Advances in Radiation Oncology (2022) 7, 100878

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Long-Term Outcomes for Patients With Atypical or Malignant Meningiomas Treated With or Without Radiation Therapy: A 25-Year Retrospective Analysis of a Single-Institution Experience

Collin L. Kent, MD,[a] Yvonne M. Mowery, MD, PhD,[a,b] Olayode Babatunde, MD,[c] Ato O. Wright, MD,[d] Ian Barak, MS,[e] Frances McSherry, MA,[e] James E. Herndon II, PhD,[e] Allan H. Friedman, MD,[f,g] Ali Zomorodi, MD,[f,g] Katherine Peters, MD, PhD,[f,g] Annick Desjardins, MD,[f,g] Henry Friedman, MD,[f,g] William Sperduto, MBS,[h] and John P. Kirkpatrick, MD, PhD[a,f,g,*]

[a]Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina; [b]Department of Head and Neck Surgery & Communication Sciences, Duke University Medical Center, Durham, North Carolina; [c]Department of Internal Medicine, Columbia University, New York, New York; [d] Department of Radiation Oncology, University of Pittsburgh Medical Center (UPMC) Pinnacle, Carlisle, Pennsylvania; [e]Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, North Carolina; [f]Department of Neurosurgery, Duke University Medical Center, Durham, North Carolina; [g]The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, North Carolina; [h]Duke University School of Medicine, Durham, North Carolina

Received July 27, 2021; accepted December 6, 2021

Abstract

Purpose: Atypical (World Health Organization [WHO] grade 2) and malignant (WHO grade 3) meningiomas have high rates of local recurrence, and questions remain about the role of adjuvant radiation therapy (RT) for patients with WHO grade 2 disease. These

Sources of support: This work had no specific funding.

Disclosures: Dr Kirkpatrick reports relevant financial activities outside of the submitted work, including research funding from Varian Medical Systems and BioMimetix and ownership in ClearSight RT, LLC. Dr Desjardins reports grants from Triphase Accelerator, Orbus Therapeutics, Symphogen, Celgene/Bristol-Myers Squibb, as well as personal fees from Istari Oncology outside of the submitted work. In addition, Dr Desjardins holds the following patents: Method of Treating Solid Tumor with Oncolytic Poliovirus (US 15/428510; licensed to Istari Oncology), Method of Treating Solid Tumor with Oncolytic Poliovirus (CA 2,892,183; licensed to Istari Oncology), Method of Treating Solid Tumor with Oncolytic Poliovirus (EP 13856989.2; licensed to Istari Oncology), Method of Treating Solid Tumor with Oncolytic Poliovirus (HK 15112399.5; licensed to Istari Oncology), Oncolytic Poliovirus for Human tumors (US 16/505,771; issued), Neoadjuvant cancer treatment (US 17/044,645; pending), Neoadjuvant cancer treatment (AU 2019247039; pending), Neoadjuvant cancer treatment (JP 2020-554198; pending), Neoadjuvant cancer treatment (South Korea 10-2020.7031272; pending), Neoadjuvant cancer treatment (Canada; pending), Neoadjuvant cancer treatment (PCT/US2019/025402; pending), Neoadjuvant cancer treatment (US 62/823,277; pending), Oncolytic Poliovirus for Human Tumors (US 17/016,699; pending), Sequential Anti-cancer Treatment (US 16/086,735; issued), and Neoadjuvant cancer treatment (China; pending). Dr Desjardins also holds stock options in Istari Oncology (<1% of all total shares issued by Istari Oncology). All other authors have no disclosures to declare.

Research data are not available at this time.

*Corresponding author: John P. Kirkpatrick, MD, PhD; E-mail: John.kirkpatrick@duke.edu

https://doi.org/10.1016/j.adro.2021.100878

patients frequently require salvage therapy, and optimal management is uncertain given limited prospective data. We report on the long-term outcomes for patients with atypical and malignant meningiomas treated with surgery and/or RT at our institution.

Methods and Materials: Data were collected through a retrospective chart review for all patients with WHO grade 2 or 3 meningiomas treated with surgery and/or RT at our institution between January 1992 and March 2017. Progression-free survival (PFS) and overall survival (OS) were described using the KaplanMeier estimator. The outcomes in the subgroups were compared with a log-rank test. A Cox proportional hazards model was used for the univariable and multivariable analyses of predictors of PFS.

Results: A total of 66 patients were included in this analysis. The median follow-up was 12.4 years overall and 8.6 years among surviving patients. Fifty-two patients (78.8%) had WHO grade 2 meningiomas, and 14 patients (21.2%) had WHO grade 3 disease. Thirty-six patients (54.5%) were treated with surgery alone, 28 patients (42.4%) with surgery and adjuvant RT, and 2 patients (3%) with RT alone. Median PFS and OS were 3.2 years and 8.8 years, respectively. PFS was significantly improved with adjuvant RT compared with surgery alone (hazard ratio, 0.36; 95% confidence interval, 0.18-0.70). Patients with Ki-67 index >10% showed a trend toward worse PFS compared with patients with Ki-67 ≤10% (hazard ratio, 0.51; 95% confidence interval, 0.25-1.04). No significant differences in PFS or OS were observed with respect to Simpson or WHO grade.

Conclusions: For patients with atypical or malignant meningiomas, adjuvant RT was associated with significantly improved PFS, and Ki-67 index >10% was associated with a trend toward worse PFS. Given the long-term survival, high recurrence rates, and efficacy of salvage therapy, patients with atypical and malignant meningiomas should be monitored systematically long after initial treatment.

Introduction

Meningiomas are the most common primary brain tumor in adults, making up approximately 37% of all cases.[1] The World Health Organization (WHO) classifies meningiomas into 3 histopathologic categories by grade: 1 (benign), 2 (atypical), and 3 (malignant/anaplastic).[2] Since updating these classifications in 2016, grades 2 and 3 meningiomas now account for an estimated 25% to 30% of these tumors.[1,3-5] Compared with benign meningiomas, atypical and malignant meningiomas exhibit more aggressive behavior and have higher rates of local recurrence.[2,6] Surgical resection is the mainstay of treatment, and although adjuvant radiation therapy (RT) is typically indicated for WHO grade 3 disease, the standard of care for WHO grade 2 meningiomas after surgery is not well defined, and recurrence rates remain high.[7-13]

Initial results from Radiation Therapy Oncology Group (RTOG) study 0539, the first prospective phase 2 trial for patients with meningioma, demonstrated 3-year progression-free survival (PFS) of 58.8% after adjuvant RT in patients with high-risk disease, defined as WHO grade 3 meningioma after any resection, recurrent WHO grade 2 disease, or new WHO grade 2 meningioma after subtotal resection.[14] However, the median follow-up in this study was limited to 4 years (4.8 years for living patients), and retrospective series with a longer follow-up may still contribute valuable information to help guide the management of these patients given the relatively long natural history for this disease and absence of prospective, randomized trials evaluating adjuvant RT for meningiomas.

In the current study, we retrospectively analyze outcomes and predictors of recurrence for all patients with grade 2 or 3 meningiomas treated at our institution over a 25-year period.

Methods and Materials

Patient selection

We retrospectively reviewed the records of all patients at our academic center who were treated with surgery and/or RT for histologically confirmed meningiomas between January 1992 and March 2017. A total of 423 patients were identified, of whom 66 (15.6%) had WHO grade 2 or 3 disease and were included in this study. The remaining 357 patients (84.4%) had WHO grade 1 meningiomas and were excluded. Patients with a previous WHO grade 1 histology were included in this analysis, provided they were treated for a grade 2 or 3 recurrence.

All patient data were collected through a retrospective chart review after prior approval from the institutional review board. Radiologic studies were initially interpreted by subspecialty expert neuroradiologists, and radiology reports were interpreted by radiation oncology resident physicians and/or faculty. When necessary, radiology images were personally reviewed by the senior radiation oncology attending physician with subspecialty expertise in central nervous system malignancies. Pathology specimens that did not initially have Ki-67 data reported were collected and reanalyzed when sufficient tissue was available.

Parameters assessed

Clinical and pathologic variables were recorded, including age, race, history of ionizing radiation or neurofibromatosis type 2, Eastern Cooperative Oncology Group performance status, tumor location, treatment type for initial diagnosis of WHO grade 2 or 3 disease and

recurrence(s) (surgery, RT, and systemic therapies), WHO grade, and Mib-1/Ki-67 index. Age at the time of diagnosis was defined as age at the time of first surgical resection or biopsy. Tumor location was classified as parasagittal/falcine, convexity, suprasellar, sphenoid ridge, posterior fossa, olfactory groove, middle fossa/Meckel's cave, tentorial/pineal, peritorcular, optic nerve sheath, and clival. Extent of resection (Simpson grade) was determined based on a review of operative notes and postoperative imaging.

RT was considered adjuvant if delivered ≤4 months after surgery and salvage if delivered beyond 4 months after histologic and/or radiographic evidence of progression or recurrence. Given changes in RT techniques, equipment, and practice patterns at our institution, treatment courses were categorized into 3 eras for subgroup analysis: pre-2001, 2001 to 2008, or 2009 to 2017. These eras corresponded to conventional external beam RT and 3-dimensional techniques; fractionated stereotactic RT (FSRT) in a relocatable headframe and 3-dimensional or intensity modulated treatment plans or single-fraction stereotactic radiosurgery (SRS) in a halo using dynamic-conformal arcs (both using 3-mm leaf-width collimator attachment); and image guided RT using a relocatable thermoplastic face mask (BrainLAB, Munich, Germany), daily image guidance with kV imaging, and/or cone beam computed tomography on a dedicated linear accelerator equipped with an integral high-resolution collimator (Novalis Tx or TrueBeam STx, Varian Medical Systems, Palo Alto, CA), respectively.

In this third group, the treatment of choice was typically hypofractionated SRS or FSRT using an intensity-modulated technique. The gross tumor volume during all these periods was based on the resection cavity and/or residual/recurrent enhancing tumor volume on magnetic resonance imaging. However, to limit normal tissue toxicity, the clinical target volume (CTV) evolved from a uniform 1 cm expansion of the gross tumor volume with an additional CTV-to-planning target volume expansion of 3 to 4 mm during the initial period to an anisotropic expansion of 5 to 10 mm in the plane of the meninges, and 2 to 3 mm expansion perpendicular to this plane into the normal brain parenchyma without an additional CTV to planning target volume margin.

Statistical analysis

Overall survival (OS) was calculated from the date of initial treatment (ie, first surgery or initiation of RT) for grade 2 or 3 disease until the date of death, and was censored at the last clinical follow-up if the patient was alive at the time of the analysis. PFS was defined as the time between initial treatment and disease progression or death if the patient died without documentation of progression. If the patient was alive without disease progression at the last follow-up, PFS was censored.

PFS and OS were described using the Kaplan-Meier estimator. Outcomes within the subgroups were compared with a log-rank test. A Cox proportional hazards model was used to analyze predictors of PFS, including patient age, WHO grade, and treatment modality (surgery and adjuvant RT vs surgery alone) in univariable and multivariable models. Age was included as a continuous variable. The analyses were performed using the SAS and R statistical packages.

Results

Patient characteristics

A total of 66 patients were treated with surgery and/or RT for atypical or malignant meningiomas at our institution between January 1992 and March 2017. The median follow-up was 12.4 years overall, and 8.6 years (interquartile range [IQR], 5.6-14.5 years) for living patients. Among all 66 patients, the survival time ranged from 0.32 to 31.6 years, and 56 patients (84.8%) had >24 months of survival. Among the 52 patients with WHO grade 2 disease, survival time ranged from 0.56 to 31.6 years, and 46 patients (88.5%) had >24 months of survival. The median age at the time of diagnosis was 57 years (IQR, 46-70 years), and sex was evenly divided (50% male). Twelve patients (18.1%) initially had WHO grade 1 meningiomas that progressed to WHO grade 2 (n = 8) or 3 disease (n = 4), with a median time of 7.3 years (range, 0.58-25.1 years) between initial WHO grade 1 diagnosis and transformation to WHO grade 2 or 3 disease.

Overall, 52 patients (78.8%) had WHO grade 2 meningiomas, and 14 patients (21.2%) had WHO grade 3 disease. Ki-67 index levels were available for 46 of 66 patients (69.7%), and Ki-67 was elevated >10% in 18 of these patients (39.1%). The remainder of the pathology specimens did not have sufficient tissue for Ki-67 analyses. The majority of patients had a good performance status, including an Eastern Cooperative Oncology Group score of 0 for 8 patients (13.1%), 1 for 30 patients (49.2%), 2 for 9 patients (14.8%), 3 for 12 patients (19.7%), and 4 for 2 patients (3.3%). The most common presenting symptoms were headache (36.3%), seizures (24.2%), weakness (24.2%), confusion (22.7%), vision change (18.1%), and ataxia (16.7%).

Thirty-six patients (54.5%) were treated with surgery alone, 28 patients (42.4%) with surgery and adjuvant RT, and 2 patients (3%) with RT alone for unresectable disease. Patients receiving adjuvant RT were treated with fractionated RT to a median dose of 55.8 Gy (IQR, 54-59.4 Gy) in 1.8 Gy per fraction. For patients treated with RT alone for unresectable disease, 1 patient was treated with single-fraction SRS to 15 Gy in 1994, and the second patient was treated with FSRT to 59.4 Gy in 33 fractions in 2013. Among those treated with surgery without adjuvant RT, 2 patients (5.6%) received adjuvant systemic

therapy: one patient received single-agent temozolomide, and the other received temozolomide and etoposide. Among those who were treated with adjuvant RT, 4 patients (14.2%) received concurrent temozolomide. Baseline patient characteristics are shown in Table 1.

There were no significant differences in baseline characteristics between patients treated with surgery alone versus surgery with adjuvant RT. However, there was a trend toward more subtotal resections (STR; Simpson grade 4) in the adjuvant RT group (66.7% vs 41.4%; $P = .066$) compared with the surgery-alone group.

Progression-free survival

With 45 of 66 patients (68.1%) having experienced disease recurrence/progression, median PFS among all 66 patients was 3.2 years (95% confidence interval [CI], 2.2-5.6 years). The 2-, 5-, and 10-year PFS rates were 65.0%, 38.4%, and 23.2%, respectively (Fig 1A). Patients treated with surgery and adjuvant RT had significantly longer PFS compared with patients treated with surgery alone (median, 5.9 vs 2.1 years; hazard ratio [HR], 0.36; 95% CI, 0.18-0.70). Three-year PFS rates for patients treated with surgery and adjuvant RT and those treated with surgery alone were 66.1% and 39.2%, respectively. For patients treated with surgery and adjuvant RT compared with surgery alone, the 2-, 5-, and 10-year PFS rates were 81.6% versus 52.3%, 57.7% versus 24.9%, and 37.7% versus 12.4%, respectively (Fig 1B).

PFS did not differ significantly for patients with WHO grade 2 versus 3 meningiomas. The median PFS for patients with WHO grade 2 meningiomas was 3.2 years, and the median PFS was not reached for patients with WHO grade 3 disease (HR, 0.49; 95% CI, 0.19-1.26). For patients with WHO grade 2 compared with grade 3 disease, the 2-, 5- and 10-year PFS rates were 62.8% versus 74.1%, 35.4% versus 52.9%, and 15.9% versus 52.9%, respectively (Fig 1C). Patients with Ki-67 index >10% showed a trend toward worse PFS compared with patients with Ki-67 ≤10% (median, 2.1 vs 2.9 years; $P = .06$). For patients with elevated Ki-67 compared with those with values ≤10%, the 2- and 5-year PFS rates were 59.3% versus 57.1% and 17.8% versus 45%, respectively (Fig E1A). There were no significant differences in PFS among the 3 eras in which patients received RT (Fig E1B), transformation status (Fig E1C), or Simpson grade (Fig E1D).

For patients with WHO grade 2 disease, patients treated with surgery and adjuvant RT compared with surgery alone, the 2-, 5-, and 10-year PFS rates were 55.7% versus 75.0%, 28.3% versus 49.5%, and 14.1% versus 22.6%, respectively (Fig 2A). For patients with WHO grade 2 disease and Ki-67 index ≤10% compared with >10%, the 2-, 5-, and 10-year PFS rates were 52.4% versus 60.0%, 42.3% versus 20.0%, and 19.0% versus 0%, respectively (Fig 2B). For patients with WHO grade 2 disease undergoing gross total resection (GTR; Simpson grades 1-3) compared with STR (Simpson grade 4), the 2-, 5-, and 10-year PFS rates were 70.8% versus 60.9%, 48.3% versus 30.4%, and 32.2% versus 13.0%, respectively (Fig 2C). No significant differences were observed between any of these groups.

In the multivariable analysis (Table 2), only age was associated with worse PFS (HR, 1.56; 95% CI, 1.19-2.05). PFS was not significantly associated with WHO grade (2 vs 3; HR, 0.74; 95% CI, 0.32-1.74) or use of adjuvant RT (yes vs no; HR, 0.58; 95% CI, 0.28-1.2).

Overall survival

At the time of the analysis, 31 of 66 patients (47.0%) were alive. The median OS for all patients was 8.8 years (95% CI, 6.7 years-not estimable). The 2-, 5-, and 10-year OS rates were 84.8%, 67.9%, and 44.3%, respectively (Fig 3A). Patients treated with surgery and adjuvant RT compared with surgery alone had a median OS of 10.0 years versus 6.8 years ($P = .30$). For patients treated with surgery and adjuvant RT compared with surgery alone, the 2-, 5-, and 10-year OS rates were 89.3% versus 80.6%, 71.2% versus 66.3%, and 48.6% versus 41.3%, respectively (Fig 3B). No significant differences in OS were observed with respect to WHO grade (Fig 3C), Ki-67 index (Fig E2A), RT era (Fig E2B), transformation status (Fig E2C), or Simpson grade (Fig E2D).

Local recurrence and salvage therapy

At the time of the analysis, 45 of 66 patients (68.1%) had received salvage treatment after recurrence. Thirty-two patients (71.1%) underwent salvage surgery, 38 patients (84.4%) underwent salvage RT, and 24 patients (53.3%) received systemic therapy. The median number of recurrences overall was 2 per patient (range, 1-9), with a median of 1 salvage surgery (range, 0-7) and median of 1 course of salvage RT (range, 0-6). For those treated with salvage RT, 11 patients (28.9%) received SRS (median dose, 15 Gy; IQR, 14-25 Gy), 19 patients (50%) received FSRT (median dose, 54 Gy; IQR, 54-57.45 Gy), and 8 patients (21.1%) received both SRS and FSRT for multiple recurrences.

Among the 24 patients treated with salvage systemic therapy, 16 (66.7%) received bevacizumab, 13 (54.2%) temozolomide, 12 (50%) hydroxyurea, 7 (29.1%) imatinib, 4 (14.2%) octreotide, 4 (14.2%) etoposide, and 3 (12.5%) somatostatin. Among the 45 patients who received salvage therapy, 27 (60%) remained alive at the time of the analysis.

Table 1 Baseline patient characteristics

	All Patients Total (N = 66)	Initial Therapy*		*P*-value†
		Surgery (n = 36)	Surgery + RT (n = 28)	
Sex, n (%)				.0831‡
Male	33 (50.0)	14 (38.9)	17 (60.7)	
Female	33 (50.0)	22 (61.1)	11 (39.3)	
Race, n (%)				.5332‡
Black	10 (15.2)	7 (19.4)	3 (10.7)	
White	46 (69.7)	22 (61.1)	22 (78.6)	
Hispanic	1 (1.5)	1 (2.8)	0 (0.0)	
Asian	1 (1.5)	1 (2.8)	0 (0.0)	
Unknown	8 (12.1)	5 (13.9)	3 (10.7)	
Age, y				.5114†
n	66	36	28	
Mean (standard deviation)	54.6 (18.22)	53.5 (19.36)	56.8 (15.91)	
Median (interquartile range)	57.0 (46.0-70.0)	53.5 (41.0-69.5)	60.0 (49.0-69.5)	
Range	10.0-87.0	10.0-87.0	20.0-78.0	
Transformed (World Health Organization grade 1-2 or 3), n (%)				.1463†
No	54 (81.8)	27 (75.0)	25 (89.3)	
Yes	12 (18.2)	9 (25.0)	3 (10.7)	
World Health Organization grade, n (%)				.2531†
2	52 (78.8)	30 (83.3)	20 (71.4)	
3	14 (21.2)	6 (16.7	8 (28.6)	
Simpson grade, n (%)				.0664†
1/2	25 (47.2)	17 (58.6)	8 (33.3)	
3	0 (0.0)	0 (0.0)	0 (0.0)	
4	28 (52.8)	12 (41.4)	16 (66.7)	
N/A	13	7	4	
MIB-11/Ki-67, n (%)				.3932†
≤10%	28 (60.9)	13 (54.2)	14 (66.7)	
>10%	18 (39.1)	11 (45.8)	7 (33.3)	
N/A	20	12	7	
Eastern Cooperative Oncology Group score, n (%)				.3397†
0	8 (13.1)	6 (17.6)	2 (8.0)	
1	30 (49.2)	17 (50.0)	12 (48.0)	
2	9 (14.8)	5 (14.7)	4 (16.0)	
3	12 (19.7)	4 (11.8)	7 (28.0)	
4	2 (3.3)	2 (5.9)	0 (0.0)	
N/A	5	2	3	
RT type, n (%)				
Stereotactic radiosurgery	2 (6.9)	0 (0.0)	2 (7.4)	
Fractionated stereotactic RT	27 (93.1)	0 (0.0)	25 (92.6)	

(*continued on next page*)

Table 1 (*Continued*)

	All Patients Total (N = 66)	Initial Therapy*		
		Surgery (n = 36)	Surgery + RT (n = 28)	*P*-value†
N/A	37	36	1	
RT era, n (%)				
Before 2001	10 (33.3)	0 (0.0)	9 (32.1)	
2001-2008	8 (26.7)	0 (0.0)	7 (25.0)	
2009-present	12 (40.0)	0 (0.0)	12 (42.9)	
N/A	36	36	0	
Follow-up time (living patients)				0.6073‡
n	31	15	16	
Mean (standard deviation)	11.4 (6.95)	12.9 (8.42)	10.0 (5.11)	
Median (interquartile range)	8.6 (5.6-14.5)	12.0 (5.0-19.8)	8.2 (7.4-13.1)	
Range	3.5-31.6	3.5-31.6	3.7-22.4	

Abbreviations: N/A, not available; RT, radiation therapy.
* Two patients were treated with RT alone.
† Kruskal-Wallis test *P* value.
‡2 test *P* value.
Statistical comparisons are between surgery and surgery + RT groups.

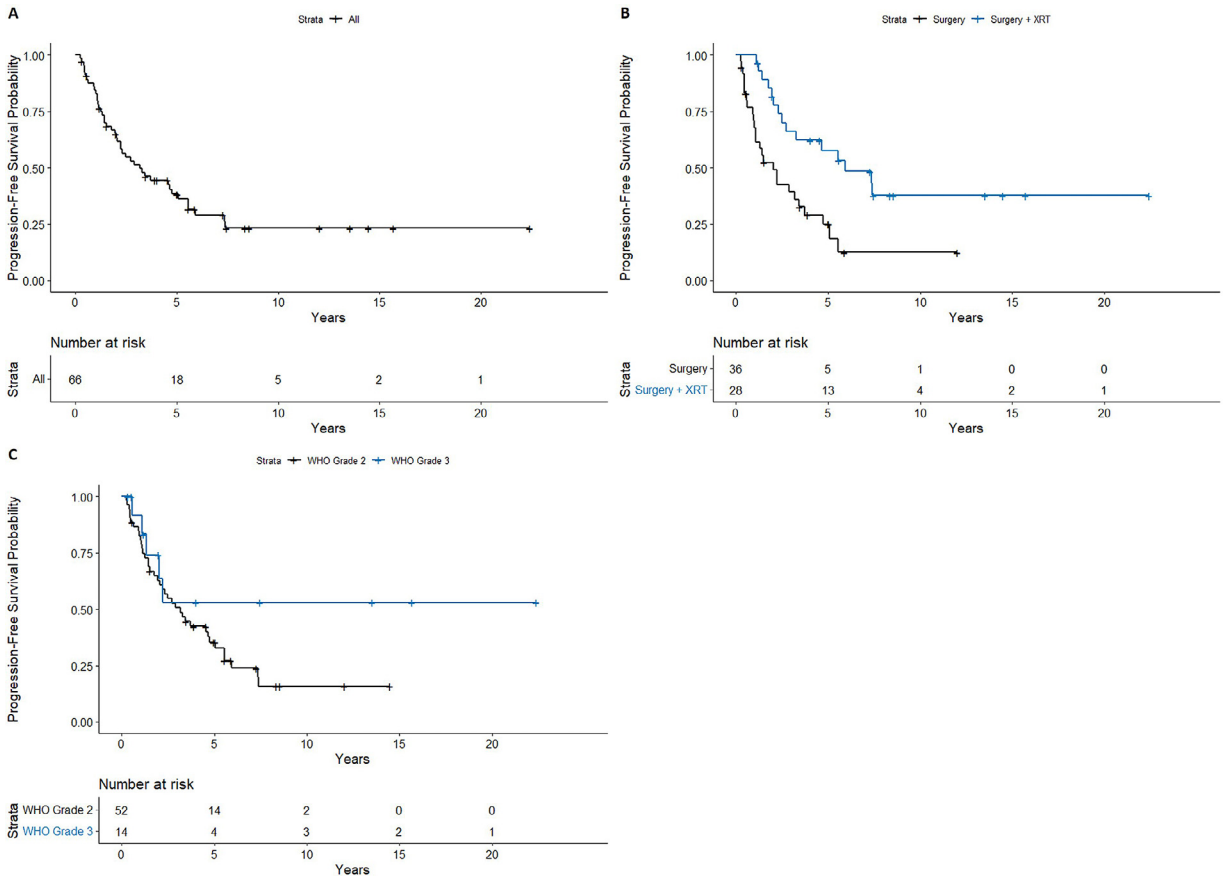

Fig. 1 Progression-free survival **(A)** for all patients and **(B)** by initial treatment and **(C)** World Health Organization (WHO) grade.

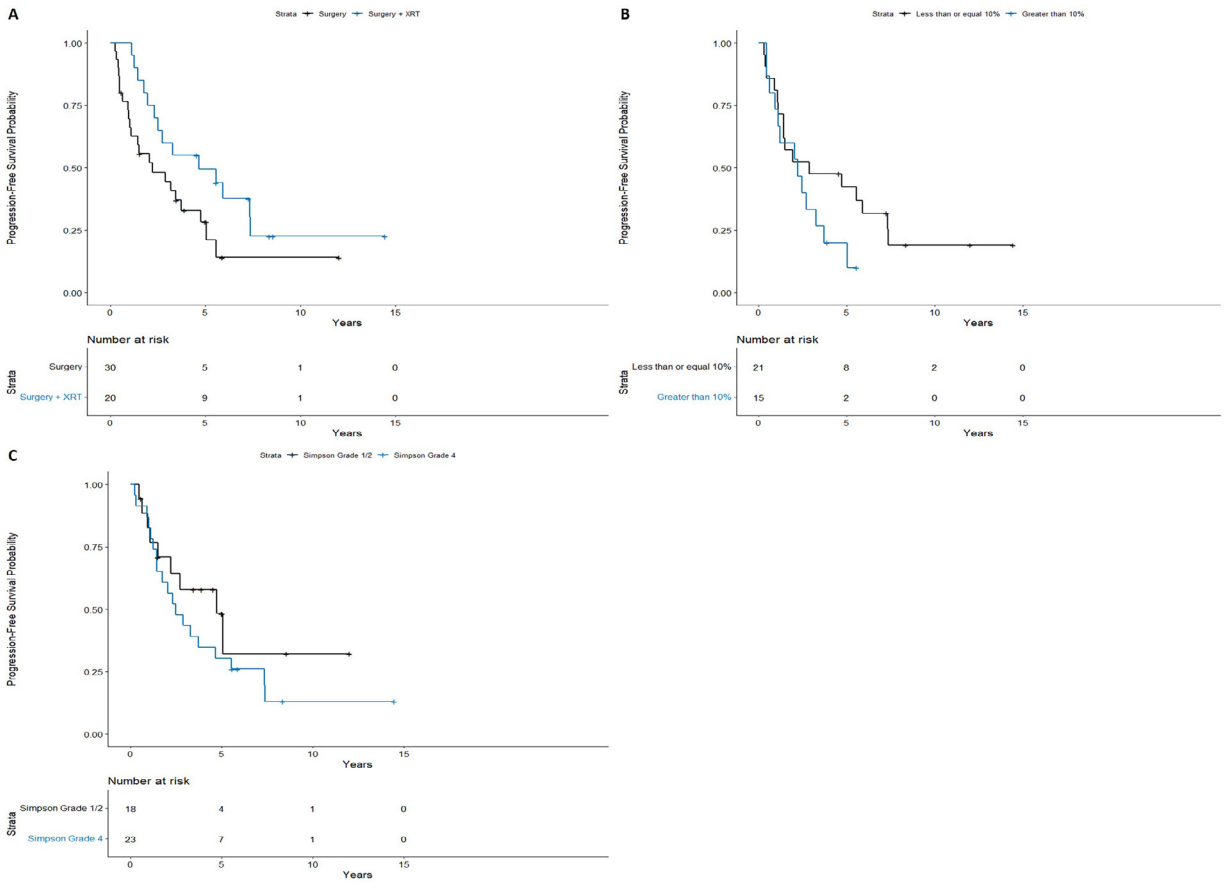

Fig. 2 Progression-free survival for patients with World Health Organization grade II meningiomas by **(A)** initial treatment, **(B)** Ki-67 index level, and **(C)** Simpson grade.

Discussion

In this retrospective study, we analyzed the outcomes of 66 patients with WHO grade 2 to 3 meningiomas treated with surgery and/or RT at our institution between 1992 and March 2017. In this cohort with a median follow-up of 12.4 years, the median PFS and OS were 3.2 and 8.8 years, with 10-year PFS and OS rates of 23.2% and 44.3%, respectively. To our knowledge, this is the longest follow-up of any published series for patients with atypical and malignant meningiomas. We observed significantly improved PFS in patients who received adjuvant RT compared with those treated with surgery alone, and there was a trend toward worse PFS in patients with Ki-67 index >10%. Forty-five patients (68.1%) were treated with salvage therapy for a total of 144 recurrences. Importantly, despite the high rates of recurrence, many patients tolerated multiple salvage therapies and exhibited long median OS of nearly 9 years.

Despite the aggressive nature and high rates of recurrence for atypical and malignant meningiomas, optimal management remains uncertain, particularly for WHO grade 2 disease. Surgery is the mainstay of treatment, but questions remain about the role of adjuvant RT, especially in the setting of GTR. Identifying the optimal treatment paradigm suffers from a lack of randomized data for these patients, and most published studies are small, retrospective series with limited follow-up. The first prospective

Table 2 Univariable and multivariable Cox proportional hazards analyses for progression-free survival

Variable	Univariable analysis, hazard ratio (95% confidence interval)	Multivariable analysis, hazard ratio (95% confidence interval)
Age (1 unit = 10 y*)	1.475 (1.138-1.912)	1.562 (1.189-2.054)
World Health Organization grade 3 vs 2	1.136 (0.51-2.531)	0.743 (0.318-1.739)
Surgery + radiation therapy vs surgery	0.686 (0.337-1.398)	0.576 (0.28-1.185)

* Age has been modeled as a continuous variable. However, in this analysis, age has been parameterized so that a 1-unit change does not represent a 1-year but 10-year change in age.

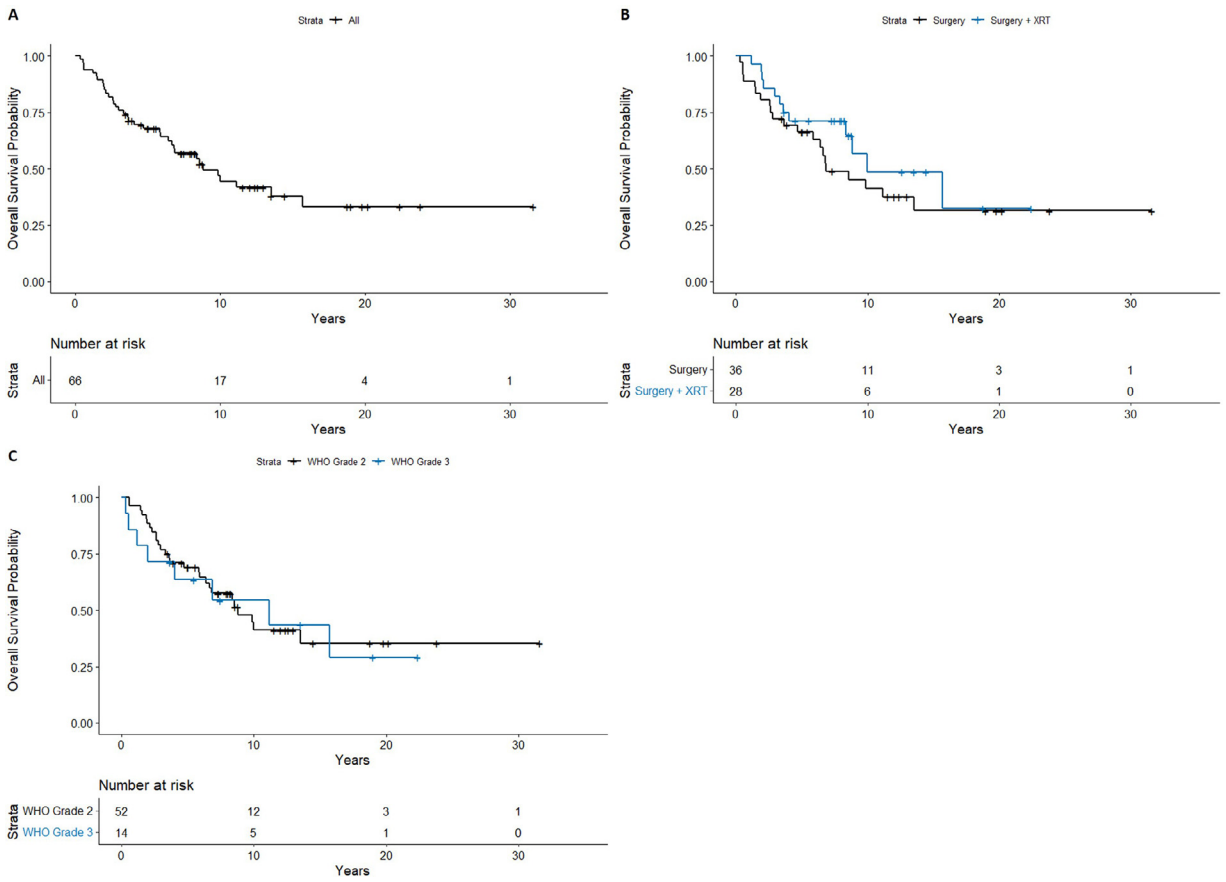

Fig. 3 Overall survival for **(A)** all patients and **(B)** by initial treatment and **(C)** World Health Organization (WHO) grade.

trial in this patient population, RTOG 0539, recently reported initial outcomes for patients stratified by low-, intermediate-, or high-risk meningiomas. Intermediate-risk disease included WHO grade 2 meningiomas after GTR or recurrent WHO grade 1 meningioma, and these patients were treated with adjuvant RT to 54 Gy.[15] High-risk patients included those with recurrent WHO grade 2 meningiomas after STR or WHO grade 3 meningiomas after any resection, and these patients were treated with adjuvant RT to 59.4 Gy. With a median follow-up of 4.0 years (4.8 years for living patients), patients with high-risk meningiomas had a 3-year PFS of 59.2% and 3-year OS of 78.6%.[14]

Our current retrospective study results are consistent with those from RTOG 0539, because we observed a 3-year PFS rate of 66.1% for patients treated with surgery and adjuvant RT and 39.2% for patients treated with surgery alone. These results are also consistent with the prospective, phase 2 EORTC 22942 study, which demonstrated that patients with WHO grade 2 meningiomas treated with adjuvant RT (60 Gy) have a 3-year PFS rate of 70%.[16] Overall, we observed 2- and 5-year PFS rates of 65.0% and 38.4%, respectively, and 2- and 5-year OS rates of 84.8% and 67.9%, respectively. Among patients who received adjuvant RT at our institution, the 2- and 5-year PFS rates were 81.6% and 57.7%, respectively, and the 2- and 5-year OS rates were 89.3% and 71.2%, respectively.

Our study demonstrated significantly improved PFS in patients who received adjuvant RT compared with patients treated with surgery alone (median, 5.9 vs 2.1 years; $P = .0017$), which is consistent with the results from other series.[7,10,11,17-22] In the largest and most recent of these series, Lee et al reported significantly higher recurrence rates in patients with atypical meningiomas treated with surgery alone compared with surgery and adjuvant RT, with a median time to recurrence of 1.9 versus 4.5 years.[17] Two large studies using data from the National Cancer Database also reported improved OS with adjuvant RT for WHO grade 2 meningiomas.[23,24]

Wang et al examined 2515 patients treated for atypical meningiomas, and found that adjuvant RT improved OS compared with no RT among patients undergoing STR (adjusted HR, 0.59; $P = .045$), but there was no survival benefit with adjuvant RT in patients who received GTR.[23] However, other studies have reported conflicting results, indicating no benefit to adjuvant RT in these patients.[25,26] Hardesty et al reported the results from 228 patients undergoing surgery for atypical meningiomas with a median follow-up of 52 months. The recurrence rate for patients who received adjuvant RT was 21%, with no difference between these patients and those treated with surgery alone (recurrence rate: 0.717; $P = .45$ for intensity modulated RT; recurrence rate: 1.27; $P = .55$ for SRS).[25]

Although the majority of series are limited to patients with atypical meningiomas, 2 studies have reported the long-term outcomes for patients with WHO grade 2 or 3 meningiomas treated with RT.[27,28] In a retrospective study of 85 patients, Adeberg et al reported 2- and 5-year PFS rates of 95% and 50% for atypical and 63% and 13% for anaplastic meningiomas treated with RT.[28] Pasquier et al reported similar outcomes for 119 patients treated with RT for WHO grade 2 or 3 disease, with 5- and 10-year disease-free survival rates of 58% and 48%, respectively.[27]

Our study also demonstrated a trend toward worse PFS in patients with Ki-67 index >10% (median, 2.1 vs 2.9 years; $P = .06$), which is consistent with the results of multiple other series.[29-33] In the current study, patients with elevated Ki-67 index >10% had 2- and 5-year PFS rates of 59.3% and 17.8%, respectively. Barrett et al evaluated the pathologic predictors of local recurrence in 97 patients with atypical meningiomas after GTR, and demonstrated that patients with Ki-67 >10% had significantly worse 3-year local recurrence rates of 34% versus 17.1% ($P = .018$).[29] Similarly, Kim et al showed Ki-67 index to be a strong predictor of treatment failure in patients treated for atypical or malignant meningiomas, with 5-year recurrence rates of 38% versus 8% for patients with Ki-67 ≥3% and <3%, respectively (log rank test: $P = .002$).[30] Although our study only showed a trend toward worse PFS with elevated Ki-67, this is likely due to being underpowered to show this difference. Ki-67 remains a valuable prognostic marker to consider when determining the optimal treatment approach for these patients.

Surprisingly, we did not find any significant differences in PFS or OS based on WHO grade. For patients with WHO grade 2 compared with grade 3 meningiomas, the median PFS was 3.2 years and not reached, respectively ($P = .13$), and the median OS was 8.8 versus 11.1 years, respectively ($P = .84$), which is likely due to the small sample size, resulting in too few patients to detect a difference. This result is in contrast with those of numerous studies that have demonstrated higher rates of recurrence and worse OS for malignant meningiomas compared with atypical.[2,28,34,35] In a retrospective analysis of 85 patients treated with RT for WHO grade 2 (n = 62) or 3 (n = 23) meningiomas, Adeberg et al reported that a higher grade was associated with worse 5-year PFS (50% vs 13%; $P = .017$) and 5-year OS (81% vs 43%; $P = .022$).[28] In contrast, Pasquier et al analyzed 115 patients treated with RT for WHO grade 2 (n = 82) or 3 (n = 37) meningiomas, and found no difference in disease-free survival or OS by grade, which is similar to the results in our current study.[27]

Although these retrospective studies, along with RTOG 0539, provide valuable information, no randomized prospective data exist to guide the management of patients with high-risk atypical or malignant meningiomas. The ongoing ROAM/EORTC-1308 and NRG-BN003 trials are evaluating adjuvant RT versus observation for patients with atypical meningiomas after GTR.[36,37] Additionally, we await longer-term follow-up date from the prospective RTOG 0539 trial of patients with high-risk meningiomas. Until these data are available, retrospective studies (including our current study, which reports the longest follow-up to date in this patient population) are critical to provide guidance for the optimal treatment of these patients.

Our study has several limitations. First, its retrospective nature inevitably introduces biases, including selection bias. Patients likely received more aggressive therapy, such as adjuvant RT, for perceived higher-risk disease. Next, although the study size of 66 patients is larger than that of most series evaluating this patient population, these numbers are still fairly small, resulting in a limited statistical power for subgroup analyses. Finally, the WHO classification system has changed over the years (2000, 2007, 2016), and our data are reported based on the classification at the time of the diagnosis. A portion of our patients may fall into different classifications using the most updated version, and some patients with benign meningiomas under the older systems possibly would be categorized as having a higher grade today. Molecular characterization of meningiomas should contribute to more rational risk stratification, and may yield insights into optimized and novel therapeutic approaches.[38] Thus, future prospective studies of WHO grade 2 and 3 meningiomas should characterize, report, and analyze the molecular characteristics of these tumors, in addition to the patient, treatment, and histologic parameters. Finally, quality of life and neurocognition were not systematically measured during this study, and measuring longitudinal changes in quality of life and neurocognition would have been informative, because the target volumes have evolved over the past 25 years.

Conclusion

This study with long-term follow-up demonstrates high rates of recurrence for atypical and malignant meningiomas, with significantly prolonged PFS with the addition of adjuvant RT to surgical resection. Elevated Ki-67 index was associated with a trend toward worse PFS, and warrants investigation as a prognostic marker in prospective studies. Given the long-term survival and efficacy of salvage therapy in this cohort, patients with atypical or malignant meningiomas should be monitored systematically long after initial treatment.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.adro.2021.100878.

References

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol*. 2018;20. iv1-iv86.
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. *Acta Neuropathol*. 2016;131:803–820.
3. Rogers CL, Perry A, Pugh S, et al. Pathology concordance levels for meningioma classification and grading in NRG Oncology RTOG Trial 0539. *Neuro Oncol*. 2016;18:565–574.
4. Pearson BE, Markert JM, Fisher WS, et al. Hitting a moving target: Evolution of a treatment paradigm for atypical meningiomas amid changing diagnostic criteria. *Neurosurg Focus*. 2008;24:E3.
5. Backer-Grondahl T, Moen BH, Torp SH. The histopathological spectrum of human meningiomas. *Int J Clin Exp Pathol*. 2012;5:231–242.
6. Modha A, Gutin PH. Diagnosis and treatment of atypical and anaplastic meningiomas: A review. *Neurosurgery*. 2005;57:538–550.
7. Aghi MK, Carter BS, Cosgrove GR, et al. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. *Neurosurgery*. 2009;64:56–60.
8. Hammouche S, Clark S, Wong AHL, Eldridge P, Farah JO. Long-term survival analysis of atypical meningiomas: Survival rates, prognostic factors, operative and radiotherapy treatment. *Acta Neurochir (Wien)*. 2014;156:1475–1481.
9. Wang YC, Chuang CC, Wei KC, et al. Long-term surgical outcome and prognostic factors of atypical and malignant meningiomas. *Sci Rep*. 2016;6:35743.
10. Zhi M, Girvigian MR, Miller MJ, et al. Long-term outcomes of newly diagnosed resected atypical meningiomas and the role of adjuvant radiotherapy. *World Neurosurg*. 2019;122:e1153–e1161.
11. Bagshaw HP, Burt LM, Jensen RL, et al. Adjuvant radiotherapy for atypical meningiomas. *J Neurosurg*. 2017;126:1822–1828.
12. Momin AA, Shao J, Soni P, et al. Outcomes of salvage radiation for recurrent world health organization grade II meningiomas: A retrospective cohort study. *J Neurooncol*. 2021;152:373–382.
13. Sun SQ, Hawasli AH, Huang J, Chicoine MR, Kim AH. An evidence-based treatment algorithm for the management of WHO Grade II and III meningiomas. *Neurosurg Focus*. 2015;38:E3.
14. Rogers CL, Won M, Vogelbaum MA, et al. High-risk meningioma: Initial outcomes from NRG Oncology/RTOG 0539. *Int J Radiat Oncol Biol Phys*. 2020;106:790–799.
15. Rogers L, Zhang P, Vogelbaum MA, et al. Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539. *J Neurosurg*. 2018;129:35–47.
16. Weber DC, Ares C, Villa S, et al. Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: A phase-II parallel non-randomized and observation study (EORTC 22042-26042). *Radiother Oncol*. 2018;128:260–265.
17. Lee G, Lamba N, Niemierko A, et al. Adjuvant radiation therapy versus surveillance after surgical resection of atypical meningiomas. *Int J Radiat Oncol Biol Phys*. 2021;109:252–266.
18. Aizer AA, Arvold ND, Catalano P, et al. Adjuvant radiation therapy, local recurrence, and the need for salvage therapy in atypical meningioma. *Neuro Oncol*. 2014;16:1547–1553.
19. Komotar RJ, Iorgulescu JB, Raper DMS, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. *J Neurosurg*. 2012;117:679–686.
20. Hemmati SM, Ghadjar P, Grün A, et al. Adjuvant radiotherapy improves progression-free survival in intracranial atypical meningioma. *Radiat Oncol*. 2019;14:160.
21. Zhu H, Bi WL, Aizer A, et al. Efficacy of adjuvant radiotherapy for atypical and anaplastic meningioma. *Cancer Med*. 2019;8:13–20.
22. Bray DP, Quillin JW, Press RH, et al. Adjuvant radiotherapy versus watchful waiting for World Health Organization grade II atypical meningioma: A single-institution experience. *Neurosurgery*. 2021;88:E435–E442.
23. Wang C, Kaprealian TB, Suh JH, et al. Overall survival benefit associated with adjuvant radiotherapy in WHO grade II meningioma. *Neuro Oncol*. 2017;19:1263–1270.
24. Rydzewski NR, Lesniak MS, Chandler JP, et al. Gross total resection and adjuvant radiotherapy most significant predictors of improved survival in patients with atypical meningioma. *Cancer*. 2018;124:734–742.
25. 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;119:475–481.
26. Yoon H, Mehta MP, Perumal K, et al. Atypical meningioma: Randomized trials are required to resolve contradictory retrospective results regarding the role of adjuvant radiotherapy. *J Cancer Res Ther*. 2015;11:59–66.
27. Pasquier D, Bijmolt S, Veninga T, et al. Atypical and malignant meningioma: Outcome and prognostic factors in 119 irradiated patients. A multicenter, retrospective study of the Rare Cancer Network. *Int J Radiat Oncol Biol Phys*. 2008;71:1388–1393.
28. Adeberg S, Hartmann C, Welzel T, et al. Long-term outcome after radiotherapy in patients with atypical and malignant meningiomas—Clinical results in 85 patients treated in a single institution leading to optimized guidelines for early radiation therapy. *Int J Radiat Oncol Biol Phys*. 2012;83:859–864.
29. Barrett OC, Hackney JR, McDonald AM, Wiley CD, Bredel M, Fiveash JB. Pathologic predictors of local recurrence in atypical meningiomas following gross total resection. *Int J Radiat Oncol Biol Phys*. 2019;103:453–459.
30. Kim D, Niemierko A, Hwang WL, et al. Histopathological prognostic factors of recurrence following definitive therapy for atypical and malignant meningiomas. *J Neurosurg*. 2018;128:1123–1132.
31. Bruna J, Brell M, Ferrer I, Gimenez-Bonafe P, Tortosa A. Ki-67 proliferative index predicts clinical outcome in patients with atypical or anaplastic meningioma. *Neuropathology*. 2007;27:114–120.
32. Vranic A, Popovic M, Cör Prestor B, Pizem J. Mitotic count, brain invasion, and location are independent predictors of recurrence-free survival in primary atypical and malignant meningiomas: A study of 86 patients. *Neurosurgery*. 2010;67:1124–1132.
33. Champeaux C, Dunn L. World Health Organization grade II meningioma: A 10-year retrospective study for recurrence and prognostic factor assessment. *World Neurosurg*. 2016;89:180–186.
34. Yang SY, Park CK, Park SH, Kim DG, Chung YS, Jung HW. Atypical and anaplastic meningiomas: Prognostic implications of clinicopathological features. *J Neurol Neurosurg Psychiatry*. 2008;79:574–580.
35. Ferraro DJ, Funk RK, Blackett JW, et al. A retrospective analysis of survival and prognostic factors after stereotactic radiosurgery for aggressive meningiomas. *Radiat Oncol*. 2014;9:38.
36. Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation versus observation following surgical resection of atypical meningioma: Study protocol for a randomised controlled trial. *Trials*. 2015;16:519.
37. U.S. National Library of Medicine. NRG-BN003: Observation or radiation therapy in treating patients with newly diagnosed grade II meningioma that has been completely removed by surgery. Available at: https://clinicaltrials.gov/ct2/show/NCT03180268. Accessed September 11, 2021.
38. Brastianos PK, Galanis E, Butowski N, et al. Advances in multidisciplinary therapy for meningiomas. *Neuro Oncol*. 2019;21(suppl 1):i18–i31.