Outcomes following Upfront Radiation versus Monitoring in Atypical Meningiomas: 16-year Experience at a Tertiary Medical Center

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Conflicts of Interest

The authors have no conflicts of interest to express.

Authorship Statement

RAM conceived the study. Data collection was performed by PCP. Analysis and interpretation of the data were done by RAM, PCP, THS, THS, SCP, GCC, JI, and HAF. The manuscript was drafted by PCP and RAM. All authors participated in revising and approving the final manuscript.
Abstract

Background: The role of post-operative upfront radiotherapy (RT) in the management of gross totally resected atypical meningiomas remains unclear. This single-center retrospective review of newly-diagnosed histologically-confirmed cases of World Health Organization (WHO) Grade II atypical meningioma at Weill Cornell Medicine from 2004-2020 aims to compare overall survival (OS) and progression free survival (PFS) of post-operative upfront radiotherapy versus observation, stratified by resection status (gross total resection [GTR]) versus subtotal resection [STR]).

Methods: 90 cases of atypical meningioma were reviewed (56% women; median age 61 years; median follow-up 41 months).

Results: In patients with GTR, hazard ratio (HR) of PFS was 0.09 for post-operative upfront RT versus observation alone (95% confidence interval [CI] 0.01-0.68; p = 0.02), though HR for OS was not significant (HR 0.46; 95% CI 0.05-4.45; p = 0.5). With RT, PFS was 100% at 12 and 36 months (compared to 84% and 63% respectively with observation); OS at 36 months was 100% (compared to 94% with observation).

In patients with STR, though PFS at 36 months was higher for RT arm versus observation (84% versus 74%), OS at 36 months was 100% in both arms. HR was not significant (HR 0.76; 95% CI 0.16-3.5; p = 0.73).

Conclusion: This retrospective study suggests post-operative upfront radiotherapy following GTR of atypical meningioma is associated with improved PFS compared to observation. Further studies are required to draw conclusions about OS.

Keywords
atypical meningioma, progression free survival, overall survival, radiotherapy, stereotactic radiosurgery
Key Points

Upfront RT is associated with improved PFS in new atypical meningioma after GTR.

Effect of upfront RT on OS in new atypical meningioma after GTR is less clear.

Retrospective study of atypical meningioma is challenged by need for long follow-up.

Importance of the Study

Timing of radiotherapy after resection of newly-diagnosed atypical meningioma remains controversial, particularly in the gross total resected tumors. Early post-operative radiotherapy appears to be useful in prolonging time to recurrence, but the effect on overall survival and optimal timing for radiotherapy remains an open question. This study summarizes over 15 years of retrospective experience with newly-diagnosed atypical meningioma at a tertiary center. The data confirms that early post-operative radiotherapy improves time to progression in newly-diagnosed atypical meningiomas that are gross total resected. The effect on overall survival was less clear. Patient retention is identified as an important barrier to following of long-term outcomes.
Introduction

Meningioma is the most common adult primary central nervous system (CNS) tumor.\(^1\) The World Health Organization (WHO) categorizes meningiomas into three grades of increasing biologic aggressiveness – WHO Grade I meningioma, WHO Grade II atypical meningioma, and WHO Grade III anaplastic/malignant meningioma.\(^2\) Despite advances in our understanding of the genetic landscape of meningioma, which have led to revisions of the histopathologic criteria for diagnosing atypical or anaplastic meningioma,\(^3\)–\(^8\) systemic treatments remain limited and management primarily depends on surgical intervention and radiotherapy. Fortunately, the majority of meningiomas are slow-growing WHO Grade I tumors. These have an indolent clinical course and can oftentimes be managed expectantly, with resection reserved for cases where consideration of age, symptoms, operative risk, and medical comorbidities favors intervention, especially in the setting of growing or symptomatic tumors. The extent of operation is broadly divided into gross total resection (GTR) or sub-total resection (STR) – classically judged by surgical impression, the modern inclusion of post-operative MRI can help with accuracy. Extent of resection is graded by the Simpson criteria, which takes into consideration the treatment of the dural attachment.\(^9\) With a complete resection, a WHO Grade I meningioma often requires no further treatment and clinically can be considered cured.

The optimal management of atypical meningiomas remains a topic of active investigation. WHO Grade II atypical meningioma is currently histologically defined by 4 to 19 mitotic figures per 10 high powered fields (with a newer threshold of 6 mitotic figures being considered), brain invasion, or at least three of the following histologic features – increased cellularity, small cells with a high nucleus-to-cytoplasm ratio, prominent nucleoli, sheet-like or pattern-less growth, or geographic necrosis. Atypical meningiomas follow a more active clinical course and require closer follow-up, as they can grow more quickly, cause more symptoms, and have higher rates of recurrence than WHO Grade I meningioma.\(^10\) Extent of resection for atypical meningiomas correlates with rates of local control.\(^11\)–\(^14\) Post-operative adjuvant radiation is often delivered with the goal of prolonging time to tumor recurrence, particularly in the setting of subtotal resection, and can be in the form of either fractionated external beam radiotherapy (EBRT) delivered in 1.8 to 2 Gray per fraction or stereotactic radiosurgery (SRS) delivered using high dose per fraction stereotactic techniques. There is good rationale and data to support adjuvant radiation following subtotal resection of atypical meningioma,\(^14\) though there is data to suggest tumors with spontaneous necrosis see less benefit.\(^15\)
One of the largest retrospective analyses of the role of RT in meningioma management was a study of 213 meningioma patients from the University of California San Francisco, that included 104 subtotal resections – of the patients that did not receive post-operative radiotherapy, the recurrence rate was 74% as compared to 29% in the upfront irradiation group. A more recent retrospective study of 2515 atypical meningiomas identified from The National Cancer Database found adjuvant radiotherapy significantly improved overall survival compared with no adjuvant radiotherapy (hazard ratio 0.59). Other studies cite 5 year progression-free rates of 77-88% in the radiotherapy group, as opposed to 43-59% in the group not radiated. However, the benefit of adjuvant radiation following gross total resection is less clear, with many large retrospective studies showing conflicting findings – with some demonstrating benefit of early post-operative upfront radiotherapy and others not.

Anaplastic meningiomas are often treated with irradiation regardless of extent of resection, given their aggressive nature and potential for rapid, early progression.

We report the outcomes of newly-diagnosed atypical meningiomas, in the context of upfront radiotherapy, at Weill Cornell Medicine over a 16-year period.

Materials and Methods

Atypical meningiomas managed at Weill Cornell Medicine between the years 2004 and 2020 were reviewed on an institutional IRB-approved protocol for demographics, date of initial surgery, extent of resection including GTR and STR (with GTR encompassing Simpson I-III), histopathologic features, presence and type of radiation treatment, and date of first progression on magnetic resonance image (MRI).

Only new diagnoses of atypical meningioma were assessed. Cases where date of initial diagnosis and first progression could not be determined because of inadequate records were excluded. Cases with only computed tomography (CT) imaging were also excluded. Primary outcomes were survival and disease progression. Pathology classification was by World Health Organization classification at time of surgery – specimens predating WHO 2016 were not re-interpreted under the new schema.
Data analysis was done in R, with results represented by Cox proportional hazards and Kaplan–Meier survival curves. Overall and progression-free survival curves were estimated by Kaplan–Meier and compared with two-sided log-rank test. All graphics were created in R version 4.0.3\textsuperscript{27} with the ggkm\textsuperscript{28} and survminer packages\textsuperscript{29}.

**Results**

Of the 120 new atypical meningioma cases identified in the pathology case records, 30 were excluded from analysis for inadequate records.

90 cases in total were analyzed, of which 56\% were women (Table 1). Median age at diagnosis was 61 years of age (range 21-96). Median follow-up was 41 months (range <1 month to 192 months). Median time elapsed from surgery to radiotherapy completion was 13 weeks.

Taking all 90 cases as a whole (including patients who had either GTR or STR), adjuvant radiotherapy was associated with significant reduced risk of progression (HR 0.32; 95\% CI 0.12-0.86; p = 0.024; Figure 1A), but no effect was seen on survival (Figure 1B).

**Gross Total Resection**

60 cases with new diagnosis of atypical meningioma had GTR. Of these, 43\% (26) had post-operative upfront radiotherapy. 16 patients received EBRT (external beam radiotherapy), from 52.2-60 Gy (Gray) delivered in 29 to 33 fractions. 10 patients received stereotactic radiosurgery (SRS). SRS was delivered variously using Varian iX (33 Gy in 3 fractions, 25 Gy in 5 fractions), Varian TrueBeam (33 Gy in 3 fractions), Novalis (24 Gy in 3 fractions, 25 Gy in 5 fractions), and CyberKnife (25 Gy in 5 fractions to 81\% isodose line). The equivalent dose in 2 Gy per fraction (EQD2) is 75.43 Gy for 33 Gy in 3 fractions, 44.57 Gy for 24 Gy in 3 fractions, and 35.71 Gy for 25 Gy in 5 fractions (assuming alpha/beta ratio 5). The remainder were observed post-operatively.

There was no statistically significant difference in age at diagnosis, follow-up duration, Simpson grading, tumor location, and mitotic count between the post-operative upfront radiotherapy group versus the observation only group (Table 2).
Post-operative upfront radiotherapy was associated with superior PFS as compared to observation alone (log-rank p-value 0.003, Figure 2A). PFS at 12 months (PFS12) and at 36 months (PFS36) was superior with the upfront RT arm compared to the observation arm (100% versus 84% at 12 months, and 100% vs 63% at 36 months, respectively). HR of tumor progression or death was 0.09 with post-operative upfront RT compared to post-operative observation (95% confidence interval [CI] 0.01-0.68; p = 0.02). However, hazard ratio was not significant for overall survival (OS) (HR 0.46; 95% CI 0.05-4.45; p = 0.50; Figure 2B). OS at 36 months (OS36) was 100% in the upfront RT group, and 94% in the observation group.

Of the 26 patients receiving post-operative upfront RT after GTR, no patients progressed during follow-up. Of the 34 patients who were observed and did not receive radiotherapy after GTR, 29% (10 of 34 cases) progressed at a median of 17.5 months. Of the 10 progressors, 2 were lost to follow-up, 2 were treated with both surgical re-resection and salvage RT, 1 was treated with salvage surgery alone, and 5 were treated with salvage RT.

**Subtotal Resection**

A total of 30 patients had a subtotal resection for newly-diagnosed atypical meningioma. Of these, 50% (15 of 30) received post-operative upfront RT while the others were observed only (Table 3). SRS was delivered variously using Varian iX (33 Gy in 3 fractions) and Novalis (25 Gy in 5 fractions). The equivalent dose in 2 Gy per fraction (EQD2) is 75.43 Gy for 33 Gy in 3 fractions, and 35.71 Gy for 25 Gy in 5 fractions (for alpha/beta ratio 5).

In patients who had STR, there was no significant difference in PFS (Figure 3A) or OS (Figure 3B) between the patients who had post-operative upfront RT versus those who were monitored (log-rank PFS p = 0.73; log-rank OS p = 1; HR 0.76 for progression or death with 95% CI 0.16-3.5, p = 0.73). Nevertheless, PFS at 12 and 36 months were better in the post-operative upfront RT group compared to post-operative observation alone – PFS12 100% compared to 85% for observation, PFS36 84% compared to 74% for observation. OS36 was 100% in both arms. Median time to progression was also longer in the post-operative upfront RT group as compared to the post-operative observation group – 40 months (mean 47 months; range 14-81 months) and 5 months (mean 11 months; range 4-23 months), respectively (p = 0.04).

Of the STR patients that received post-operative RT, five patients progressed – only one received SRS (the other four received EBRT). Median time to progression in the EBRT group was 51 months (range 14-81 months);
time to progression for the lone SRS progressor was 40 months. No statistically significant difference in PFS was found between SRS or EBRT (log-rank \( p = 0.4 \)). There were no deaths in any of the STR patients receiving post-operative RT (either SRS or EBRT).

Three patients in the observation arm progressed. All 3 of these progressors were treated with salvage RT.

**Discussion**

Atypical meningioma occupies a middle position between the indolent WHO Grade I meningioma and the aggressive anaplastic meningioma, and encompasses tumors with a wide range of clinical behaviors. Management of gross totally resected atypical meningioma remains controversial.

This study retrospectively assessed the effect of post-operative upfront radiotherapy on outcomes in newly-diagnosed atypical meningioma. The practice pattern in our cohort showed about 46% of patients received radiotherapy (43% for GTR, 50% for STR). In patients who had GTR, post-operative upfront RT was associated with superior PFS at 12 and 36 months compared to observation, and hazard ratio for PFS was 0.09 (95% interval [CI] 0.01-0.68; \( p = 0.02 \)). Hazard ratio for OS did not reach significance, though OS at 12 months and 36 months were superior in the post-operative upfront RT group. In patients who had STR, PFS at 12 and 36 months were numerically superior for the patients who had post-operative upfront RT compared to those who were observed, though HR for progression or death was not significant. Multiple prior studies have demonstrated improved outcomes with post-operative upfront RT following STR, and the failure to replicate those results in our dataset likely reflects lack of sufficient power in the subtotal resections group.

It is worth noting that there has been a substantial increase in the use of SRS for the treatment of meningioma in recent years, likely representing its increased convenience to patients, improving SRS techniques/capability, and the potential for decreased toxicity with improved cognitive outcomes.

Limitations of our study include its single-center and retrospective nature as well as patients lost to follow-up without serial imaging. Pathology was not re-interpreted based on changes made to the atypical meningioma classification in WHO 2016 (namely, brain invasion). The associations with outcomes identified in the study also may be confounded by clinical factors at point of care that are not apparent retrospectively during chart review. This is especially the case with patients with subtotally resected tumors, a population which has the
potential to be much more heterogeneous, with many more confounding clinical factors that may affect the
decision of whether to treat with adjuvant radiation. The group who did not receive postoperative radiotherapy
had a much higher median age than the radiated group. While this did not reach statistical significance, the age
difference spanned nearly two decades. In practice, factors such as age – a surrogate for life expectancy,
comorbid conditions, and functional status – are taken into consideration in selecting cases for radiotherapy, and
are difficult to extricate from the effect of radiotherapy itself on outcomes. Atypical meningioma patients who
have had gross total resections are may also exhibit these confounding factors.

In general, atypical meningiomas are inherently challenging to study because of their much smaller numbers
compared to WHO Grade I meningiomas and protracted clinical course. Despite review of over fifteen years-
worth of retrospective data at a busy urban tertiary academic medical center, there were significant obstacles to
data integrity because of the long follow-up course of atypical meningiomas. A significant number of cases
were referred in for second or third recurrence, and did not have adequate original outside records for the
purpose of this study, which limited the number of cases that could be analyzed. Furthermore, patients who
were clinically stable had a tendency to discontinue follow-up within several years, likely due to lack of desire
to continue indefinitely with clinical visits and MRIs. Social factors, such as relocation outside the metropolitan
area or changes in health insurance policy, may also have played a role in limiting individual follow-up.
Although the longest follow-up for all cases was 192 months, such extended follow-up was rare, with median
follow-up of only 41 months. A longer follow-up period may have captured more progressions, particularly
given that median time to progression for the post-operative upfront RT groups approached time for median
follow-up (40 months).

Prospective multi-center clinical trials, such as the ongoing NRG-BN003 or ROAM/EORTC-1308, have the
potential to circumvent many of these issues, with both incentive and resources directed at retention – however
the expense in coordinating such multi-year multi-center efforts is high.

Future improvements in the management of atypical meningiomas will be dependent on a better molecular
understanding of these tumors and clearer patient stratification in this heterogeneous space. DNA methylation-
based classifiers promise to supplement histologic classification in predicting prognosis and outcomes and
creating more accurate patient groups. Additionally, radiotracers such as gallium-68 (68Ga)–labeled
dodecanetetraacetic acid–tyrosine-3-octreotate (DOTATATE) and DOTA-(Tyr3)-octreotide (DOTATOC) have
may better delineating the extent of meningiomas for radiotherapy planning, and for discriminating meningioma
from necrosis or non-tumor tissue.\textsuperscript{33,34} DOTATATE may improve assessment of disease extent particularly in recurrent or residual disease.\textsuperscript{35} Dynamic contrast imaging has also been explored as a potential biomarker in stratification of meningiomas.\textsuperscript{36}

In conclusion, the role of adjuvant radiotherapy in the context of the gross totally resected atypical meningioma remains contentious. This retrospective analysis of newly-diagnosed atypical meningiomas at a tertiary academic medical center identified an association of post-operative upfront radiotherapy with prolonged progression free survival in patient who had gross total resection. Overall survival was also numerically superior at 12 months and 36 months however the hazard ratio was not significant. In the group of patients who had subtotal resections, progression free survival was numerically superior at 12 months and 36 months in the post-operative upfront radiotherapy group, but hazard ratio for progression or death was not statistically significant. At less than half the size of the gross total resection group, this subtotal resection portion of the analysis may have been underpowered. The long follow-up course for atypical meningioma renders it an especially difficult entity to study. Individual clinical factors are likely to continue to drive the decision for adjuvant radiotherapy, particularly for subtotal resections. Multicenter prospective randomized studies such as ROAM/EORTC-1308 and NRG-BN003 (both already underway) will be important in providing more definitive answers about the role of adjuvant radiotherapy in gross totally resected atypical meningiomas.
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-Oncology. 2018;20(suppl_4):iv1-iv86. doi:10.1093/neuonc/noy131

2. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathologica. 2007;114(2):97-109. doi:10.1007/s00401-007-0243-4

3. Weber RG, Bostrom J, Wolter M, et al. Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: Toward a genetic model of meningioma progression. Proceedings of the National Academy of Sciences. 1997;94(26):14719-14724. doi:10.1073/pnas.94.26.14719

4. Murakami M, Hashimoto N, Takahashi Y, Hosokawa Y, Inazawa J, Mineura K. A consistent region of deletion on 1p36 in meningiomas: identification and relation to malignant progression. Cancer Genetics and Cytogenetics. 2003;(1):8.

5. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic Analysis of Non-NF2 Meningiomas Reveals Mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013;339(6123):1077-1080. doi:10.1126/science.1233009

6. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. Brain Tumor Pathology. 2016;33(4):237-247. doi:10.1007/s10014-016-0271-7

7. Abedalthagafi M, Bi WL, Aizer AA, et al. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. Neuro-Oncology. 2016;18(5):649-655. doi:10.1093/neuonc/nov316

8. Strickland MR, Gill CM, Nayyar N, et al. Targeted sequencing of SMO and AKT1 in anterior skull base meningiomas. Journal of Neurosurgery. 2017;127(2):438-444. doi:10.3171/2016.8.JNS161076

9. Simpson D. The Recurrence Of Intracranial Meningiomas After Surgical Treatment. Journal of Neurology, Neurosurgery, and Psychiatry. 1957;20(1):22.

10. 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. International Journal of Radiation Oncology*Biology*Physics. 2008;71(5):1388-1393. doi:10.1016/j.ijrobp.2007.12.020

11. Goyal LK, Suh JL, Mohan DS, Prayson RA, Lee J, Barnett GH. Local control and overall survival in atypical meningioma: a retrospective study. International Journal of Radiation Oncology*Biology*Physics. 2000;46(1):57-61. doi:10.1016/S0360-3016(99)00349-1

12. Jo K, Park H-J, Nam D-H, et al. Treatment of atypical meningioma. Journal of Clinical Neuroscience. 2010;17(11):1362-1366. doi:10.1016/j.jocn.2010.03.036

13. Gabeau-Lacet D, Aghi M, Betensky RA, Barker FG, Loeffler JS, Louis DN. Bone involvement predicts poor outcome in atypical meningioma. Journal of Neurosurgery. 2009;111(3):464-471. doi:10.3171/2009.2.JNS08877

14. Park HJ, Kang H-C, Kim IH, et al. The role of adjuvant radiotherapy in atypical meningioma. Journal of Neuro-Oncology. 2013;115(2):241-247. doi:10.1007/s11060-013-1219-y

15. Sun SQ, Cai C, Murphy RK, et al. Management of atypical cranial meningiomas, part 2: predictors of progression and the role of adjuvant radiation after subtotal resection. Neurosurgery. 2014;75(4):356-363.
16. Wara WM, Sheline GE, Newman H, Townsend JJ, Boldrey EB. Radiation Therapy of Meningiomas. *American Journal of Roentgenology*. 1975;123(3):453-458. doi:10.2214/ajr.123.3.453

17. Wang C, Kaprelian TB, Suh JH, et al. Overall survival benefit associated with adjuvant radiotherapy in WHO grade II meningioma. *Neuro-oncology*. 2017;19(9):1263-1270. doi:10.1093/neuonc/nox007

18. Barbaro NM, Gutin PH, Wilson CB, Sheline GE, Boldrey EB, Wara WM. Radiation Therapy in the Treatment of Partially Resected Meningiomas. *Neurosurgery*. 1987;20(4):525-528. doi:10.1227/00006123-198704000-00003

19. Taylor BW, Marcus RB, Friedman WA, Ballinger WE, Million RR. The Meningioma Controversy: Postoperative radiation therapy. *International Journal of Radiation Oncology*Biology*Physics*. 1988;15(2):299-304. doi:10.1016/S0360-3016(98)90008-6

20. 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). *Radiotherapy and Oncology*. 2018;128(2):260-265. doi:10.1016/j.radonc.2018.06.018

21. 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(1):56-60. doi:10.1227/01.NEU.0000330399.55586.63

22. Hardesty DA, Wolf AB, Brachman DG, et al. The impact of adjuvant stereotactic radiosurgery on atypical meningioma recurrence following aggressive microsurgical resection. *Journal of Neurosurgery*. 2013;119(2):475-481.

23. Sun SQ, Kim AH, Cai C, et al. Management of atypical cranial meningiomas, part 1: predictors of recurrence and the role of adjuvant radiation after gross total resection. *Neurosurgery*. 2014;75(4):347-355.

24. Jenkinson MD, Waqar M, Farah JO, et al. Early adjuvant radiotherapy in the treatment of atypical meningioma. *Journal of Clinical Neuroscience*. 2016;28:87-92.

25. 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(4):790-799. doi:10.1016/j.ijrobp.2019.11.028

26. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *J Neurosurg*. 2010;113(2):202-209. doi:10.3171/2010.1.JNS091114

27. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2020. https://www.R-project.org/

28. Way M. *Ggkm: Kaplan-Meier Survival Curves with Numbers at Risk Below*.; 2016.

29. Kassambara A, Kosinski M, Biecek P. *Survminer: Drawing Survival Curves Using “Ggplot2”.*; 2020. https://CRAN.R-project.org/package=survminer

30. Amsbaugh M, Ugiliweneza B, Burton E, Skirboll S, Woo S, Boakye M. Patterns of Care and Outcomes of Adjuvant Radiotherapy for Meningiomas: A Surveillance, Epidemiology, and End Results and Medicare Linked Analysis. *Cureus*. 8(4). doi:10.7759/cureus.567

31. 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(1):519. doi:10.1186/s13063-015-1040-3
32. Sahm F, Schrmpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. The Lancet Oncology. 2017;18(5):682-694. doi:10.1016/S1470-2045(17)30155-9

33. Sommerauer M, Burkhardt J-K, Frontzek K, et al. 68Gallium-DOTATATE PET in meningioma: A reliable predictor of tumor growth rate? Neuro Oncol. 2016;18(7):1021-1027. doi:10.1093/neuonc/now001

34. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE Uptake in PET Imaging Discriminates Meningioma and Tumor-Free Tissue. J Nucl Med. 2015;56(3):347-353. doi:10.2967/jnumed.114.149120

35. Ivanidze J, Roytman M, Lin E, et al. Gallium-68 DOTATATE PET in the Evaluation of Intracranial Meningiomas. Journal of Neuroimaging. 2019;29(5):650-656. doi:10.1111/jon.12632

36. Chidambaram S, Pannullo SC, Roytman M, et al. Dynamic contrast-enhanced magnetic resonance imaging perfusion characteristics in meningiomas treated with resection and adjuvant radiosurgery. Neurosurgical Focus. 2019;46(6):E10. doi:10.3171/2019.3.FOCUS1954
Figure Legends

Figure 1 Hazard Ratio for Progression or Death in Atypical Meningioma

Across all patients with newly-diagnosed atypical meningioma following GTR or STR, post-operative upfront RT was associated with (A) reduced HR of progression, (B) but not of death.

Figure 2 PFS and OS of Observation versus Upfront RT following GTR

(A) Post-operative upfront RT (EBRT or SRS) following GTR in newly-diagnosed atypical meningioma is associated with improved PFS compared to post-operative observation alone (log-rank p = 0.003). (B) No improvement in OS with RT post-op compared to observation alone post-op (log-rank p = 0.5).

Figure 3 PFS and OS of Observation versus Upfront RT following STR

Post-operative upfront RT (EBRT or SRS) following STR in newly-diagnosed atypical meningioma is not statistically significant by (A) PFS nor (B) OS.
Table 1 Characteristics of All Cases

| Parameter                                | All (n=90) |
|------------------------------------------|------------|
| Age at diagnosis, years, median (IQR)    | 61 (29)    |
| Female, n(%)                             | 50 (56%)   |
| Follow-up, months, median (IQR)          | 41 (45)    |

Presenting Symptoms, n(%)

- Headache: 27 (30%)
- Motor: 27 (30%)
- Seizure: 17 (19%)
- Cognitive: 15 (17%)
- Vision Changes: 13 (14%)
- Sensory: 12 (13%)
- Auditory Changes: 2 (2%)
- Light-headedness: 1 (1%)
- Syncope: 1 (1%)
- Proptosis: 1 (1%)
- Asymptomatic: 11 (12%)

Tumor Location, n(%)

- Convexity / Parasagittal: 56 (62%)
- Sphenoid Wing (n=17), Sella (3), Anterior Skull Base (3), Posterior Fossa (4), Convexity (n=31), Parasagittal (25)
|                                      | 34 (38%)       | Foramen Magnum (2), Tentorial (5) | 60 (67%) | 30 (33%) |
|--------------------------------------|----------------|----------------------------------|----------|----------|
| Gross Total Resection (GTR), n(%)    |                |                                  |          |          |
| Subtotal Resection (STR), n(%)       |                |                                  |          |          |

IQR (Interquartile Range)
Table 2 Characteristics of Gross Total Resected Cases

| Gross Total Resection for Newly-Diagnosed Atypical Meningioma | Post-Operative Upfront RT (n=26) | Post-Operative Observation (n=34) | p |
|---------------------------------------------------------------|----------------------------------|----------------------------------|---|
| Age at diagnosis, median, years (IQR)                         | 60.6 (24)                        | 61.1 (32)                        | 0.90 |
| Female, n(%)                                                 | 15 (58%)                         | 19 (56%)                         |   |
| Follow-up, median, months (IQR)                              | 37 (38)                          | 44 (39)                          | 0.57 |
| Simpson                                                      |                                  |                                  |    |
| I                                                            | 23                               | 23                               | 0.10 |
| II                                                           | 3                                | 4                                |   |
| III                                                          | 0                                | 4                                |   |
| Unspecified                                                  | 0                                | 3                                |   |
| Location                                                     |                                  |                                  |    |
| Convexity/Parasagittal                                       | 19                               | 22                               | 0.68 |
| Other                                                        | 7                                | 12                               |   |
| Mitotic Count, median (IQR)                                   | 5 (2)                            | 4 (2)                            | 0.79 |
| EBRT Regimens, total dose / fractions (n)                     | 52.2Gy/29fx (1); 54Gy/30fx (10); 59.4Gy/33fx (2); 60Gy/30fx (2); Unspecified (1) | | |
| SRS Regimens, total dose / fractions (n)                      | 24Gy/3fx (1); 25Gy/5fx (7); 33Gy/3fx (2) | | |

No statistically significant difference between the two groups in age, median follow-up, Simpson grade, location (convexity/parasagittal versus all other locations), or mitoses. “Other” locations include anterior skull base, clivus, foramen magnum, posterior fossa, sella, sphenoid wing, and tentorium. Interquartile Range (IQR).
### Table 3 Characteristics of Subtotally Resected Cases

| Subtotal Resection for Newly-Diagnosed Atypical Meningioma | Post-Operative Upfront RT (n=15) | Post-Operative Observation (n=15) | p |
|-----------------------------------------------------------|----------------------------------|----------------------------------|---|
| Age at diagnosis, median, years (IQR)                     | 56 (17)                          | 73 (19)                          | 0.08 |
| Female, n(%)                                              | 9 (60%)                          | 7 (47%)                          | |
| Follow-up, median, months (IQR)                           | 65 (56)                          | 39 (42)                          | 0.35 |
| Simpson IV                                                | 15                               | 15                               | |
| Simpson V                                                 | 0                                | 0                                | |
| Location                                                  |                                  |                                  | |
| Convexity / Parasagittal                                  | 7                                | 8                                | 1 |
| Other                                                     | 8                                | 7                                | |
| Mitotic Count, median (IQR)                               | 4 (0)                            | 6 (3)                            | 0.1 |
| EBRT Regimens, total dose / fractions (n)                 | 50.4Gy/28fx (1); 54Gy/30fx (2); 59.4Gy/33fx (3); 60Gy/30fx (2); 60.4Gy/33fx (1); Unspecified (1) | | |
| SRS Regimens, total dose / fractions (n)                  | 25Gy/5fx (2); 30Gy/6fx (1); 33Gy/3fx (2) | | |

No statistically significant differences between upfront and non-upfront RT cases, although median age of non-RT group was higher. Other locations include meningiomas in anterior skull base, foramen magnum, posterior fossa, sella, sphenoid wing, and tentorium. Interquartile Range (IQR).
Figure 1

A

Postop Upfront RT

| Group          | Event Rate | Log-Rank p-value |
|----------------|------------|------------------|
| No (N=40)      | Reference  | N/A              |
| Yes (N=41)     | 0.32       | 0.12 - 0.86      |

AgeSegmented

| Group          | Event Rate | Log-Rank p-value |
|----------------|------------|------------------|
| <30 (N=25)     | Reference  | N/A              |
| <60 (N=25)     | 0.95       | 0.22 - 5.03      |
| 30-60 (N=30)   | 0.95       | 0.22 - 5.03      |

Extent/Resection

| Group          | Event Rate | Log-Rank p-value |
|----------------|------------|------------------|
| GTM (N=40)     | Reference  | N/A              |
| STR (N=30)     | 1.44       | 0.58 - 3.59      |

# Events: 21, Global p-value (Log-Rank): 0.18815
AIC: 169.92, Concordance Index: 0.68

B

Postop Upfront RT

| Group          | Event Rate | Log-Rank p-value |
|----------------|------------|------------------|
| No (N=40)      | Reference  | N/A              |
| Yes (N=41)     | 0.29       | 0.033 - 2.66     |

# Events: 6, Global p-value (Log-Rank): 0.22496
AIC: 41.44, Concordance Index: 0.65
Figure 2

Progression-Free Survival

No. at risk

Overall Survival

No. at risk

Observation RT

Observation RT

Observation RT
