of Fig. 1. Interestingly, not only average and median age of *IDH*-mutated astrocytomas are very similar, but also the age distributions among both grades are virtually identical (Fig. 2).

Age has been determined to be a strong prognostic factor for malignant glioma. Recent analysis of the effect of age revealed no significant impact of age on survival in A II *IDH*mut and AA III *IDH*mut; however, a significant impact was observed in *IDH* wild-type astrocytomas [14]. Analysis of the age impact on survival in the present three series revealed no difference. Stratification of patients in four age groups, 18–29, 30–39, 40–49 and over 50 demonstrated a trend ($p = 0.067$; log-rank test) for patients over 50 exhibiting a poorer outcome (Fig. 3). Whether this is a truly tumor inherent effect is questionable in light of the increased mortality from a spectrum of other causes of patients over the age of 50. Nevertheless, the effect of age on the survival in patients with *IDH*-mutant astrocytoma is

lower than assumed from the previous series [4, 8, 9, 15] not stratified for this molecular hallmark.

Clinical course

The natural clinical course of gliomas cannot be determined any more as nearly all patients diagnosed with anaplastic WHO grade III glioma will have received post-surgical adjuvant therapy and a considerable fraction of patients with WHO grade II glioma does so, too. Thus the groups compared here are very heterogeneous with respect to treatment and therefore comparisons of survival time need to ignore the potential beneficial effect of therapy.

The effect of grading on survival was detectable among *IDH*-mutated astrocytomas but not as substantial as would be expected from the experience with WHO2007 graded astrocytomas. In the MD Anderson series there was no significant difference ($p = 0.432$; log-rank test) in overall survival (OS) between patients receiving the integrated diagnoses A II *IDH*mut and AA III *IDH*mut. Cases from TCGA ($p = 0.059$; log-rank test) and those from the Heidelberg series ($p = 0.093$) with the integrated diagnoses of A II *IDH*mut tended to fare better than those AA III *IDH*mut; however, the difference was not significant in each cohort. Median OS for all three groups combined was 3978 days (10.9 years) for A II *IDH*mut and 3404 days (9.3 years) for AA III *IDH*mut and the difference was also not significant ($p = 0.055$; log-rank test).

In fact, the difference in survival of A II *IDH*mut and AA III *IDH*mut in comparison to A II WHO2007 and AA III WHO2007 can be demonstrated on the TCGA series. While the effect of grading is not significant in the *IDH*-mutated astrocytomas ($p = 0.059$; log-rank test), the difference in A II WHO2007 and AA III WHO2007 ($p = 0.002$; log-rank test), including both *IDH*-mutant and *IDH* wild-type cases, is as marked as expected and matches well with other WHO graded series. Quite obvious is the initial strong drop in survivals of the AA III WHO2007 patients due to the tumors identified as GBMs by molecular means. As expected the slope of this survival curve approaches that for AA III *IDH*mut at longer survival times.

Kaplan–Meier diagrams for OS of patients with integrated diagnoses for the three studies and for WHO graded TCGA cases are shown in the right panels of Fig. 1.

Interestingly, a previous [5] as well as a more recent study by the German Glioma Net (GGN) also failed to see a significant difference in OS between *IDH*-mutated astrocytoma receiving WHO grades II and III [22]. The lack of grading impact on OS in those *IDH*-mutated astrocytomas nicely matches the observations by the MD Anderson, the Heidelberg and the TCGA series. Further, in a highly actual report based on exome sequencing of WHO grade II and WHO grade III patients from Japan as well as analysis of the low-grade glioma data provided by TCGA no substantial effect of WHO grade on overall survival in *IDH*-mutated gliomas was reported [19].

Implications for future diagnostic approach

Prior studies showing substantial survival difference between grade II and III astrocytoma included a mix of *IDH*-mutant and *IDH* wild-type cases, and in keeping with current thinking, these entities are best kept distinct, based on their biologic and clinical differences.

Accordingly, the results clearly indicate that current WHO grading lacks power in prognosticating the clinical course of *IDH*-mutant astrocytoma into distinct patient risk groups. We believe that there is insufficient evidence for the use of current morphological criteria (mainly mitotic activity) as the basis for the diagnosis of anaplasia with all clinical consequences that follow from this designation. The MD Anderson series has previously been analyzed for the impact of mitotic count on survival and there was no survival difference between *IDH*-mutated astrocytomas with single mitoses and those with 4 or more mitoses per 1000 tumor cells [14]. Following WHO 2007 criteria astrocytomas with 4 or more mitoses per 10 high power fields would be graded WHO III and patients would receive aggressive postoperative treatment. It appears plausible that identifying factors that define survival risk groups will require different parameters as compared to those applied in WHO2007.

In fact, it was previously shown that GBM IDH_{mut} exhibit clinical outcomes similar or slightly favorable to that of WHO grade III anaplastic astrocytomas without *IDH* mutation [6]. This raises the question whether *IDH*-mutant tumors with histologic features of GBM should receive a WHO grade III designation. It also raises the question whether the term GBM is appropriate for these tumors, which while conceivable from the historic point of view lacks a logical basis when looking at the genetics and the clinical outcome of these tumors.

Conclusions

The data show that *IDH*-mutant astrocytomas WHO grades II and III are much more similar in respect to age at presentation and overall survival than suggested by previous series not separated for *IDH* status. Our current grading algorithms are insufficient for differentiating between grades II and III in *IDH*-mutant astrocytoma.

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Fig. 1. Box-plots (left panels) and survival statistics (right panels). A II IDHmut in red, AA III IDHmut in blue and GBM IDHmut in black. Three upper pairs depict the IDH-mutant only series from MD Anderson, Heidelberg and TCGA after receiving an integrated diagnosis. The lower pair depicts the TCGA A II WHO2007 and A III WHO2007 without exclusion of IDH wild-type cases. Survival on X-axis in right panels is given in days

Fig. 2.
Age distribution of first tumor diagnosis of A II IDHmut (*red*) and AA III IDHmut (*blue*) of 1245 tumors of the combined MD Anderson, TCGA and Heidelberg series. *Plots* are normalized

Fig. 3.
Age-related survival (in days) in combined group of WHO II and III *IDH*-mutant from all three series

Table 1

Clinical data of 1360 tumors with integrated diagnosis included

Series	Integrated diagnosis	Number	Average age	Median age	Median OS	<i>p</i> value A II versus AA III
MD Anderson	A II IDHmut	132	37.6	36	<i>n</i> = 263	4104
	AA III IDHmut	131	37.1	35		3801
Heidelberg	A II IDHmut	437	38.8	37	<i>n</i> = 68	Not reached
	AA III IDHmut	324	39.1	37		5100
	GBM IDHmut	105	42.0	40		
TCGA	A II IDHmut	114	37.5	36	<i>n</i> = 221	2875
	AA III IDHmut	107	38.2	36		2052
	GBM IDHmut	10	40.9	42		

Survival data for the Heidelberg series was only available from 68 patients with astrocytomas

OS overall survival in days