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Favorable Long-Term Outcomes of Chordoid Meningioma Compared With the Other WHO Grade 2 Meningioma Subtypes

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BACKGROUND: WHO grade 2 meningiomas, including atypical, chordoid, and clear cell subtypes, form a heterogenous group of meningiomas with varying aggressiveness and clinical behavior.

OBJECTIVE: To demonstrate the differences of clinical-histopathological characteristics and long-term outcomes among these 3 subtypes.

METHODS: A total of 609 consecutive patients diagnosed with WHO grade 2 meningiomas (543 atypical meningiomas [AMs], 36 chordoid meningiomas [CMs], and 30 clear cell meningiomas [CCMs]) from 2010 to 2018 were enrolled in this study. We compared the clinical-histopathological characteristics and long-term outcomes in these 3 subtypes and assessed survival differences among the subtypes. Targeted panel sequencing of meningioma-relevant genes was performed in the cases of CM.

RESULTS: The patients with CCM were significantly younger than those with AM ($P < .001$) and CM ($P = .016$). CMs were more likely to receive gross total resection than AMs and CCMs ($P = .033$). The Ki-67 index was lower ($P < .001$) while the progesterone receptors-positive rate was higher ($P = .034$) in CM than in AM and CCM. Importantly, survival analysis demonstrated that CM had better progression-free survival ($P = .022$) and overall survival ($P = .0056$) than non-CM tumors. However, the PFS of CM was still worse than WHO grade 1 meningiomas ($P < .001$). Alterations in *NF2* (20.6%) and *KMT2C* (26.5%) were associated with poorer PFS in CM ($P = .013$ for *NF2*; $P = .021$ for *KMT2C*).

CONCLUSION: Patients with CM had better long-term postoperative outcomes than the other WHO grade 2 subtypes. A lower Ki-67 index, higher PR status, higher extent of resection, and lower frequency of *NF2* alteration might contribute to favorable clinical outcomes of CM.

KEY WORDS: WHO grade 2 meningioma, Chordoid meningioma, Atypical meningioma, Clear cell meningioma, Progesterone receptor

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Meningioma, originating from the arachnoid cells, is the most common intracranial neoplasms and accounts for around 39.0% of primary central nervous system (CNS) tumors.[1] Meningiomas can be classified into 3 malignancy grades and 15 histological subtypes according to the newest 2021 World Health Organization (WHO) criteria of CNS tumors.[2] Around 80% of meningiomas are WHO grade 1, accompanied with benign behaviors. Approximately 20% are WHO grade 2 and 3 characterized by aggressive clinical features and frequent tumor recurrence.

WHO grade 2 meningiomas, including atypical meningioma (AM), chordoid meningioma (CM), and clear cell meningioma (CCM), are the category that is clinically problematic because of relatively large case volume, highly heterogenous clinical behaviors, and controversy

ABBREVIATIONS: AM, atypical meningioma; **ART,** adjuvant radiotherapy; **CCM,** clear cell meningioma; **CM,** chordoid meningioma; **CNS,** central nervous system; **EANO,** European Association of Neuro Oncology; **GTR,** gross total resection; **KPS,** Karnofsky performance score; **OS,** overall survival; **PFS,** progression-free survival; **PR,** progesterone receptor; **STR,** subtotal resection; **Vim,** vimentin; **WHO,** World Health Organization.

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in optimal management. AM is the most common grade 2 subtype, accounting for approximately 15% to 20% of all meningiomas, and has been by far the most extensively investigated grade 2 meningiomas.[3] CM is a rare subtype of WHO grade 2 meningiomas and only accounts for 0.32% to 1.0% of all meningiomas.[4-6] CM is histologically characterized by cords of eosinophilic, often vacuolated cells in an abundant mucoid matrix. CCM accounts for only 0.2%–0.8% of all meningiomas.[7,8] CCM is histologically characterized by sheets of rounded or polygonal clear cells and perivascular and interstitial collagen. Current literature regarding CM and CCM consists of isolated case reports and a small number of institutional series. To the best of our knowledge, only 22 studies with 423 CM cases have been reported until now[4-6,9-27] while less than 20 studies reported the outcomes of CCM. Owing to the limited case numbers of CM and CCM, few studies have comprehensively investigated the clinical, pathological, and prognosis differences among these 3 histological subtypes of grade 2 meningiomas.[26,28]

In this study, we systematically analyzed and compared the clinical-histopathological characteristics and long-term outcomes of 609 patients diagnosed with WHO grade 2 meningiomas at a single neurosurgical center. Outcome difference between CM and non-CM grade 1 and 2 tumors was also investigated.

METHODS

Study Ethics

This study was approved by the Human Subjects Institutional Review Board in our hospital and omitted the consent process because of the retrospective nature of the study.

Patient Population and Clinical Data

Five hundred forty-three patients with AM, 36 with CM, and 30 with CCM , who were treated at our hospital from 2010 to 2018, were identified and included in this study. The inclusion criteria were as follows: (1) Patients were pathologically diagnosed as AM, CM, or CCM and (2) clinical, pathological, and follow-up information was available. For outcome comparison, we also included 746 WHO grade 1 meningiomas whose follow-up information was already available from other studies conducted at our hospital during the same period. Clinical characteristics, including sex, age at diagnosis, tumor location, symptom duration, and extent of resection, were extracted from the medical records. Tumor location was categorized as nonmidline convexity, parasagittal/falx, skull base, and spine. Symptom duration was defined as the time from symptom onset to hospitalization. Simpson grades were confirmed by postoperative MRI. Simpson grades I to III and Simpson grades IV and V were classified as gross total resection (GTR) and subtotal resection (STR), respectively.

Histopathological Review

Pathological diagnosis was reviewed according to the 2016 WHO classification criteria. Two experienced pathologists (Dr Chen and Dr Wang) reviewed the sections. Progesterone receptor (PR) and Ki-67 that were part of routine pathological diagnostic markers at our center were stained with immunohistochemistry and reviewed. The Ki-67 index was obtained by counting 500 to 1000 tumor cells in 10 consecutive high-power fields and calculating the percentage of Ki-67 immunopositive cells **(Supplemental Digital Content 1**, **Figure 1A and B**, http://links.lww.com/NEU/D523). PR status was categorized as negative and positive based on the presence of immunopositive cells (negative = 0%; positive ≥1%) **(Supplemental Digital Content 1**, **Figure 1C and D**, http://links.lww.com/NEU/D523).

Follow-up

The last follow-up dated on October 30, 2021. Postoperatively, patients were followed up through phone or outpatient service according to the 2016 meningioma EANO guidelines.[29] Recurrence or progression was confirmed by enhanced T1WI MR images. Death was referred to as death of tumor progression. Progression-free survival (PFS) was defined as the time from surgery to tumor recurrence or progression. In the case of recurrent tumors, PFS was the time from surgery to tumor rerecurrence or reprogression. Overall survival (OS) was defined as the time from surgery to death.

Targeted Sequencing

Next-generation sequencing (NGS) was performed on CMs. The protocol was described previously.[30] Two samples failed the DNA quality control, and NGS was performed for the remaining 34 CM samples. The process of NGS is shown in **Supplemental Digital Content 2**, http://links.lww.com/NEU/D524.

Statistical Analysis

Statistical analysis was performed using R software (version 3.4.1). The R packages, including "foreign," "compareGroups," "glue," "survival," "survminer," "ggplot2," "tidyverse," "ggpubr," were used in this study. The Student *t*-test and Mann-Whitney *U* test were used to compare continuous variables with normal distribution and skewed distribution, respectively. The χ^2 test was used to compare categorical variables. The Kaplan-Meier method and Log-rank test were used to evaluate PFS and OS, respectively. Univariate and multivariate Cox regression analyses were used to identify independent predictors of tumor progression. A 2-sided *P*-value < .05 was defined as statistically significant.

RESULTS

Clinicopathological Characteristics Comparisons Between Different Subtypes

In our cohort, the clinical characteristics are summarized in Table 1. No significant gender difference was observed among the 3 subtypes ($P = .486$). The mean age of patients with CCM was significantly less than that of AM ($P < .001$) and CM ($P = .016$), and patients with CM tended to be younger than patients with AM ($P = .051$) (Figure 1A-1C). CCM had a significant predominance of spinal location ($P < .001$). AMs were more

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TABLE 1. Clinical Characteristics of the 3 Subtypes of WHO Grade 2 Meningiomas

Subtypes	ALL (609)	Atypical (543)	Chordoid (36)	Clear cell (30)	*P* (overall)	*P* (AM vs CM)	*P* (AM vs CCM)	*P* (CM vs CCM)
Age	54.09 (13.63)	55.11 (13.00)	49.78 (13.28)	40.73 (17.17)	<.001***	.051	<.001***	.016*
Sex					.486	.748	.748	1.000
Male	310 (50.90%)	281 (51.75%)	16 (44.44%)	13 (43.33%)				
Female	299 (49.10%)	262 (48.25%)	20 (55.56%)	17 (56.67%)				
Tumor location					<.001***	.074	<.001***	.008**
Convexity	228 (37.44%)	209 (38.49%)	15 (41.67%)	4 (13.33%)				
Parasagittal	154 (25.29%)	148 (27.26%)	4 (11.11%)	2 (6.67%)				
Skull base	212 (34.81%)	180 (33.15%)	16 (44.44%)	16 (53.33%)				
Spinal or jugular foramen area	15 (2.46%)	6 (1.10%)	1 (2.78%)	8 (26.67%)				
Symptom					.365	.598	1.000	.598
Headache	175 (28.74%)	155 (28.55%)	8 (22.22%)	12 (40%)				
Weakness and numbness	100 (16.42%)	92 (16.94)	7 (19.44%)	5 (16.67%)				
Seizure	59 (9.69%)	53 (9.76%)	5 (13.89%)	1 (3.33%)				
Dizziness	60 (9.85%)	56 (10.31%)	3 (8.33%)	1 (3.33%)				
Visual/hearing/speech disturbance	88 (14.45%)	72 (13.26%)	10 (27.78%)	6 (20%)				
Facial paralysis	14 (2.30%)	12 (2.21%)	1 (2.78%)	1 (3.33%)				
Cognitive decline	14 (2.30%)	14 (2.58%)	0	0				
Memory loss	12 (1.97%)	12 (2.21%)	0	0				
Asymptomatic	83 (13.63%)	77 (14.18%)	2 (5.56%)	4 (13.33%)				
Symptom duration	6.34 (13.96)	6.07 (13.83)	6.21 (8.10)	11.45 (20.16)	.121	.998	.100	.282
KPS	90 (70-100)	90 (70-100)	80.0 (80-100)	90 (70-100)	.660	.636	.708	.636
Extent of resection					.011*	.033*	.796	.033*
GTR (Simpson I-III)	520 (85.39%)	460 (84.71%)	35 (97.22%)	25 (83.33%)				
STR (Simpson IV-V)	89 (14.61%)	83 (15.29%)	1 (2.78%)	5 (16.67%)				
Recurrent status					.022*	.046*	.433	.421
De novo	446 (73.23%)	389 (71.64%)	33 (91.67%)	24 (80.00%)				
Recurrent	163 (26.77%)	154 (28.36%)	3 (8.33%)	6 (20.00%)				

GTR, gross total resection; KPS, Karnofsky performance score; STR: subtotal resection.

frequently located in the parasagittal/falx region (27.26%), and CMs were more common in the nonmidline convexity (41.67%). No symptom duration difference was observed among the 3 tumor subtypes (P = .121) (Figure 1D-1F). The median preoperative KPS was 90 (range, 60-100), and there was no preoperative KPS difference among the 3 subtypes (P = .660). CMs were more likely to be removed with GTR compared with their counterparts (both P = .033). No difference on the extent of resection was observed between AMs and CCMs (P = .796). The proportion of *de novo* CM patients was significantly higher than patients with AMs (P = .046). However, the difference between CM and CCM was not significant (P = .069). The immunohistochemical characteristics are summarized in Table 2. The Ki-67 index of CM was significantly lower than that of AM (P < .001). It was also lower than that of CCM, although not statistically significant (P = .076). No difference in the Ki-67 index was observed between AMs and CCMs (P = .198) (Figure 1G-1I). PR-positive expression was more frequent in CM compared with AM (P = .015), but was not different from CCM.

Long-Term Follow-up Outcomes

During the mean follow-up period of 75.53 ± 31.76 (median: 74.25, range: 34.50-152.75) months, 231 patients were lost. The remaining 378 patients (320 AMs, 34 CMs, 24 CCMs) with detailed follow-up information were enrolled for further survival analysis. A total of 217 patients undertook postoperative radiation therapies, including 188 AMs (58.75%), 15 CMs (44.12%), and 14 CCMs (58.33%). The fraction of having adjuvant radiotherapy (ART) was not significantly different between the 3 subtypes (P = .259). Gamma Knife was applied in 32 patients, including 29 AMs (90.63%) and 3 CCMs (9.37%). The remaining 185 cases received conventional fractionated beam radiotherapy, including 159 AMs (85.94%), 15 CMs (8.11%), and 11 CCMs (5.95%). For conventional beam radiotherapy, the mean total dose was 56.3 ± 2.2 Gy (range: 30-60 Gy). For Gamma Knife treatment, the prescription dose was 14.0 Gy at 50% and 28.0 Gy at 100%.

A total of 137 patients (36.24%), including 121 AMs (37.81%), 7 CMs (20.59%), and 9 CCMs (37.5%), experienced tumor recurrence during the follow-up, and 95 patients (25.13%), including 87 AMs (27.19%), 2 CMs (5.88%), and 6 CCMs (25.00%), died of tumor progression (Table 3). The relapse rates were not statistically different among the 3 subtypes (P = .138) while the mortality rate of CM was significantly lower than that of AM (P = .036) and CCM (P = .038).

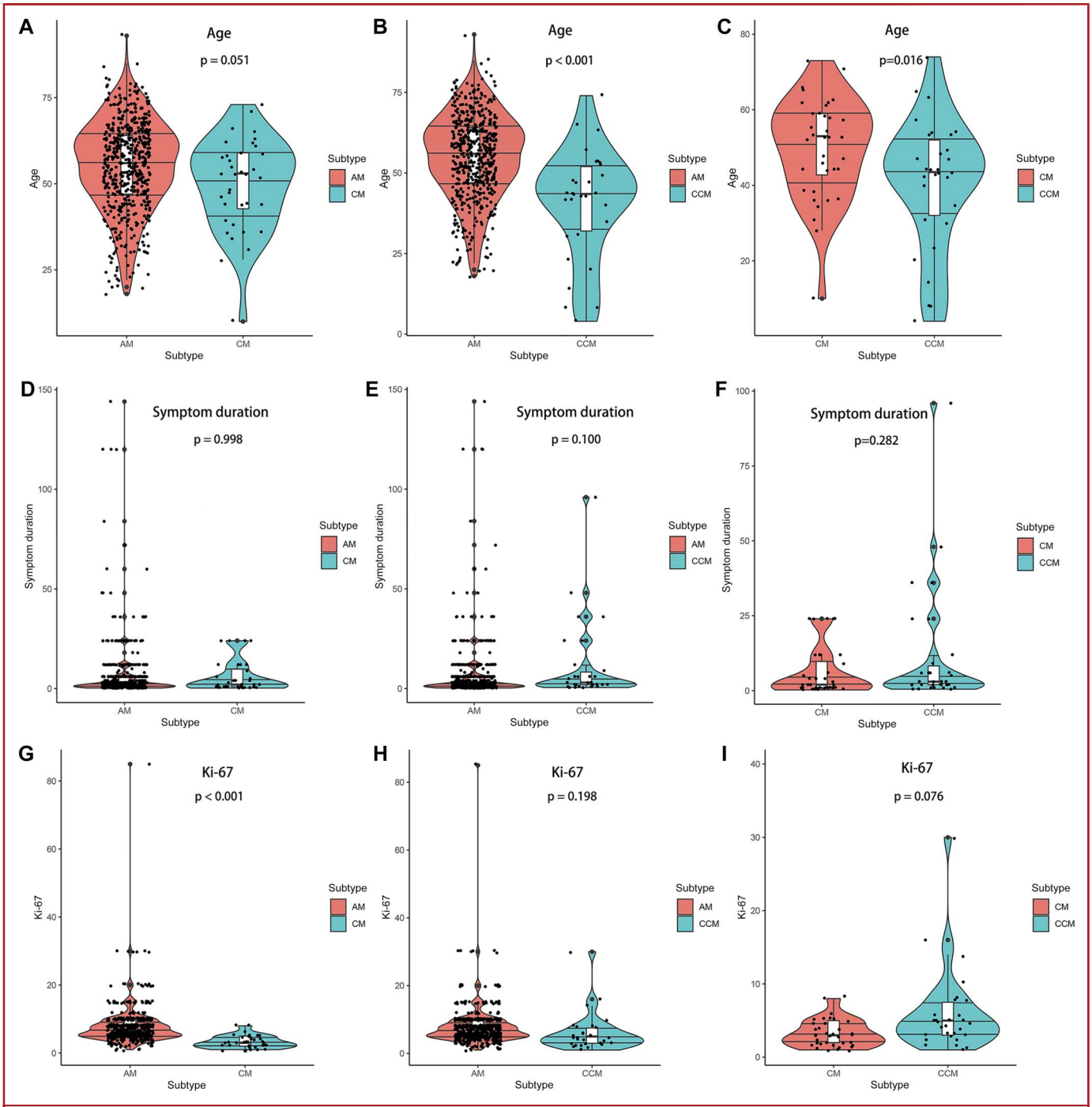

FIGURE 1. *Age, symptom duration, and Ki-67 index comparisons between AM, CM, and CCM.* **A-C**, *Violin plot of age of diagnosis between AM and CM* **A**, *AM and CCM* **B**, *and CM and CCM* **C**. **D-F**, *Violin plot of symptom duration between AM and CM* **D**, *AM and CCM* **E**, *and CM and CCM* **F**. **G-I**, *Violin plot of Ki-67 index between AM and CM* **G**, *AM and CCM* **H**, *and CM and CCM* **I**. *AM, atypical meningioma; CCM, clear cell meningioma; CM, chordoid meningioma.*

Survival Analysis Comparisons

The survival analysis demonstrated that CM had better PFS than AM ($P = .019$) (Figure 2A). A tendency of increased PFS was also found with CM compared with CCM ($P = .19$) (Figure 2B). However, no PFS difference was observed between AM and CCM ($P = .43$) (Figure 2C). We, therefore, divided the patients into the

TABLE 2. Histopathological Characteristics of Different Subtypes of WHO Grade 2 Meningiomas

Subtypes	ALL (609)	Atypical (543)	Chordoid (36)	Clear cell (30)	*P* (overall)	*P* (AM vs CM)	*P* (AM vs CCM)	*P* (CM vs CCM)
Ki-67	7.36 (5.28)	7.70 (5.28)	3.25 (1.86)	6.03 (5.72)	<.001***	<.001***	.198	.076
PR					.034*	.015*	.298	.365
Negative	352 (57.89%)	323 (59.48%)	14 (38.89%)	15 (50.00%)				
Positive	256 (42.11%)	220 (40.52%)	22 (61.11%)	15 (50.00%)				
EMA					.435	.868	.868	1.000
Negative	83 (13.63%)	71 (13.06%)	7 (19.44%)	5 (16.67%)				
Positive	526 (86.37%)	472 (86.92%)	29 (80.56%)	25 (83.33%)				
Vim					1.000	1.000	1.000	1.000
Negative	2 (0.33%)	2 (0.37%)	0 (0%)	0 (0%)				
Positive	607 (99.67%)	541 (99.63%)	36 (100%)	30 (100%)				

PR, progesterone receptor; Vim, vimentin.

CM and non-CM (AM and CCM combined) groups for further survival analysis. Our results demonstrated that patients with CM had a significantly better PFS than non-CM grade 2 patients (P = .02) (Figure 2D). We next enrolled 746 WHO grade 1 meningiomas, including 188 fibrous, 149 psammomatous, 97 meningothelial, 93 angiomatous, 87 microcystic, 61 secretory, 54 transitional, 14 lymphoplasmacyte-rich, and 3 metaplastic subtypes, for PFS comparisons. When compared with these grade 1 tumors, the PFS of CM (P < .001) (Figure 2E) and non-CM WHO grade 2 meningiomas (P < .001) (Figure 2F) was significantly shorter.

Compared with AM (P = .005) (Figure 3A) and CCM (P = .036) (Figure 3B), the OS of CM was significantly longer. However, no OS difference was observed between AM and CCM (P = .57) (Figure 3C). The longer OS of CM was maintained when compared with non-CCM combining AM and CCM (P = .006) (Figure 3D).

Prognostic Factors of WHO Grade 2 Meningiomas

Age and Ki-67 were converted to binary categorical variables using a relapse-related receiver operation curve. The optimal

TABLE 3. Long-Term Outcomes of the 3 Subtypes of WHO Grade 2 Meningioma

			Nonchordoid (N = 344)						
Subtypes	ALL N = 378	Chordoid N = 34	Atypical N = 320	Clear cell N = 24	*P* (overall)	*P* (AM vs CM)	*P* (AM vs CCM)	*P* (CM vs CCM)	*P* (CM vs Non-CM)
Follow-up duration (mo)	75.53 (31.76)	94.60 (31.21)	73.25 (30.32)	93.81 (43.18)					
Adjuvant radiotherapy					.259	.435	1.000	.636	.144
No radiotherapy	161 (42.59%)	19 (55.88%)	132 (41.25%)	10 (41.67%)					
Radiotherapy	217 (57.41%)	15 (44.12%)	188 (58.75%)	14 (58.33%)					
Recurrence	137 (36.24%)	7 (20.59%)	121 (37.81%)	9 (37.5%)	.138	.216	1.000	.393	.071
Death	95 (25.13%)	2 (5.88%)	87 (27.19%)	6 (25.00%)	.025*	.036*	1.000	.038*	.012**
PFS	109.6	NA	109.7	84.9	.048*	.019*	.430	.192	.022*
3-y	74.58 (69.71-77.78)%	87.80 (70.59-95.25) %	72.48 (67.04-77.18) %	82.17(59.17-92.92) %					
5-y	61.35 (55.51-66.66) %	76.82 (57.17-88.31)%	59.22(52.74-65.12) %	65.74(40.83-82.17) %					
8-y	52.49 (45.37-59.11) %	76.82(57.17-88.31) %	50.28 (42.41-57.63) %	49.30 (23.29-70.95) %					
OS	NA	NA	NA	NA	.018*	.005**	.571	.036*	.006**
3-y	84.79 (80.64-88.11) %	97.06 (80.90-99.58) %	83.21 (78.50-86.98) %	87.30 (65.58-95.72) %					
5-y	74.67 (69.33-79.23) %	93.46 (76.12-98.34) %	72.70 (66.68-77.82) %	71.63 (46.85-86.35) %					
8-y	66.99 (60.49-72.67) %	93.46 (76.12-98.34) %	63.31 (55.87-69.84) %	71.63 (46.85-86.35) %					

CCM, clear cell meningioma; CM, chordoid meningioma; NA, not available; OS, overall survival; PFS, progression-free survival.

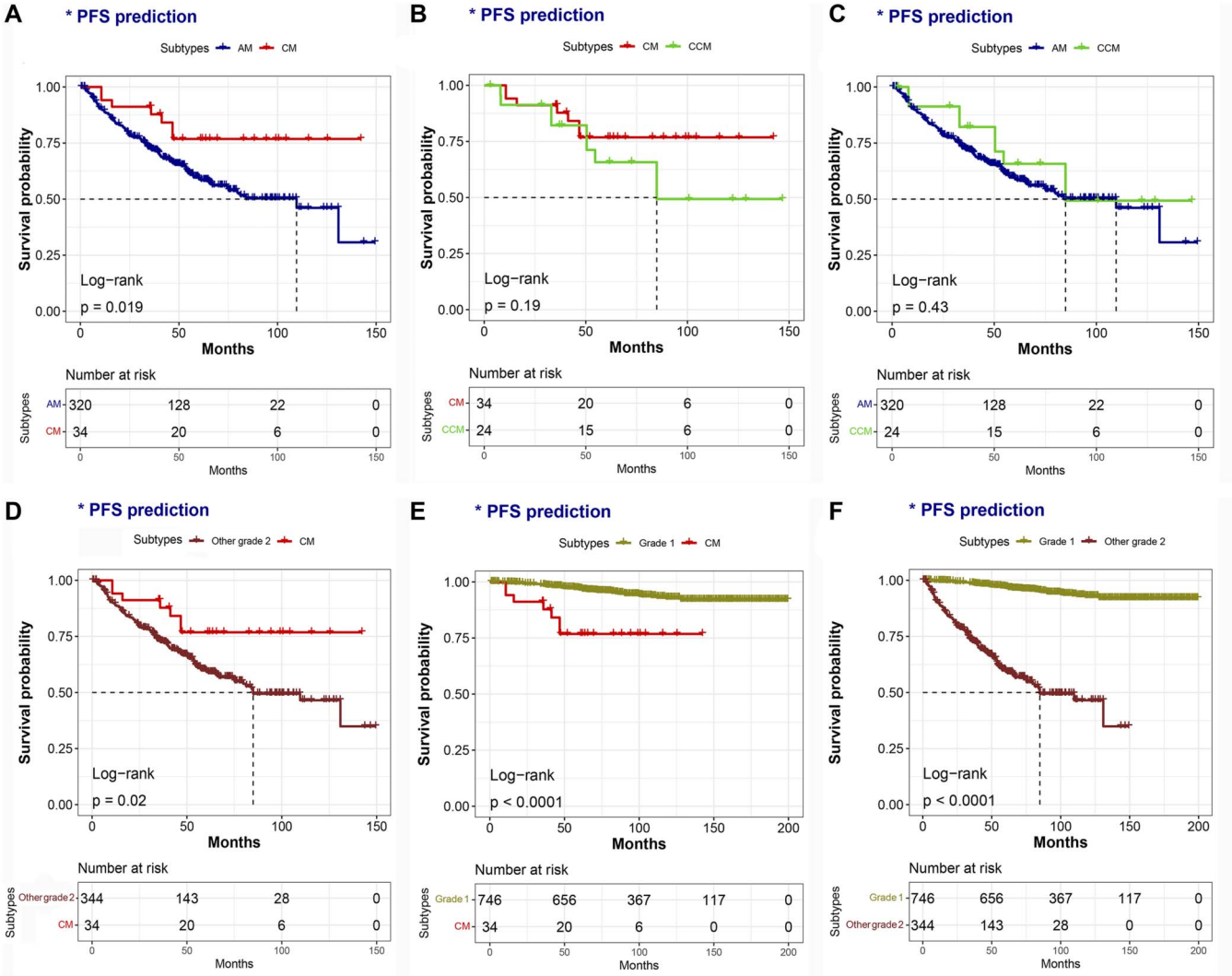

FIGURE 2. *Kaplan-Meier PFS curves of patients with WHO grade 1 and 2 meningiomas.* **A**, *PFS in AM and CM.* **B**, *PFS in CM and CCM.* **C**, *PFS in AM and CCM.* **D**, *PFS in CM and non-CM (WHO grade 2).* **E**, *PFS in CM and WHO grade 1 meningiomas.* **F**, *PFS in WHO grade 1 meningiomas and non-CM WHO grade 2 meningiomas. AM, atypical meningioma; CCM, clear cell meningioma; CM, chordoid meningioma; PFS, progression-free survival; WHO, World Health Organization.*

cutoffs of age and Ki-67 were 57.5 years and 7.5%, respectively **(Supplemental Digital Content 3**, http://links.lww.com/NEU/D525, **Supplemental Digital Content**, **Figure 1A and B**, http://links.lww.com/NEU/D523). Because no difference in PFS was observed among Simpson I-III resections (GTR) (P = .350) **(Supplemental Digital Content 3**, http://links.lww.com/NEU/D525,s **Supplemental Digital Content**, **Figure 2**, http://links.lww.com/NEU/D524), we simply classified extent of resection (EOR) as GTR and STR for further survival analysis. For PFS, univariate survival analysis demonstrated that tumor subtype (P = .025), age (P < .001), Ki-67 index (P < .001), PR expression (P = .002), tumor recurrent status (P < .001), extent of resection (P = .004), and ART (P < .001) were significant prognostic factors. Because age, Ki-67 index, and PR expression are considered the characteristics that are inherently linked to tumor subtype, we chose and included tumor subtype as a tumor intrinsic parameter and recurrent status, extent of resection, and ART as treatment-related factors for multivariate survival analysis, to determine whether tumor subtype was an independent factor affecting PFS. The results demonstrated that along with extent of resection (P = .045), recurrent status (P < .001), and ART (P < .001), tumor subtype (P = .015) was deemed an independent prognostic factor for PFS (Table 4). For OS, univariate survival analysis demonstrated that tumor subtype (P = .015), age (P = .002), Ki-67 index (P < .001), PR expression (P = .018), tumor recurrent status (P < .001), extent of resection (P = .018), and ART (P < .001) were significant prognostic factors. The multivariate

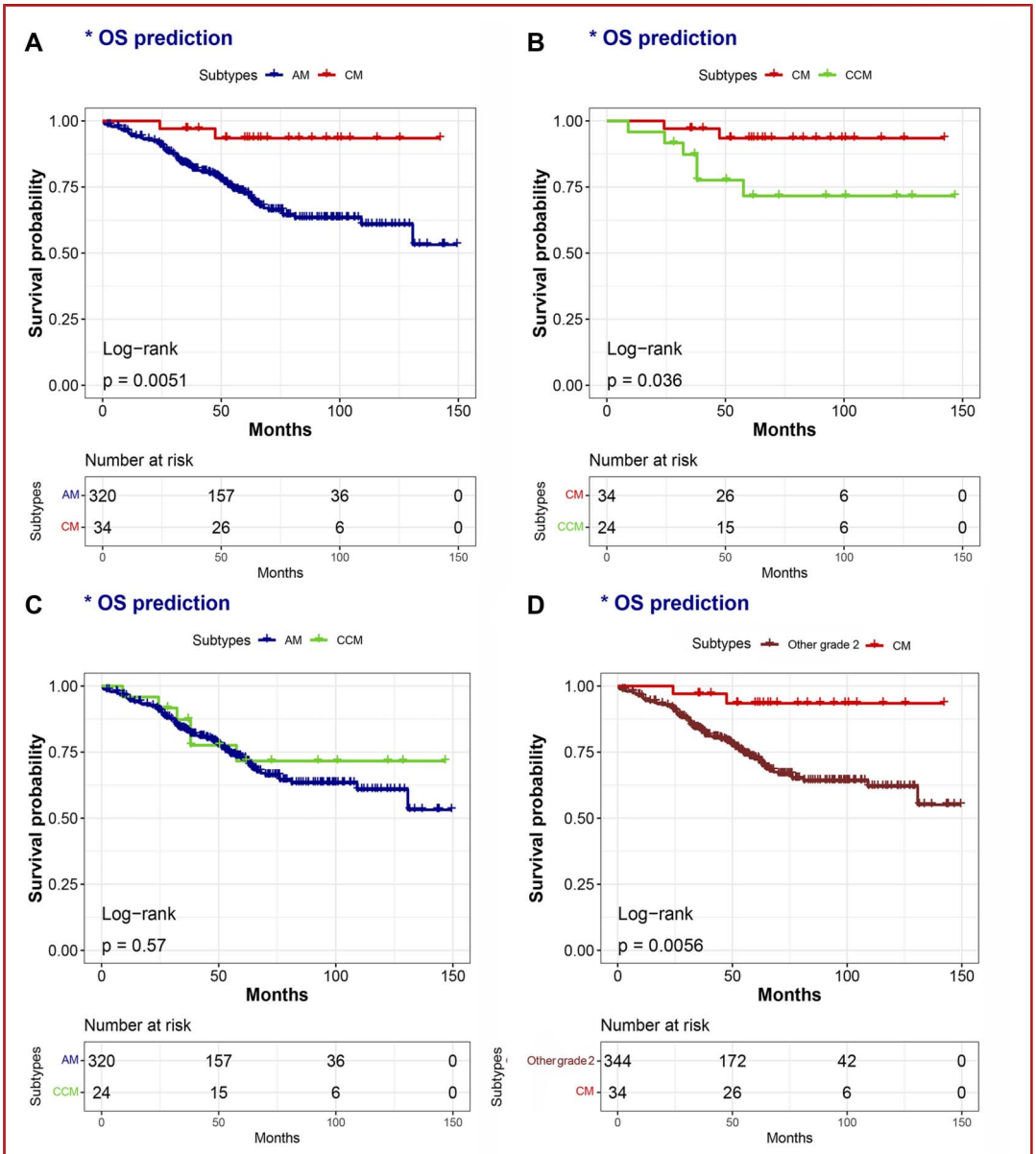

FIGURE 3. *Kaplan-Meier OS curves of patients with WHO grade 2 meningiomas.* **A**, *OS in AM and CM.* **B**, *OS in CM and CCM.* **C**, *OS in AM and CCM.* **D**, *OS in CM and non-CM (WHO grade 2). AM, atypical meningioma; CCM, clear cell meningioma; CM, chordoid meningioma; OS, overall survival; WHO, World Health Organization.*

analysis showed that tumor subtypes (P = .033), recurrent status (P < .001), and ART (P < .001) were independent prognostic factors.

Molecular Alteration and Prognosis of CMs

We finally focused on CM and examined the potential relationship between genetic alterations and outcomes. Our results showed that no tumor had *CDKN2A/B* loss or *TERT* promoter mutation, suggesting that they all belong to grade 2 meningiomas according to the newest WHO CNS5 meningioma classification. *NF2* mutation was detected in 7 tumors (20.59%), whereas *AKT1*, *TRAF7*, and *PBRM1* mutations were found in 2 tumors (5.9%), 2 tumors (5.9%), and 1 tumor (2.9%), respectively. *KMT2C* and *KMT2D* mutations, which were reported to be frequently mutated in CMs,[20] was observed in 9 (26.47%) and 7 (20.59%) patients, respectively (Figure 4A). Survival analysis demonstrated that *NF2* mutation (P = .013) (Figure 4B) and *KMT2C* mutation (P = .021) (Figure 4C) were associated with poorer PFS for CMs. However, *KMT2D* mutation had no association with PFS (P = .57) (Figure 4D).

TABLE 4. Survival Analysis for PFS and OS of WHO Grade 2 Meningiomas

	PFS				OS			
	Univariate Cox analysis		Multivariate Cox analysis		Univariate Cox analysis		Multivariate Cox analysis	
Characters	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Subtypes (non-CMs/CMs)	0.418 (0.195-0.895)	.025[a]	0.659 (0.471-0.921)	.015[a]	0.174 (0.043-0.707)	.015[a]	0.215 (0.052-0.884)	.033
Sex (male/female)	0.932 (0.666-1.304)	.681			1.035 (0.692-1.548)	.866		
Age (<57.5 y/>57.5 y)	1.903 (1.344-2.694)	<.001[c]			1.962 (1.282-3.003)	.002[b]		
Ki-67 (<7.5%/>7.5%)	2.364 (1.625-3.438)	<.001[c]			2.534 (1.638-3.920)	<.001[c]		
PR (negative/positive)	0.578 (0.412-0.812)	.002[b]			0.610 (0.406-0.919)	.018[a]		
Tumor location (nonmidline convexity/parasagittal flax/skull base/spinal)	1.154 (0.948-1.406)	.154			1.126 (0.898-1.412)	.304		
Extent of resection (GTR/STR)	1.773 (1.198-2.624)	.004[b]	1.510 (1.010-2.258)	.045[a]	1.745 (1.098-2.774)	.018[a]	1.366 (0.851-2.193)	.196
Recurrent status (*de novo* status/recurrent status)	4.038 (2.879-5.664)	<.001[c]	4.580 (3.215-6.525)	<.001[c]	4.193 (2.801-6.276)	<.001[c]	3.866 (2.565-5.828)	<.001[c]
ART (no/yes)	0.541 (0.387-0.757)	<.001[c]	0.396 (0.280-0.561)	<.001[c]	0.506 (0.337-0.758)	<.001[c]	0.436 (0.290-0.656)	<.001[c]

ART, adjuvant radiotherapy; CM, chordoid meningioma; KPS, Karnofsky performance score; OS, overall survival; PR, progesterone receptor; PFS, progression-free survival.
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.

DISCUSSION

Clinical management of WHO grade 2 meningioma is challenging and lacks consensus mostly because of heterogenous clinical behaviors.[2] CM is a distinct subtype classified as WHO grade 2 meningiomas. First reported in 1988 by Kepes et al,[11] CM was graded as WHO grade 2 in 2007[31] based on the reports of high recurrence rate even after GTR.[4,6,26] However, the clinicopathological characteristics, molecular genetics, and long-term outcomes of CM are still not clear owing to its small case number.

A key finding of our work was that the PFS and OS of CM were better than those of non-CM. This is consistent with a small case series of CM (N = 12) showing its better prognosis than non-chordoid grade 2 meningiomas.[20] Zhang et al[26] compared CM with CCM and found CM to have a lower recurrence rate and mortality than CCM. On the other hand, Soni et al[28] reported that CCM portended a worse PFS and OS prognosis than nonCCM grade 2 tumors. However, the reasons for an apparently better prognosis of CM remained unclear because of the low incidence of the disease.

We showed that compared with CCM and AM, CM generally had more benign clinicopathological characteristics, most notably a lower Ki-67 index and higher positive PR expression. The Ki-67 index correlated with the risk of recurrence and malignancy of meningioma.[32,33] Mirian et al[34] showed that the Ki-67 index was an important marker for time to recurrence, and Choy et al[35] revealed that Ki-67 >5.0% strongly predicted recurrence. Previously, PR was reported to be positive in 39%–88% of meningiomas.[36,37] Several studies have demonstrated that PR-positive patients had more favorable clinical outcomes.[38] Furthermore, the PR expression level seemed to be associated with *NF2* mutations, an important initial event in meningioma development.[39] The lower Ki-67 index and higher rate of positive PR in CM than non-CM might be the tumor intrinsic features that underlie the benign nature and better outcome of CM.

Genetically, our results demonstrated that *KMT2C*, *KMT2D*, and *NF2* alterations were common in CMs. In addition, *KMT2C* and *NF2* mutations were associated with poorer PFS for CMs, which was consistent with the results reported by Georgescu et al[24] and Daoud et al.[20] *KMT2C* and *KMT2D* are type 2 lysine methyltransferases. *KMT2C/D* forms the core of Complex Proteins Associated with Set1 complexes and mediates monomethylation and trimethylation of H3K4me1 and H3K4me3, respectively. Daoud et al[20] recently demonstrated frequent *KMT2C/D* mutations in CMs, but did not reveal the correlation between mutations and prognosis. *NF2* mutations were present in 40%–60% of meningiomas and are well-known to be associated with tumor recurrence.[40,41] Studies showed that *NF2* mutation occurred in around 60% of AMs,[20,42-44] which was significantly higher than that in CMs. The low *NF2* mutation frequency in CMs might underlie its relative favorable outcome in grade 2 meningiomas.

The location of meningioma affects the extent of resection. Tumors located in nonmiddle convexity are easier to achieve GTR. Several studies showed that GTR is a significant predictor for better PFS of WHO grade 2 meningiomas.[45,46] Hardesty et al[47] demonstrated that GTR prolonged the PFS of patients with WHO grade 2 meningiomas. In our cohort, a large fraction of CMs were nonmidline convexity meningiomas (41.67%), which

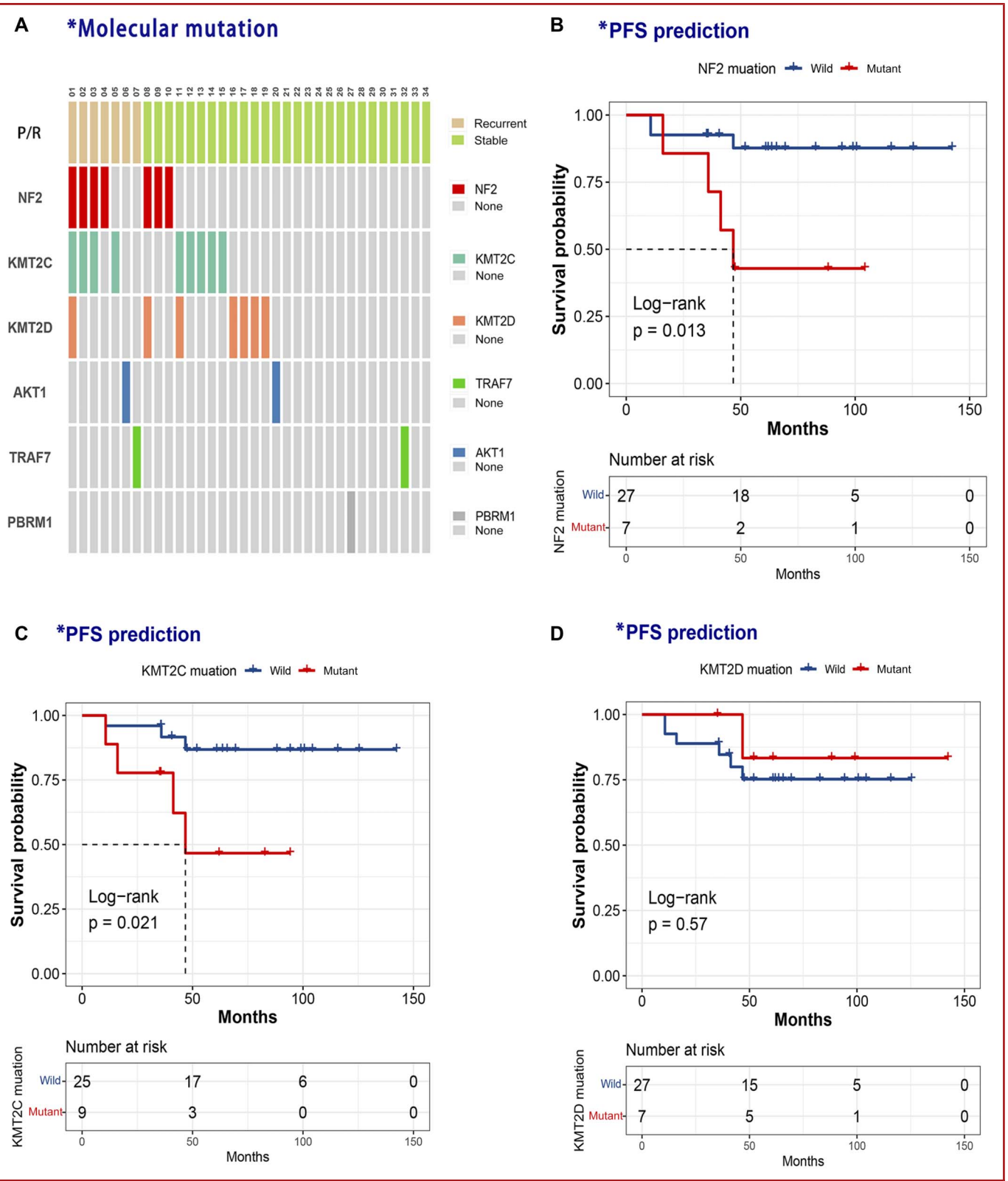

FIGURE 4. *The gene mutations and prognosis of CM.* **A**, *The gene mutations and progression/recurrence (P/R) of CM.* **B**, *PFS in NF2 wild and mutant types.* **C**, *PFS in KMT2C wild and mutant types.* **D**, *PFS in KMT2D wild and mutant types. CM, chordoid meningioma; PFS, progression-free survival.*

probably led to the significantly higher likelihood of GTR of CMs as compared with non-CM tumors, contributing to lower recurrence rates. On the other hand, patients with recurrent meningiomas were more likely to recur. George et al[48] analyzed 712 patients and found that the median PFS of recurrent patients was 35 months and that of de novo patients was 68 months. In addition, the time between surgeries decreased with each reoperation.

The 2016 EANO guidelines recommended that ART should be considered for WHO grade 2 meningiomas after STR.[29] Recent large systematic reviews also supported the benefit of ART for patients with AM after STR.[29,49] However, studies on ART after AM GTR reported varying results, and prospective trial data are missing.[50,51] Analysis of our cohort showed that ART significantly improved the PFS ($P < .001$) and OS ($P < .001$) of patients with WHO grade 2 meningiomas, regardless of GTR or STR, indicating that ART is beneficial for grade 2 patients. Although CMs had a relatively favorable outcome than the other grade 2 subtypes, it is still worse than grade 1 diseases, with a 5-year PFS rate of 76.8%, which is not satisfying. These observations support the notion that radiation is still beneficial for CMs, perhaps particularly for those with *KMT2C* and *NF2* alterations.

To the best of our knowledge, this is the first study to systematically compare CM with the other WHO grade 2 meningiomas and found CM to follow a more favorable long-term clinical course after surgery. Further studies with larger cohorts are warranted to validate our results.

Limitations

First, our study was retrospective in design, and recall bias and selection bias may exist. Second, our study may not exclude AM and CCM patients with *TERT* promoter mutation and *CDKN2A/B* loss who should be classified as WHO grade 3 based on the 2021 WHO meningioma diagnostic criterion.

CONCLUSION

CM showed unique clinicopathological characteristics and relatively benign behavior postoperatively, thus clinically representing a distinct subtype of WHO grade 2 meningioma. The long-term outcomes of CM were better than those of the other WHO grade 2 subtypes and worse than those of WHO grade 1 meningiomas.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

REFERENCES

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. *Neuro-Oncology* 2021;23(suppl 3):iii1-iii105.
2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol.* 2021;23(8):1231-1251.
3. Streckert EMS, Hess K, Sporns PB, et al. Clinical, radiological, and histopathological predictors for long-term prognosis after surgery for atypical meningiomas. *Acta Neurochir (Wien).* 2019;161(8):1647-1656.
4. Couce ME, Aker FV, Scheithauer BW. Chordoid meningioma: a clinicopathologic study of 42 cases. *Am J Surg Pathol.* 2000;24(7):899-905.
5. Epari S, Sharma MC, Sarkar C, Garg A, Gupta A, Mehta VS. Chordoid meningioma, an uncommon variant of meningioma: a clinicopathologic study of 12 cases. *J Neurooncol.* 2006;78(3):263-269.
6. Yang Y, Li D, Cao XY, et al. Clinical features, treatment, and prognostic factors of chordoid meningioma: radiological and pathological features in 60 cases of chordoid meningioma. *World Neurosurg.* 2016;93:198-207.
7. Li P, Yang Z, Wang Z, et al. Clinical features of clear cell meningioma: a retrospective study of 36 cases among 10, 529 patients in a single institution. *Acta Neurochir (Wien).* 2016;158(1):67-76.
8. Wang XQ, Huang MZ, Zhang H, et al. Clear cell meningioma: clinical features, CT, and MR imaging findings in 23 patients. *J Comput Assist Tomogr.* 2014;38(2):200-208.
9. Guini M, Khoulali M, Raouzi N, Oulali N, Moufid F. [Extra-axial chordoid meningioma: a case report]. *Pan Afr Med J.* 2021;38:123.
10. Di Ieva A, Laiq S, Nejad R, et al. Chordoid meningiomas: incidence and clinicopathological features of a case series over 18 years. *Neuropathology.* 2015;35(2):137-147.
11. Kepes JJ, Chen WYK, Connors MH, Vogel FS. "Chordoid" meningeal tumors in young individuals with peritumoral lymphoplasmacellular infiltrates causing systemic manifestations of the Castleman syndrome. A report of seven cases. *Cancer.* 1988;62(2):391-406.
12. Jee TK, Jo KI, Seol HJ, Kong DS, Lee JI, Shin HJ. Clinical features and treatment outcome of chordoid meningiomas in a single institute. *J Korean Neurosurg Soc.* 2014;56(3):194-199.
13. Passacantilli E, Lapadula G, Caporlingua F, et al. Chordoid meningioma: a retrospective series of seven consecutive cases. *Neurol Sci.* 2013;34(11):1985-1989.
14. Wang XQ, Mei GH, Zhao L, et al. Clinical features and treatment of intracranial chordoid meningioma: a report of 30 cases. *Histopathology.* 2013;62(7):1002-1017.
15. Zhu HD, Chen H, Xie Q, et al. Chordoid meningioma: a retrospective study of 17 cases at a single institution. *Chin Med J (Engl).* 2013;126(4):789-791.
16. Lin JW, Ho JT, Lin YJ, Wu YT. Chordoid meningioma: a clinicopathological study of 11 cases at a single institution. *J Neurooncol.* 2010;100(3):465-473.
17. Lin JW, Lu CH, Lin WC, et al. A clinicopathological study of the significance of the proportion of choroid morphology in chordoid meningioma. *J Clin Neurosci.* 2012;19(6):836-843.
18. Bondy M, Lee Ligon B. Epidemiology and etiology of intracranial meningiomas: a review. *J Neurooncol.* 1996;29(3):197-205.
19. Durand A, Labrousse F, Jouvet A, et al. WHO grade II and III meningiomas: a study of prognostic factors. *J Neurooncol.* 2009;95(3):367-375.
20. Daoud EV, Zhu K, Mickey B, et al. Epigenetic and genomic profiling of chordoid meningioma: implications for clinical management. *Acta Neuropathol Commun.* 2022;10(1):56.
21. Prokopienko M, Wierzba-Bobrowicz T, Grajkowska W, Stepien T, Sobstyl M. Chordoid meningioma. Case report and review of the literature. *Niger J Clin Pract.* 2022;25(1):1-4.
22. Tahta A, Genc B, Cakir A, Sekerci Z. Chordoid meningioma: report of 5 cases and review of the literature. *Br J Neurosurg.* 2020:1-8.
23. Yagi C, Yamamuro S, Ozawa Y, Yoshimura S, Sumi K, Yoshino A. A case of tuberculum sellae chordoid meningioma treated via extended endoscopic endonasal trans-sphenoidal surgery. *NMC Case Rep J.* 2020;7(2):53-56.
24. Georgescu MM, Nanda A, Li Y, et al. Mutation status and epithelial differentiation stratify recurrence risk in chordoid meningioma-A multicenter study with high prognostic relevance. *Cancers (Basel).* 2020;12(1):225.
25. Kumar A, Bhaskar S, Bhardwaj M, Gupta LN. Foramen magnum chordoid meningioma in a 22-Year-old female. *Asian J Neurosurg.* 2018;13(3):834-837.
26. Zhang GJ, Zhang YS, Zhang GB, et al. Prognostic factors, survival, and treatment for intracranial World Health organization grade II chordoid meningiomas and clear-cell meningiomas. *World Neurosurg.* 2018;117:e57-e66.

27. Sadashiva N, Poyuran R, Mahadevan A, Bhat DI, Somanna S, Devi BI. Chordoid meningioma: a clinico-pathological study of an uncommon variant of meningioma. *J Neurooncol.* 2018;137(3):575-582.
28. Soni P, Shao J, Momin A, et al. Clear cell histology portends a worse prognosis than other WHO grade II histologies. *J Neurooncol.* 2021;151(2):307-312.
29. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol.* 2016;17(9):e383-e391.
30. Hua L, Alkhatib M, Podlesek D, et al. Two predominant molecular subtypes of spinal meningioma: thoracic NF2-mutant tumors strongly associated with female sex, and cervical AKT1-mutant tumors originating ventral to the spinal cord. *Acta Neuropathol.* 2022;144(5):1053-1055.
31. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* 2007;114(2): 97-109.
32. Barrett OC, Hackney JR, McDonald AM, Willey CD, Bredel M, Fiveash JB. Pathological predictors of local recurrence in atypical meningiomas following gross total resection. *Int J Radiat Oncol Biol Phys.* 2019;103(2):453-459.
33. Tyagi A, Chakrabarty A, Franks A. MIB1 proliferation index in meningiomas: does it predict recurrence? A clinicopathological study. *Br J Neurosurg.* 2004;18(4): 357-361.
34. Mirian C, Skyrman S, Bartek J Jr, et al. The ki-67 proliferation index as a marker of time to recurrence in intracranial meningioma. *Neurosurgery.* 2020;87(6): 1289-1298.
35. Choy W, Ampie L, Lamano JB, et al. Predictors of recurrence in the management of chordoid meningioma. *J Neurooncol.* 2016;126(1):107-116.
36. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. *J Clin Pathol.* 2004;57(10):1033-1037.
37. Kuroi Y, Matsumoto K, Shibuya M, Kasuya H. Progesterone receptor is responsible for benign biology of skull base meningioma. *World Neurosurg.* 2018;118: e918–e924.
38. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: opposing prognostic indicators in meningiomas. *J Neurosurg.* 2006; 105(2):163-173.
39. Karsy M, Azab MA, Abou-Al-Shaar H, et al. Clinical potential of meningioma genomic insights: a practical review for neurosurgeons. *Neurosurg Focus.* 2018; 44(6):E10.
40. Peyre M, Kalamarides M. Molecular genetics of meningiomas: building the roadmap towards personalized therapy. *Neurochirurgie.* 2018;64(1):22-28.
41. Birzu C, Peyre M, Sahm F. Molecular alterations in meningioma: prognostic and therapeutic perspectives. *Curr Opin Oncol.* 2020;32(6):613-622.
42. Meta R, Boldt HB, Kristensen BW, Sahm F, Sjursen W, Torp SH. The prognostic value of methylation signatures and NF2 mutations in atypical meningiomas. *Cancers (Basel).* 2021;13(6):1262.
43. Nassiri F, Liu J, Patil V, et al. A clinically applicable integrative molecular classification of meningiomas. *Nature.* 2021;597(7874):119-125.
44. Williams EA, Santagata S, Wakimoto H, et al. Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. *Acta Neuropathol Commun.* 2020;8(1):171.
45. Champeaux C, Wilson E, Shieff C, Khan AA, Thorne L. WHO grade II meningioma: a retrospective study for outcome and prognostic factor assessment. *J Neurooncol.* 2016;129(2):337-345.
46. Fernandez C, Nicholas MK, Engelhard HH, Slavin KV, Koshy M. An analysis of prognostic factors associated with recurrence in the treatment of atypical meningiomas. *Adv Radiat Oncol.* 2016;1(2):89-93.
47. Hardesty DA, Wolf AB, Brachman DG, et al. The impact of adjuvant stereotactic radiosurgery on atypical meningioma recurrence following aggressive microsurgical resection. *J Neurosurg.* 2013;119(2):475-481.
48. Richardson GE, Gillespie CS, Mustafa MA, et al. Clinical outcomes following Re-operations for intracranial meningioma. *Cancers (Basel).* 2021;13(19):4792.
49. Kaur G, Sayegh ET, Larson A, et al. Adjuvant radiotherapy for atypical and malignant meningiomas: a systematic review. *Neuro Oncol.* 2014;16(5):628-636.
50. Song D, Xu D, Han H, et al. Postoperative adjuvant radiotherapy in atypical meningioma patients: a meta-analysis study. *Front Oncol.* 2021;11:787962.
51. He L, Zhang B, Zhang J, Guo Z, Shi F, Zeng Q. Effectiveness of postoperative adjuvant radiotherapy in atypical meningioma patients after gross total resection: a meta-analysis study. *Front Oncol.* 2020;10:556575.

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Supplemental Digital Content 1.
Supplemental Figure 1. Immunohistochemical staining for PR and Ki-67 in CM specimens. A: Ki-67 index <5%. B: Negative PR expression. C: Ki-67 index ≥5%. D: Positive PR expression.
Supplemental Digital Content 2. The process of next-generation sequencing.
Supplemental Digital Content 3.
Supplemental Figure 1. The relapse-related receiver operation curves (ROC) of age and Ki-67. A: The relapse-related ROC of age, with cutoff 57.5 years. B: The relapse-related ROC of Ki-67, with cutoff 7.5%.
Supplemental Figure 2. The Kaplan-Meier plot of Simpson grades and PFS.