Allelic loss of 9p21.3 is a prognostic factor in 1p/19q codeleted anaplastic gliomas

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ABSTRACT

Objectives: We aimed to study the potential clinical relevance of 9p allelic loss, with or without copy number variation, in 1p/19q codeleted anaplastic oligodendroglial tumors (AOTs).

Methods: This study enrolled 216 patients with 1p/19q codeleted AOT. The prognostic value of 9p allelic loss was investigated using a French nation-wide prospective registry, POLA (prise en charge des tumeurs oligodendrogliales anaplasiques) and high-density single nucleotide polymorphism arrays. We validated our results using the Repository of Molecular Brain Neoplasia Data (REMBRANDT) dataset.

Results: The minimal common region of allelic loss in chromosome arm 9p was 9p21.3. Allelic loss of 9p21.3, detected in 41.7% of tumors, was associated with shorter progression-free and overall survival rates in univariate ($p = 0.008$ and $p < 0.001$, respectively) and multivariate analyses ($p = 0.009$ and $p = 0.009$, respectively). This finding was validated in the REMBRANDT dataset in univariate and multivariate analysis ($p = 0.01$ and $p = 0.01$, respectively).

Conclusion: Our study highlights a novel potential prognostic biomarker in 1p/19q codeleted AOT. Further prospective studies are warranted to investigate our finding. ***Neurology*® 2015;85:1325–1331**

GLOSSARY

AOT = anaplastic oligodendroglial tumor; **CN-LOH** = copy neutral loss of heterozygosity; **HR** = hazard ratio; **MCR** = minimal common region; **OS** = overall survival; **PCV** = procarbazine-CCNU-vincristine; **PFS** = progression-free survival; **POLA** = prise en charge des tumeurs oligodendrogliales anaplasiques; **REMBRANDT** = Repository of Molecular Brain Neoplasia Data; **RT** = radiotherapy; **WHO** = World Health Organization.

Anaplastic or World Health Organization (WHO) grade III oligodendroglial tumors (AOTs), including anaplastic oligodendrogliomas and anaplastic oligoastrocytomas, form a heterogeneous subgroup of diffuse gliomas in adults. So far, 3 major histomolecular subgroups with major clinical relevance have been individualized based on 2 molecular biomarkers: (1) 1p/19q codeleted AOT in approximately 80% of the cases, (2) non-1p/19q codeleted and *IDH*-mutated AOT in approximately 10% of the cases, and (3) non-1p/19q codeleted and *IDH* wild-type AOT in approximately 10% of the cases.[1,2] Of note, almost all 1p/19q codeleted AOTs are also *IDH1*/*IDH2* mutated and *TERT* promoter mutated.[3]

Patients with 1p/19q codeleted AOTs have better prognosis and better response to radiotherapy (RT) plus procarbazine-CCNU-vincristine (PCV) chemotherapy compared with their non-1p/19q codeleted counterparts.[4,5] However, in both studies, the median overall survival (OS) in the 1p/19q codeleted subgroup had a broad range of 95% confidence interval (from 6.4 to more than 12 years in one study and a 5-year OS rate from 60.3% to 86.4% in the other study),[4,5] suggesting that some patients would have a less favorable prognosis. Identification of novel biomarkers in this tumor subgroup would help to better stratify patients with 1p/19q codeleted AOT.

Although promising novel somatic mutations in *CIC* (capicua transcriptional repressor) and *FUBP1* (far upstream element binding protein 1) have been identified in 1p/19q codeleted

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AOT, their clinical significance remains unclear.[6] Additional prognostic markers are still needed to better stratify the largest group of patients with AOT (i.e., 1p/19q codeleted AOT).

We have recently shown that 9p allelic loss, including monoallelic loss (i.e., hemizygous deletion), monoallelic loss without copy number change (i.e., copy neutral loss of heterozygosity or acquired uniparental disomy [CN-LOH]), and biallelic loss (i.e., homozygous deletion), is frequent in AOT.[7] Since 1p/19q codeletion confers a homogeneous glioma phenotype, we have only analyzed AOT harboring this genomic aberration.[1] In the present study enrolling a larger number of patients, we addressed the prognostic value of 9p allelic loss in 1p/19q codeleted AOT from the POLA (prise en charge des tumeurs oligodendrogliales anaplasiques) Network, a French nationwide cohort prospectively enrolling all newly diagnosed patients with AOT. The clinical impact of 9p allelic loss has been validated using the publicly available Repository of Molecular Brain Neoplasia Data (REMBRANDT) dataset.[8]

METHODS After local diagnosis of newly (with no history of brain tumor) diagnosed AOT, patients were enrolled in the POLA registry. The tumor was then centrally reviewed and characterized for 1p/19q and *IDH* statuses.[7] Participating centers were invited to follow medical guidelines consisting of RT alone that was subsequently changed to RT plus PCV when the results of the European Organization for Research and Treatment of Cancer and the Radiation Therapy Oncology Group phase III clinical trials were updated.[4,5] However, participating centers were allowed to select other options (chemotherapy alone or RT plus chemotherapy).

We downloaded the clinical data from the REMBRANDT dataset at https://caintegrator.nci.nih.gov/rembrandt/legal.jsp on February 1, 2015.

Patients. From the POLA registry, 216 patients with a centrally reviewed diagnosis of newly diagnosed AOT were included in the present study. For all individuals, fresh-frozen tumor tissues were available for genomic and pathologic investigations.

From the REMBRANDT dataset, we used, as a validation cohort, 241 gliomas (WHO grades II and III) including 51 samples exhibiting 1p/19q codeletion.

Standard protocol approvals, registrations, and patient consents. All patients provided their written informed consent for molecular analysis. The study was approved by the ethics committee of the Hôpital Universitaire La Pitié-Salpêtrière.

Single nucleotide polymorphism array. DNA extraction was performed as previously reported.[8] Single nucleotide polymorphism (SNP) array hybridizations were outsourced to Integragen, as previously reported.[7] Two types of platforms were used: HumanCNV370-Quad and Human610-Quad from Illumina (San Diego, CA). Using these normalized $\log_2$(ratio) and B-allele frequency values, copy number abnormalities were identified with the SNP-FASST2 (fast adaptive states segmentation technique 2) segmentation algorithm implemented in the Nexus software. Single copy gains and losses were defined with $\log_2$(ratio) values of 0.25 and −0.25, respectively, while 2 or more than 2 copies of gains and losses were defined by $\log_2$(ratio) values of 0.7 and −1.1, respectively. A chromosome region was identified as allelic loss if ≥95% of the SNP probes in a DNA segment of at least 500 kb exhibited B-allele frequencies of ≥0.8 or ≤0.2. Allelic loss, with a copy number of 2, was considered to be CN-LOH. The 1p/19q codeletion was defined as loss of at least 90% of the probes mapped on 1p and 19q with concurrent chromosomes 1 and 19 centromeric breakpoints. Minimal common regions (MCRs) of gain and loss were identified using the cghMCR package (v1.18) by aligning samples based on chromosome segments defined by genes using the CNTools package (v1.22). Briefly, MCRs are defined as contiguous spans having at least a recurrence rate of 0.75 across samples. If 2 or more altered segments are separated by less than 500 kb, the entire region spanned by the segments is considered to be one altered span. In addition, to further confirm these results, we used an independent approach to reduce copy number dimensions of the SNP array set without losing information, using the CGHregions package (v1.24),[8] and we performed 10,000 permutations to obtain a false discovery rate p value from the log-rank p value related to every genomic aberration using the CGHtest package (v1.1).[9]

We further explored our findings using a validation cohort from the REMBRANDT dataset.[10] The CEL files from the Affymetrix GeneChip Human 100K SNP array set were downloaded from http://array.nci.nih.gov and clinical data were downloaded from https://caintegrator.nci.nih.gov/rembrandt/legal.jsp on February 1, 2015. We obtained total copy number from CEL files using the aroma.affymetrix package (v2.13.1) with the CRMAv2 algorithm.[11] When paired (tumor and germline) DNA was available, we estimated allele-specific copy number using parent-specific copy number segmentation (PSCBS package v0.43).[12] We performed allele-specific copy number segmentation in nonpaired samples (only tumor DNA) using the CalMaTe algorithm (v0.11).[13]

Statistical analyses. All analyses were performed with R-project (v3.0.2).[14] Comparisons of the clinical features of 1p19q codeleted AOT, with vs without 9p allelic loss, were performed with Fisher exact test for discrete variables, t test for continuous variables, and otherwise, the Mann–Whitney U test was used.

Survival analysis was performed using the *survival* package (v2.37-7) in R.[15] Progression-free survival (PFS) was calculated from initial diagnosis to tumor progression, death, or last follow-up. OS was calculated from initial diagnosis to death or last follow-up. Radiologic tumor progression was defined as any increase of contrast-enhancing tumor area more than 25% or an additional contrast-enhancing area. Clinical tumor progression was defined as significant deterioration of neurologic status. Survivals were plotted using the Kaplan-Meier method and compared using the log-rank test and Cox proportional hazard ratio. Variables with p value <0.2 in univariate analysis were included as covariates in the multivariate analysis: (1) age, as categorical variable, dichotomized at the median of the whole cohort, i.e., 50 years; (2) Karnofsky performance status, as categorical variable ≥70% vs <70%; and (3) treatments received, i.e., RT plus PCV, RT alone, RT plus temozolomide, and other chemotherapies alone. Interactions were not considered. Patients with no missing data were retained for multivariate analysis. The POLA cohort is prospective starting in 2009 with median follow-up of 2.5 years; thus, to allow more robust comparisons of medians, we have selected PFS and OS rate at 3 years.

In the REMBRANDT dataset analysis, the variables 1p/19q codeletion and phenotype (unknown, mixed, oligodendroglioma, and astrocytoma) were included as covariates in the Cox proportional hazard ratio. Interactions were not considered.

Statistical significance was defined as a p value <0.05; all tests were 2-sided.

RESULTS

Population. Two hundred sixteen patients with 1p/19q codeleted AOT enrolled in the POLA registry between 2009 and 2013 were included in the present study. The distribution of the main clinical features of the patients is summarized in table 1. The frequency of chromosome aberrations is represented in figure e-1 on the *Neurology*® Web site at Neurology.org. We used the REMBRANDT dataset as a validation series (241 gliomas, 51 harboring 1p/19q codeletion).

MCR of allelic loss in chromosome arm 9p MCR(9p). The MCR(9p) is the genomic region 9p21.3 (from 21957144 to 21999312) including *C9orf53*, *CDKN2A*, and *CDKN2B* (figure 1).

Overall, 9p21.3 allelic loss was detected in 90 of 216 patients (41.7%). The mechanisms of 9p21.3 allelic loss were CN-LOH, hemizygous deletion, and homozygous deletion in 44 cases (48.9%), 39 cases (43.3%), and 7 cases (7.8%), respectively (figure 1). Accordingly, in the REMBRANDT dataset, 9p21.3 allelic loss was detected in 21 of 51 1p/19q codeleted samples (41.1%). The mechanisms of 9p21.3 allelic loss in 1p/19q codeleted samples from the REMBRANDT dataset were CN-LOH, hemizygous deletion, and homozygous deletion in 12 cases (57.1%), 8 cases (38.1%), and 1 case (4.8%), respectively (data not shown).

Table 1 Clinical characteristics of patients exhibiting anaplastic oligodendroglial tumor without and with 9p21.3 allelic loss

Variable	1p/19q codeletion without 9p21.3 allelic loss (n = 126)	1p/19q codeletion with 9p21.3 allelic loss (n = 90)	p Value
Age, y, median (IQR)	47.7 (39.3–55.5)	53.3 (45.1–60.3)	0.005
Phenotype			0.8
Oligodendroglioma (%)	109 (86.5)	76 (84.4)	
Oligoastrocytoma (%)	17 (13.5)	14 (15.6)	
Surgery			0.4
Resection (%)[a]	115 (91.3)	78 (87.6)	
Biopsy (%)	11 (8.7)	11 (12.4)	
Karnofsky performance status, median (IQR)	90 (80–90)	90 (80–90)	0.4
Treatment			0.7
Radiotherapy + PCV	14	15	
Radiotherapy	44	32	
Chemotherapy	10	10	
Radiotherapy + TMZ	22	16	

Abbreviations: IQR = interquartile range; PCV = procarbazine-CCNU-vincristine; TMZ = temozolomide.
[a] Partial plus total gross surgical resection.

Clinico-molecular correlations. Patients with 1p/19q codeleted AOT with 9p21.3 allelic loss were older than their 9p21.3 intact counterparts ($p = 0.005$). The distribution of histologic phenotype, surgical procedure (biopsy vs surgery including partial and total gross resection), and medical treatments according to the 9p21.3 status was similar (table 1).

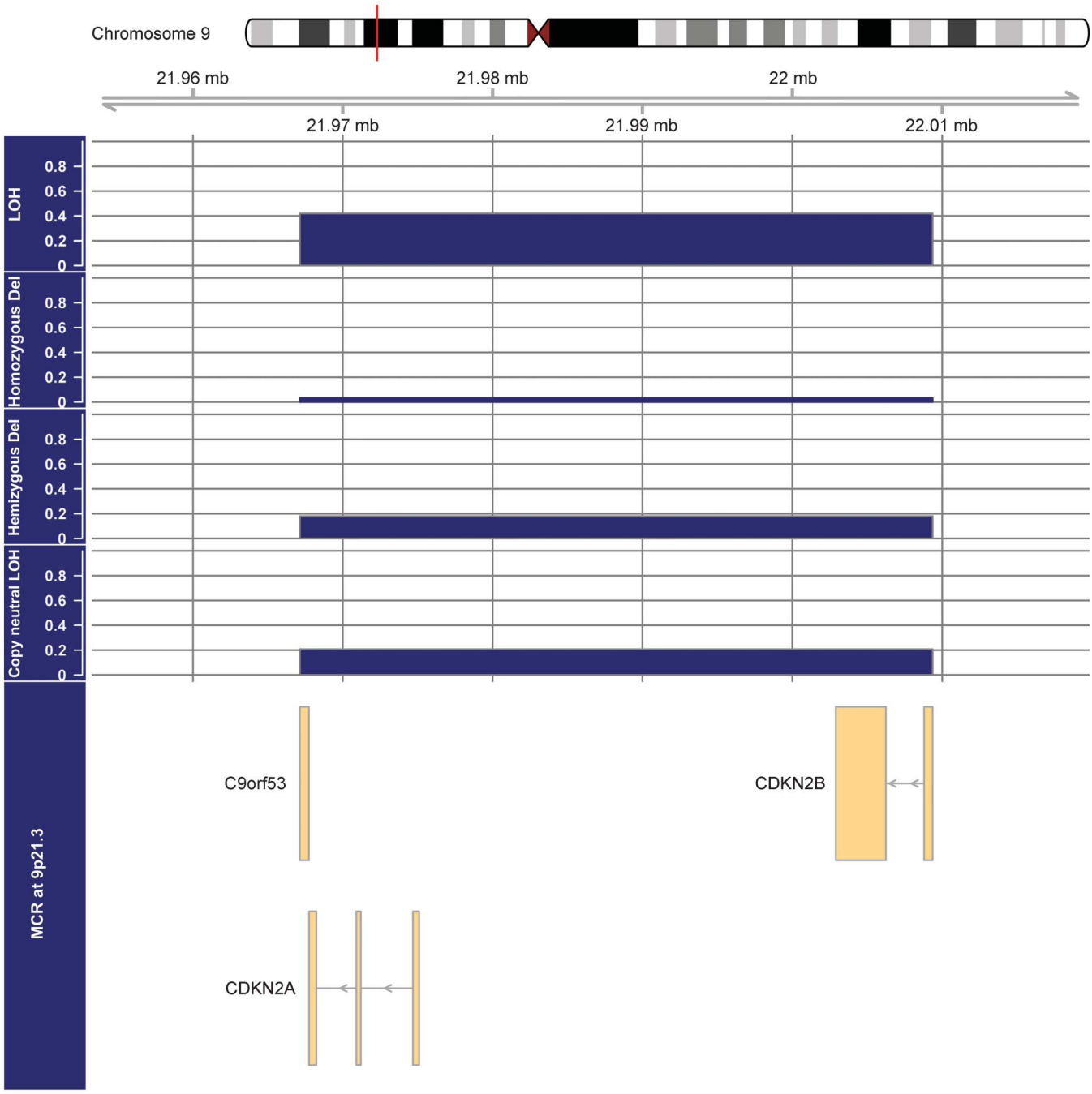
Allelic loss of 9p21.3 was associated with shorter PFS and OS in univariate analysis ($p = 0.008$ and $p < 0.001$, respectively) (table 2, figure 2, A and B). We have corrected log-rank p value in order to identify additional potential genomic aberrations associated with prognosis in 1p/19q codeleted AOT performing 10,000 permutations. Of note, the sole genomic alteration with a false discovery rate log-rank p value <0.05 was *CDKN2A* locus (figure e-1).

In multivariate analysis for PFS, 9p21.3 allelic loss was the sole factor associated with a shorter 3-year PFS rate (41% vs 71%, $p = 0.009$, hazard ratio [HR] = 2.2 [1.2–4]). For OS, 9p21.3 allelic loss was associated with shorter 3-year OS rate (70% vs 97%, $p = 0.009$, HR = 8.5 [1.7–42.4]) (table 2). Accordingly, in the REMBRANDT dataset, 9p21.3 allelic loss was also an independent prognostic marker associated with shorter 3-year OS rate in 1p/19q codeleted gliomas (44% vs 81%, $p = 0.01$, HR = 3.3 [1.2–8.9]) (table 3). Although it is in the setting of a large heterogeneous pathologic group that does not integrate molecular features, 9p21.3 allelic loss was also an independent prognostic biomarker in WHO grades II and III gliomas from the REMBRANDT dataset (table e-1).

DISCUSSION

Up to now, no additional genomic biomarker has been identified to stratify 1p/19q codeletion AOTs. The present study highlights 9p21.3 allelic loss (including homozygous deletion, hemizygous deletion, and CN-LOH) as an independent prognostic factor for PFS and OS in patients with 1p/19q codeleted AOT. The independent prognostic value of 9p21.3 allelic loss was validated in an independent cohort using the REMBRANDT dataset. In addition, patients exhibiting 1p/19q codeleted with 9p21.3 allelic loss tend to be older. The most frequent mechanism of 9p21.3 allelic loss was CN-LOH (48.9%) while the 9p21.3 hemizygous deletion represented 43.3% of the cases. These mechanisms of 9p21.3 allelic loss were also validated in the REMBRANDT dataset. This result may explain why this biomarker was not identified in previous studies analyzing exclusively copy number changes (i.e., comparative genomic hybridization, quantitative PCR) or allelic status (i.e., microsatellites analysis).

Figure 1 Minimal common region of allelic loss in a 1p/19q codeleted anaplastic oligodendroglial tumor harboring 9p21.3 allelic loss



The different panels show the frequencies of the different mechanisms of loss of heterozygosity (LOH). MCR = minimal common region.

The MCR(9p) encompasses *CDKN2A* and *CDKN2B*. We have recently shown in a smaller series of AOTs that 9p CN-LOH is associated with *CDKN2A* underexpression.[7] The *CDKN2A* locus encodes, by alternate splicing, for 2 major cell cycle–regulating proteins, p16INK4A and p14ARF. Protein p16INK4A inactivates cyclin-dependent kinases that phosphorylate the retinoblastoma protein, resulting in a G1 phase arrest, while p14ARF stabilizes p53 by inducing MDM2 degradation.[16] *CDKN2A* acts therefore as a "double" tumor suppressor gene and its silencing promotes oncogenesis and tumor growth in various cancers including diffuse gliomas. For instance, *CDKN2A* homozygous deletion is observed in 52% of glioblastomas, a more aggressive subtype of diffuse glioma.[17] The present study also supports a clinical value of 9p21.3 allelic loss in AOT.

A practical consequence is that patients with 1p/19q codeleted AOTs with 9p21.3 allelic loss should be monitored closely. While the very long survival of AOTs with 1p/19q codeletion alone raises the

Table 2 Prognostic value of clinical features and 9p23.1 allelic loss in 1p/19q codeleted anaplastic oligodendroglial tumors

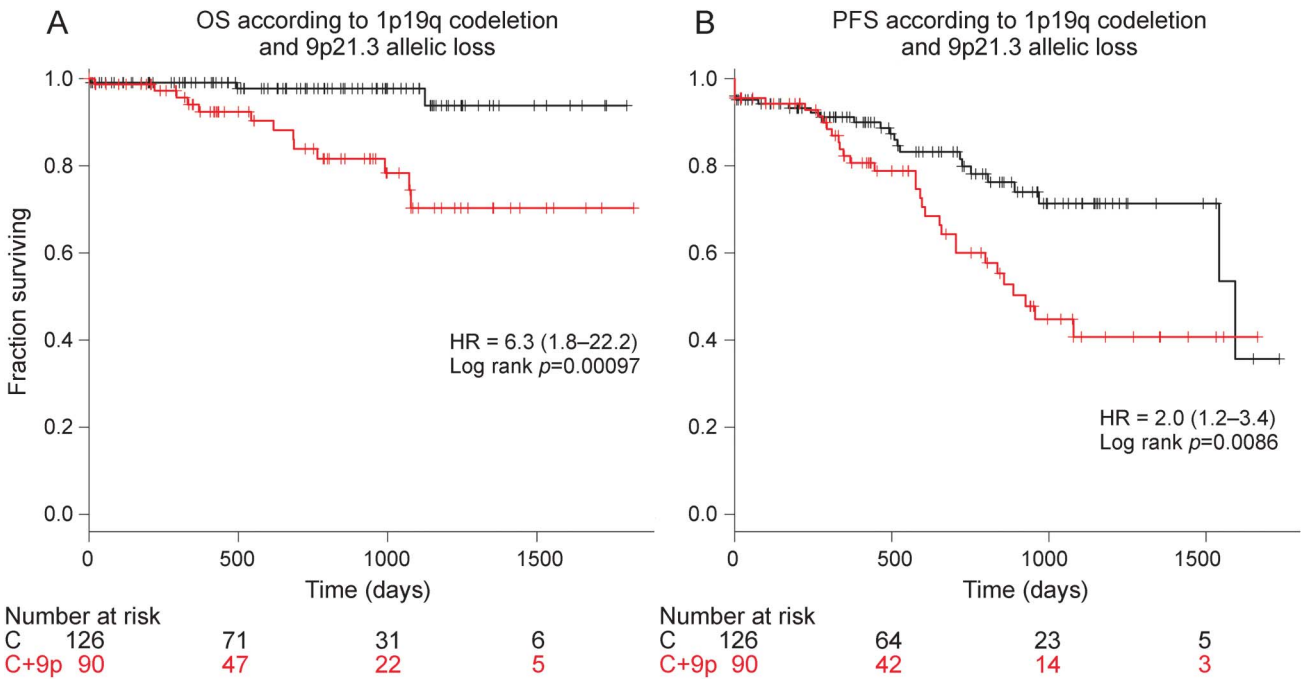
Variable	No.[a]	3-y PFS, %	*p* Value	HR (95% CI)	*p* Value	3-y OS, %	*p* Value	HR (95% CI)	*p* Value
Age			0.06		0.2		0.04		0.7
>50 y	104	48		1.4 (0.7–2.5)		76		1.2 (0.4–3.9)	
≤50 y	112	68				93			
KPS score			0.6				0.11		0.06
≥70	134	62				85		0.2 (0.03–1.1)	
<70	13	50				75			
Surgery			0.5				0.9		
Biopsy	22	55				82			
Resection[b]	193	58				86			
Phenotype			0.5				0.9		
AOD	185	85				85			
AOA	31	95				92			
Treatment			0.3				0.01		0.001
RT-PCV	29	75				100		0.29 (0.1–0.6)	
RT	76	64				86			
CT	20	62				91			
RT-TMZ	38	32				73			
9p23.1 allelic loss			0.008		0.009		0.0009		0.009
Yes	90	41		2.2 (1.2–4)		70		8.5 (1.7–42.4)	
No	126	71				97			

Abbreviations: AOA = anaplastic oligoastrocytoma; AOD = anaplastic oligodendroglioma; CI = confidence interval; CT = chemotherapy; HR = hazard ratio; KPS = Karnofsky performance status; OS = overall survival; PCV = procarbazine-CCNU-vincristine; PFS = progression-free survival; RT = radiotherapy; TMZ = temozolomide.

[a] Size number may not total 216 because of missing data.

[b] Partial plus total gross surgical resection.

Figure 2 Kaplan-Meier curves in 1p/19q codeleted anaplastic oligodendroglial tumor according to 9p21.3 loss



Progression-free survival (PFS) (A) and overall survival (OS) (B) according to 9p23.1 allelic status. C = 1p/19q codeletion without 9p21.3 allelic loss; C+9p = 1p/19q codeletion with 9p21.3 allelic loss; HR = hazard ratio.

Table 3 Prognostic value of clinical features and 9p23.1 allelic loss in 1p/19q codeleted gliomas from the REMBRANDT dataset

Variable	No.	3-y OS, %	*p* Value	HR (95% CI)	*p* Value
9p23.1 allelic loss			0.01		0.01
Yes	21	44		3.3 (1.2–8.9)	
No	30	81			
Phenotype			0.2		0.9
Unclassified	5	33		1 (0.6–1.6)	
Mixed	2	100			
Oligo	25	58			
Astro II and III	16	58			

Abbreviations: Astro II and III = WHO grades II and III astrocytomas; CI = confidence interval; HR = hazard ratio; Oligo = oligodendroglioma; OS = overall survival.

question of delaying RT to preserve long-term cognitive functions, this strategy could be questionable in patients exhibiting 1p/19q codeleted AOTs with 9p21.3 allelic loss.

Additional studies investigating the significance of the 9p21.3 allelic loss in patients with 1p/19q codeleted AOT are warranted to investigate and validate our findings. Indeed, although our study is based on a multicentric prospective cohort, the follow-up of patients remains short.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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