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1p/19q codeletion and IDH1/2 mutation identified a subtype of anaplastic oligoastrocytomas with prognosis as favorable as anaplastic oligodendrogliomas

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Background. Anaplastic astrocytoma (AA), anaplastic oligoastrocytoma (AOA), and anaplastic oligodendroglioma (AO) are the major histological subtypes of World Health Organization grade III gliomas. More evidence suggests that AOA is unlikely to be a distinct entity, and re-evaluation of this issue has been recommended. In this study, we divided AOA into 2 subgroups, according to molecular biomarkers, and compared the survivals between them.

Methods. One hundred nine patients with histological diagnosis of anaplastic gliomas enrolled in the study. Molecular biomarkers evaluated included 1p/19q codeletion and IDH1/2 mutation. Kaplan-Meier plots were compared by log-rank method.

Results. There was no significant difference between AA and AOA with regard to the frequencies of biomarkers and survival plots. According to the status of biomarkers, AOA was classified into 2 subgroups (AOA1 and AOA2), for which Kaplan-Meier plots were significantly different ($P = .001$ for both progression-free survival [PFS] and overall survival [OS]). AOA1 with 1p/19q codeletion and/or IDH1/2 mutation showed similar Kaplan-Meier plots with AO ($P = .169$ for PFS and $P = .523$ for OS). AOA2 without either biomarker showed similar Kaplan-Meier plots with AA ($P = .369$ for PFS and $P = .271$ for OS). In addition, patients with AO and AOA1 had significantly longer PFS and OS than did patients with AA and AOA2 ($P < .001$ for both PFS and OS).

Conclusions. AOA is a heterogeneous group and can be divided into 2 subgroups with significantly different prognoses according to the status of 1p/19q and IDH1/2. This will be helpful in estimating patients' prognosis and guiding reasonable therapy for patients with anaplastic gliomas.

Keywords: anaplastic gliomas, 1p/19q, IDH1/2, prognosis, stratification.

Malignant gliomas are the most common primary intracranial neoplasm in adults. World Health Organization (WHO) grade III glioma is a heterogeneous group and is mainly classified into anaplastic astrocytoma (AA), anaplastic oligoastrocytoma (AOA), and anaplastic oligodendroglioma (AO). The accurate histological diagnosis of anaplastic glioma is of great importance for estimating patients' prognosis and guiding reasonable therapy but is always a subjective diagnosis, in particular for AOA.[1]

The diagnostic criteria, in particular for AOA, are highly subjective to interobserver variation. AOA is a mixture of astrocytic and oligodendroglial components, having no definite border with AA and AO. The European Organization for Research and Treatment of Cancer (EORTC) trial studied interobserver variation of the pathological diagnoses. With use of a review panel, 114 cases were classified by 9 independent pathologists. The panel reached a consensus on 52% of AO and in only 8% of the AOA.[1] Smith et al reviewed 162 cases and found unanimous agreement among 3 pathologists for histological subtype classification in 69% (36 of 52) of oligodendrogliomas, 13% (4 of 31) of mixed oligoastrocytomas, and 76% (60 of 79) of astrocytomas on the presence of 1p/19q codeletion in diffuse glioma.[2]

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More evidence suggests that AOA is unlikely to be a distinct entity, and re-evaluation of this issue was recommended. AOA is a heterogeneous group with considerable survival variant. Some studies found that AOA and AO are similar in prognosis and, therefore, often treated as one group.[3,4] On the contrary, several studies maintained that AA and AOA should be considered as one unit in grade III gliomas, according to their similar prognosis.[5,6] Furthermore, Park et al reported that the median survivals of AA, AOA, and AO were 29 months, 37 months, and 79 months, respectively. All the differences were significantly different ($P < .05$).[7] The reason for the contradictory results lies in the heterogeneity in AOA.

Concerning the subjectivity in pathological diagnoses and the heterogeneity of AOA in prognoses, this study was designed to stratify AOA based on molecular biomarkers. According to the status of chromosome 1p/19q and IDH1/2, AOA was divided into 2 distinct subgroups. The prognoses between them were compared.

Material and Methods

Patients

A total of 109 patients (71 male and 38 female) with histological diagnosis of primary supratentorial gliomas of grade III in Beijing Tiantan Hospital from May 2009 through December 2011 were enrolled in the study. All patients provided written informed consent for the current study, and the clinical study was approved by the Medical Ethics Committee of Capital Medical University. All specimens were independently re-evaluated by 2 experienced neuro-pathologists who were blinded to the clinical outcome of the patients, according to the 2007 WHO classification of the CNS tumors.[8] In case of a discrepancy, the 2 observers simultaneously reviewed the slides to achieve a consensus (Fig. 1). Patients who underwent needle biopsies before resection and/or prior adjuvant therapy (radiotherapy or chemotherapy) were excluded from the analysis. These were done to create a more uniform patient population, which could be propitious to the study.

Recorded Variables

The progression-free survival (PFS) was defined as the period from the first operation to the time of tumor recurrence or evidence of progression based on magnetic resonance imaging (MRI). Patients who were recurrence-free at last follow-up were considered as a censored event in analysis. Overall survival (OS) was defined as the period from the first operation to death or last follow-up. Patients who were still alive at last follow-up were considered as a censored event in analysis.

Treatment

All the gliomas in our institution were treated according to the National Comprehensive Cancer Network guidelines. Maximal tumor bulk resection while preserving the vital eloquent cortex was the principle goal during operation. Intraoperative subcortical electrical stimulation was performed when necessary. Extent of resection

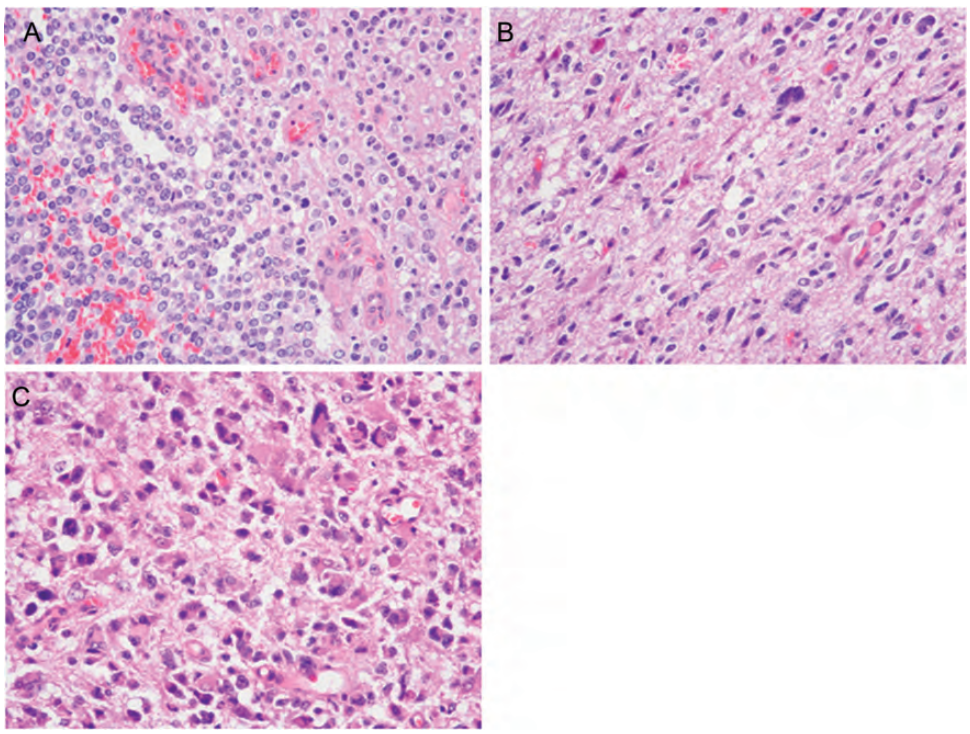

Fig. 1. Histopathological feature of WHO grade III gliomas, including anaplastic oligodendroglioma (A), anaplastic oligoastrocytoma (B), and anaplastic astrocytoma (C).

was assessed by the intraoperative ultrasound. Postoperative radiotherapy was routinely delivered to patients within 1 month after operation. The total dose was 60 Gy, which was divided into 30 daily fractions of 2 Gy each. Meanwhile, postoperative chemotherapy was given; the common course of chemotherapy was 4–6 cycles, which depended on the tolerance of toxic effect. The adjuvant chemotherapy drugs were mainly nimustine or temozolomide.

Detection of Deletion of 1p/19q by the Fluorescence In Situ Hybridization (FISH) Method

1p/19q codeletion was detected by FISH method, as was described previously.[9] The assessment and interpretation of FISH results were made according to guidelines defined by the SIOP Europe Neuroblastoma Pathology and Biology and Bone Marrow Group.[10] For each probe, >100 nonoverlapping nuclei were enumerated per hybridization. Tumors with >30% of nuclei showing DNA loss were defined as tumor with chromosomal loss.

IDH1/2 Sequence Analysis

Genomic DNA was isolated from snap-frozen tissue with use of the QIAmp DNA mini-kit, as described by the manufacturer (Qiagen). A fragment of 254 bp length spanning the catalytic domain of IDH1 including codon 132 was amplified using the sense primer IDH1 F: 5′-ACCAAATGGCACCATACG-3′ and the antisense primer IDH1 R: 5′-TTCATACCTTGCTTAATGGGG-3′. A fragment of 293 bp length spanning the catalytic domain of IDH2 including codon 172 was amplified using the sense primer IDH2 F: 5′-GCTGCAGTGGGA CCACTATT-3′ and the antisense primer IDH2 R: 5′-T GTGGCCTTGTACTGCAGAG′. Polymerase chain reaction (PCR) using standard buffer conditions, 30 ng of DNA, and GoTaq DNA Polymerase (TaKaRa, Japan) included 35 cycles with denaturing at 95°C for 30 s, annealing at 54°C for 45 s, and extending at 72°C for 50 s in a total volume of 25 μL. The PCR amplification product was sent to Beijing Tianyi Huiyuan Bioscience and Technology Incorporation for sequencing.

Statistical Analysis

Statistical analysis was performed using SPSS, version 13.0, for Windows (SPSS). Pearson's χ^2 test and Fisher's exact test were used to compare the frequencies between groups. Kaplan-Meier method was used for survival analysis. Probability value was obtained from 2-sided tests, with a statistical significance of $P < .05$.

Results

Basic Characteristics

The basic clinical characteristics of the patients in this study are summarized in Table 1. A total of 109 patients with primary grade III gliomas that were surgically treated in our center met the inclusion criteria. There were 71 men and 38 women. The mean age of this cohort was 44 ± 12 years, 72 (66.1%) aged <50 years and 37 (33.9%) aged ≥ 50. AA was pathologically confirmed in 40 patients (36.7%), AOA in 45 patients (41.3%), and AO in 24 patients (22.0%). The median follow-up period for all the 109 patients was 16.0 months (range, 1.0–32.0 months). A total number of 35 patients had died.

Table 1. Clinicopathological characteristics of 109 patients with WHO grade III glioma

Characteristic	No. of Patients (%)
Age (yrs)	
Mean	44 ± 12
Range	17–67
Sex	
Male	71 (65.1)
Female	38 (34.9)
Tumor resection	
GTR	79 (72.5)
STR	25 (22.9)
PR	5 (4.6)
Chemotherapy	
Yes	101 (92.7)
No	8 (7.3)
Radiotherapy	
Yes	99 (90.8)
No	10 (9.2)
Pathology	
AA	40 (36.7)
AOA	45 (41.3)
AO	24 (22.0)
1p/19q co-deletion	
Yes	43 (39.5)
No	64 (58.7)
N/A	2 (1.8)
IDH1/2 mutation	
Yes	42 (38.5)
No	56 (51.4)
N/A	11 (10.1)

Abbreviations: GTR, gross-total resection; N/A, not available; PR, partial resection; STR, subtotal resection.

Frequencies of 1p/19q Codeletion and IDH1/2 Mutation in AO, AOA, and AA (Fig. 2A)

FISH for chromosome 1p and 19q was available in 107 cases. Among them, 43 (40.2%) had 1p/19q codeletion (including 17 in AO, 17 in AOA, and 9 in AA). The frequencies of 1p/19q codeletion in AO, AOA, and AA were 70.8%, 38.6%, and 23.1%, respectively. The frequency of 1p/19q codeletion in patients with AO was significantly higher than that in patients with

AOA and AA ($P = .011$ and $P < .001$, respectively). However, the frequencies of 1p/19q codeletion between AOA and AA were not significantly different ($P = .127$).

DNA sequencing for IDH1/2 was available in 98 patients. Among them, 42 (42.9%) had IDH1/2 mutation (including 16 in AO, 13 in AOA, and 13 in AA). The frequencies of IDH1/2 mutation in AO, AOA, and AA were 76.2%, 31.7%, and 36.1%, respectively. The frequency of IDH1/2 mutation in patients with AO was significantly higher than that in patients with AOA and AA ($P = .001$ and $P = .004$, respectively). However, the frequencies of IDH1/2 mutation between AOA and AA were not significantly different ($P = .683$).

PFS and OS in AO, AOA, and AA (Table 2 and Fig. 3A and B)

Patients with AO had longer PFS than did those with AOA and AA. The median PFS among patients with AOA and AA was 17 and 12 months, respectively, which were significantly shorter than that for patients with AO ($P = .002$ and $P < .001$, respectively). However, the PFS among patients with AOA and AA were not significantly different ($P = .267$).

Patients with AO had longer OS than did those with AOA and AA. The median OS among patients with AOA and AA was 32 and 18 months, respectively, which were significantly shorter than that for patients with AO ($P = .098$ and $P = .018$, respectively).

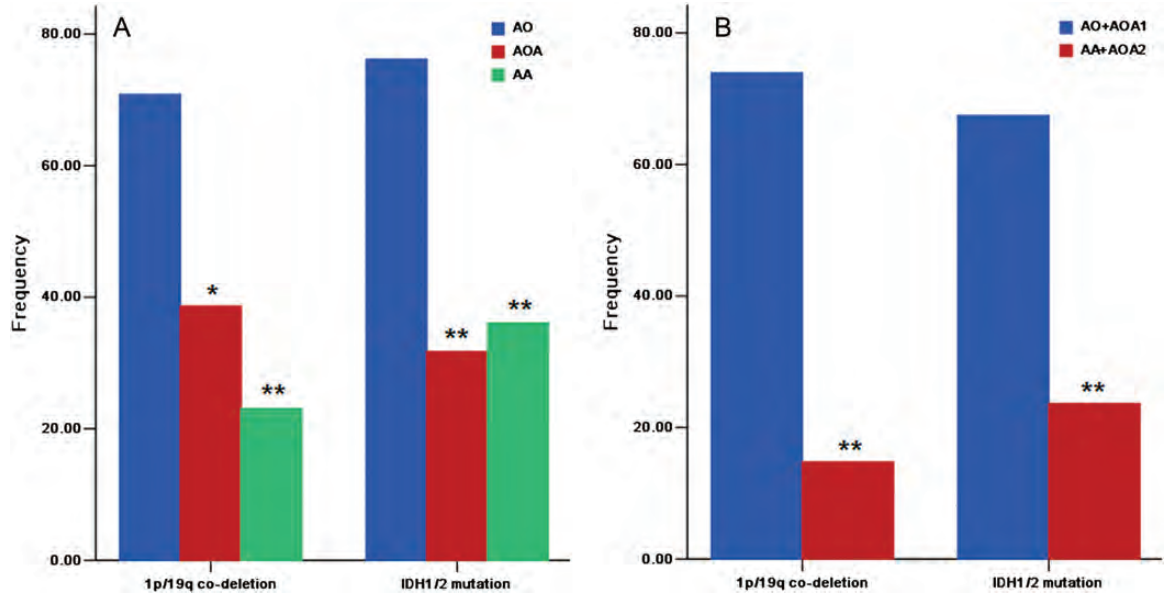

Fig. 2. Different frequencies of 1p/19q codeletion and IDH1/2 mutation between different groups. (A) AO shows significantly higher frequencies of 1p/19q codeletion and IDH1/2 mutation than do AOA and AA, and the frequencies between AOA and AA are not significantly different. (B) AO and AOA1 show significantly higher frequencies of 1p/19q codeletion and IDH1/2 mutation than do AA and AOA2. Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma.

Table 2. Progression-free survival (PFS) and overall survival (OS) among patients with anaplastic glioma in different groups

Characteristics	Median PFS (INR)	PFS rates				*P* value*	Median OS (INR)	Overall survival rates				*P*-value*
		6-mon	12-mon	18-mon	24-mon			6-mon	12-mon	18-mon	24-mon	
AA	12.0	82.5	49.7	39.6	39.6		18.0	100.0	79.3	48.2	48.2	
AOA	17.0	80.0	66.7	46.9	21.5		32.0	95.6	82.0	66.4	57.8	
AO	N/A	95.8	95.8	88.5	69.7	.001	N/A	100.0	95.8	91.0	77.2	.075
AOA1	24.0	100.0	90.5	69.1	34.5		32.0	100.0	100.0	93.8	84.4	
AOA2	10.5	62.5	45.8	27.5	20.6	.001	17.5	91.7	66.7	42.8	34.2	.001
AO + AOA1	N/A	97.8	93.3	79.9	60.3		32.0	100.0	97.8	88.9	80.5	
AA + AOA2	11.0	75.0	48.2	33.5	28.8	<.001	18.0	96.9	74.6	46.4	41.8	<.001

*There were significant differences between AA, AOA, and AO in terms of PFS ($P = .001$) and OS ($P = .075$). Patients with AO had longer PFS and OS than those with AOA or AA. However, the PFS or OS for patients with AOA and AA were not significantly different. There were significant differences between AOA1 and AOA2 in terms of PFS and OS. The difference between AO and AOA1 was not significant. The difference between AA and AOA2 was not significant either. Patients with AO + AOA1 had longer PFS and OS than those with AA + AOA2 ($P < .001$ for both). Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; OS, overall survival; PFS, progression-free survival.

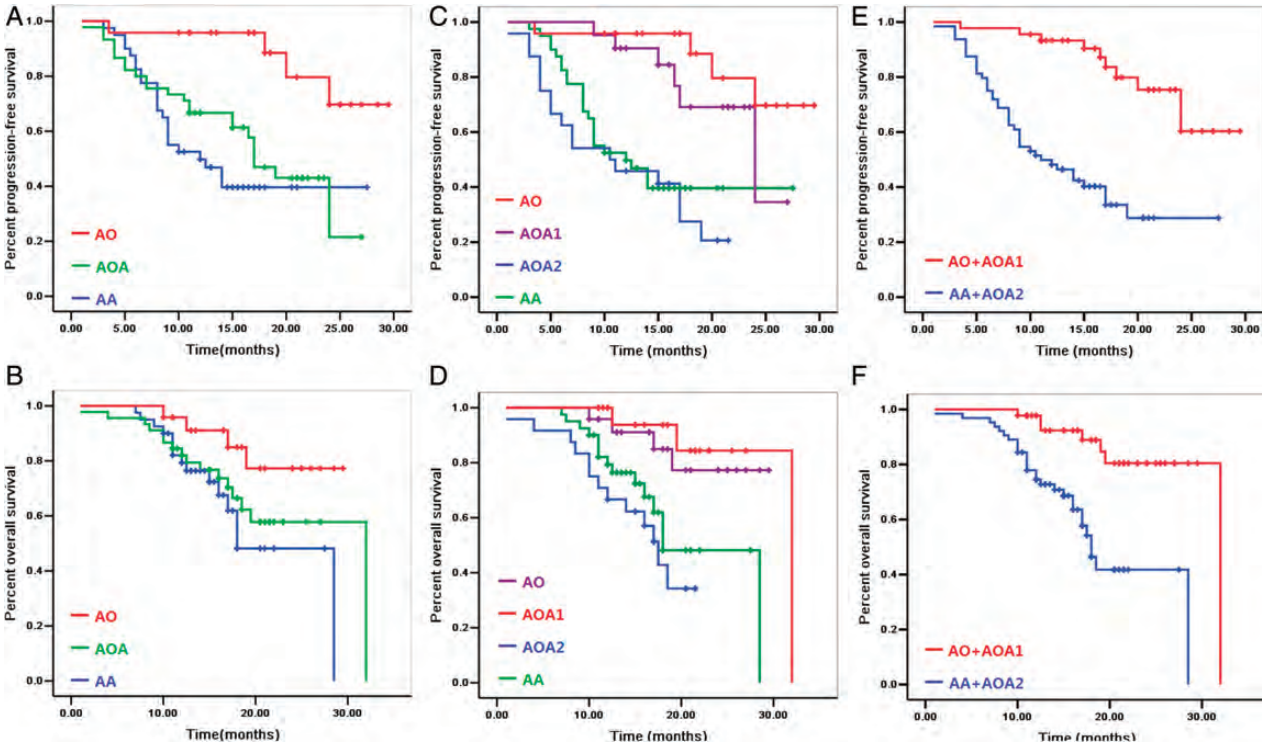

Fig. 3. (A and B) The prognoses of AA and AOA are not significantly different ($P = .267$ for PFS and $P = .405$ for OS, respectively). The prognoses of AA and AO are significantly different ($P < .001$ for PFS and $P = .018$ for OS, respectively). The prognoses of AO and AOA are significantly different ($P = .002$ for PFS and $P = .098$ for OS, respectively). (C and D) The prognoses of AOA1 and AOA2 are significantly different ($P = .001$ for both PFS and OS). The prognoses of AOA1 and AO are not significantly different ($P = .169$ for PFS and $P = .523$ for OS, respectively); the prognoses of AOA2 and AA are not significantly different either ($P = .369$ for PFS and $P = .271$ for OS, respectively). (E and F): Patients with AO and AOA1 had significantly longer PFS and OS than those with AA and AOA2 ($P < .001$ for both PFS and OS). Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; OS, overall survival; PFS, progression-free survival.

However, the OS among patients with AOA and AA was not significantly different ($P = .405$).

1p/19q Codeletion and IDH1/2 Mutation Were Correlated with Better Prognosis in Patients with Grade III Gliomas

1p/19q codeletion and IDH1/2 mutation were both correlated with longer PFS and OS among patients with grade III gliomas (data not shown). Patients with 1p/19q codeletion had longer PFS and OS than did those without 1p/19q codeletion ($P < .001$ for PFS and $P = .001$ for OS). IDH1/2 mutation was correlated with longer PFS and OS among patients with grade III gliomas ($P = .013$ for PFS and $P = .052$ for OS).

Stratification of AOA Based on Molecular Biomarkers (Tables 2 and 3, Figs. 2B and 3C–F)

AOA could be classified into 2 subgroups with different prognoses based on 1p/19q codeletion and IDH1/2 mutation. One subgroup with 1p/19q codeletion and/or IDH1/2 mutation was termed as AOA1, and the other one without either biomarkers was termed as AOA2.

Patients with AOA1 had significantly longer PFS than did those with AOA2 (Fig. 3C). The median PFS among patients with AOA1 was significantly longer than that among patients with AOA2 (24.0 months vs. 10.5 months; $P = .001$). The PFS among patients with AOA1 and AO were not significantly different (24.0 months vs. unavailable; $P = .169$). The PFS among patients with AOA2 and AA was not significantly different either (10.5 months vs. 12.0 months; $P = .369$).

Patients with AOA1 had significantly longer OS than did those with AOA2 (Fig. 3D). The median OS among patients with AOA1 was significantly longer than that among patients with AOA2 (32.0 months vs. 17.5 months; $P = .001$). The OS among patients with AOA1 and AO was not significantly different (32.0 months vs. unavailable; $P = .523$). The OS among patients with AOA2 and AA was not significantly different either (17.5 months vs. 18.0 months; $P = .271$).

AO and AOA1 exhibited significantly higher frequencies of 1p/19q codeletion and IDH1/2 mutation than did AA and AOA2 (Fig. 2B, $P < .001$ for both). The PFS among patients with AO and AOA1 was significantly longer than that among patients with AA and AOA2 (Fig. 3E, unavailable vs. 11.0 months, $P < .001$). Similarly, the OS among patients with AO and

Table 3. Univariate associations with survival among patients with grade III glioma

Factors	Median PFS (months)	*P* value	Median OS (months)	*P* value
Stratification				
AO + AOA1	N/A	<.001	32.0	<.001
AA + AOA2	12.0		18.0	
Histological subtypes				
AO	N/A	.001	N/A	.075
AOA	17.0		32.0	
AA	12.0		18.0	
Chemotherapy				
Yes	24.0	.089	32.0	.158
No	8.0		17.0	
Radiotherapy				
Yes	20.0	.527	32.0	.235
No	15.0		19.5	
Extent of resection				
GTR	24.0	.037	32.0	.046
Non-GTR	14.0		18.0	

Abbreviations: GTR, gross total resection; N/A, not available.

AOA1 was significantly longer than that among patients with AA and AOA2 (Fig. 3F, 32.0 months vs. 18.0 months, $P < .001$).

To control the influence of histological types, extent of surgical resection, chemotherapy, and radiotherapy on the stratification of grade III gliomas, Cox regression analyses were used for the adjustment of these factors. Log-rank analyses of these factors are shown in Table 3. Cox regression confirmed AO + AOA1 to be independently associated with longer PFS (odds ratio, 0.519; 95% confidence interval, 0.374–0.721; $P < .001$) and longer OS (odds ratio, 0.552; 95% confidence interval, 0.369–0.826; $P = .004$).

Discussion

The current WHO classification recognizes 3 histological types of grade III gliomas: including AA, AOA, and AO. AOA is a heterogeneous group with considerable survival variant. This heterogeneity might result from the subjectivity of pathological diagnoses of AOA. In consideration of necrosis that was of great significance in grading of oligdendroglial neoplasms, we excluded all the samples with necrosis.[6] In the present study, we found that AOA could be divided into 2 subgroups with significantly different prognoses according to the status of 1p/19q and IDH1/2. The subgroup with 1p/19q codeletion and/or IDH1/2 mutation had better prognosis, similar to AO, and the other subgroup without such genetic signatures had worse prognosis, similar to AA. Therefore, according to our results, AOA with 1p/19q codeletion and/or IDH1/2 mutation could be treated along with AO, and AOA without this genetic signature could be treated along with AA.

AOA Is a Heterogeneous Group with Considerable Survival Variant

In our study, we found that patients with AO had longer PFS and OS than did patients with AOA and AA, and the PFS or OS was not significantly different between AOA and AA. This was in accordance with the findings of Winger[5] and Miller.[6] However, there were conflicting findings about the prognoses of AOA. Tortosa et al found no significant difference between AO and AOA ($P = .26$), but AOA had significantly better prognosis than did AA ($P = .01$).[3] Similarly, Shirai et al found that AOA and AO had significantly better prognosis than did AA ($P = .01$ and $P < .01$, respectively), but the difference between AO and AOA was not significant ($P = .14$).[4] Furthermore, Park et al found that all the differences between AA, AOA, and AO were significant ($P < .05$).[7] These conflicting findings might result from the heterogeneity of AOA in respective of prognosis. These available evidences suggest that AOA is unlikely to be a distinct entity, and re-evaluation was recommended.[11]

One possible reason for the heterogeneity in AOA might be the disagreement among pathologists for the definition of oligoastrocytic gliomas.[1,2,12,13] As we know, there was no efficient diagnostic marker and the diagnostic criteria for AOA were highly subjective to interobserver variation. It was well established that the WHO criteria for the histological diagnosis of oligoastrocytoma include the recognition of neoplastic glial cells with convincing astrocytic and oligodendroglial phenotypes.[8] Oligoastrocytomas show an intimate mixture of both oligodendroglial and astrocytic tumor cells. However, there are also many tumors composed of cells with phenotypical characteristics intermediate to oligodendroglial and astrocytic differentiation.[8] The poor characterization of these cell lineages and a lack of reliable marker results in considerable subjectivity in histological evaluation, interobserver variability for oligoastrocytomas that was significantly higher than astrocytomas and oligodendrogliomas.[1,14,15] More objective histological criteria for the grade and lineage of gliomas are helpful.[16]

In the present study, we found that AA and AOA exhibit similar frequencies of 1p/19q codeletion and IDH1/2 mutation. Although the incidence of IDH1/2 mutation was lower, compared with those in the reports from Europe or America, it was similar to Jiang's result that the frequency of IDH1/2 mutation in Chinese AOA was 45.8%. Therefore, ethnic differences might partially explain it.[17–20] Although AOA and AA showed a lot of similarities in both clinical outcomes and molecular biomarker characteristics, it is still not safe to assume that they could be treated as a single unit, because AOA was a heterogeneous entity.

Stratification of AOA Based on Molecular Markers (Fig. 4)

1p/19q codeletion and IDH1/2 mutation were objective molecular markers for favorable prognoses in anaplastic

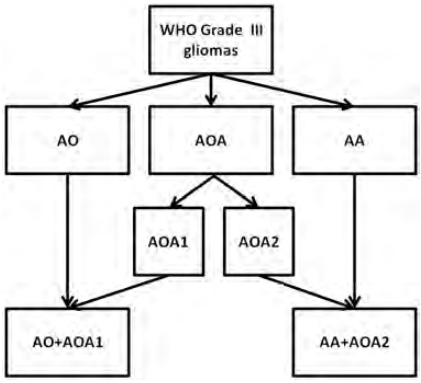

Fig. 4. AOA is a heterogeneous group and can be divided into 2 subgroups with significantly different prognoses according to the status of 1p/19q and IDH1/2. AOA1 has more favorable prognosis, similar to AO, and should be treated as mildly as AO. To the opposite, AOA2 has poorer prognosis, similar to AA, and should be treated with stricter regimens. Abbreviations: AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma.

gliomas, and they were used to divide AOA into 2 subgroups with significantly different prognoses. The stratification of AOA based on molecular biomarkers justified individual therapeutic regimens for AOA. AOA1 (subgroup of AOA with 1p/19q codeletion and/or IDH1/2 mutation) has more favorable prognosis and should be treated as mildly as AO, as was reported that anaplastic oligdenrogliomas could be treated without radiotherapy.[21] To the opposite, AOA2 (subgroup of AOA without any of these signatures) has poorer prognosis, similar to AA, and should be treated with stricter regimens. Cox regression analysis showed that AO and AOA1 was an independent factor to predict better prognosis. This stratification of AOA could help in estimating patients' prognosis and guiding reasonable therapy.

Study Limitation

Some limitations existed in this study. This series of patients was not large, and the median PFS and OS in several subgroups were not available because of the relatively short follow-up. In the future, we would expand our sample and re-evaluate this stratification with long-term follow-up survival in larger samples.

Conclusions

AOA is a heterogeneous group and can be divided into 2 subgroups with significantly different prognoses according to the status of 1p/19q and IDH1/2. This will be helpful in estimating patients' prognosis and guiding reasonable therapy for patients with anaplastic glioma.

Conflict of interest statement. None declared.

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