JNS

CLINICAL ARTICLE

J Neurosurg 136:1517–1524, 2022

Adjuvant radiation versus observation with salvage radiation after gross-total resection of WHO grade II meningiomas: a propensity score–adjusted analysis

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OBJECTIVE After gross-total resection (GTR) of a newly diagnosed WHO grade II meningioma, the decision to treat with radiation upfront or at initial recurrence remains controversial. A comparison of progression-free survival (PFS) between observation and adjuvant radiation fails to account for the potential success of salvage radiation, and a direct comparison of PFS between adjuvant and salvage radiation is hampered by strong selection bias against salvage radiation cohorts in which only more aggressive, recurrent tumors are included. To account for the limitations of traditional PFS measures, the authors evaluated radiation failure-free survival (RFFS) between two treatment strategies after GTR: adjuvant radiation versus observation with salvage radiation, if necessary.

METHODS The authors performed a retrospective review of patients who underwent GTR of newly diagnosed WHO grade II meningiomas at their institution between 1996 and 2019. They assessed traditional PFS in patients who underwent adjuvant radiation, postoperative observation, and salvage radiation. For RFFS, treatment failure was defined as time from initial surgery to failure of first radiation. To assess the association between treatment strategy and RFFS while accounting for potential confounders, a multivariable Cox regression analysis adjusted for the propensity score (PS) and inverse probability of treatment weighted (IPTW) Cox regression analysis were performed.

RESULTS A total of 160 patients underwent GTR and were included in this study. Of the 121 patients who underwent observation, 32 (26.4%) developed recurrence and required salvage radiation. PFS at 3, 5, and 10 years after observation was 75.1%, 65.6%, and 45.5%, respectively. PFS at 3 and 5 years after salvage radiation was 81.7% and 61.3%, respectively. Of 160 patients, 39 received adjuvant radiation, and 3- and 5-year PFS/RFFS rates were 86.1% and 59.2%, respectively. In patients who underwent observation with salvage radiation, if necessary, the 3-, 5-, and 10-year RFFS rates were 97.7%, 90.3%, and 87.9%, respectively. Both PS and IPTW Cox regression models demonstrated that patients who underwent observation with salvage radiation treatment, if necessary, had significantly longer RFFS (PS model: hazard ratio [HR] 0.21, $p < 0.01$; IPTW model: HR 0.21, $p < 0.01$).

CONCLUSIONS In this retrospective, nonrandomized study, adjuvant radiation after GTR of a WHO II meningioma did not add significant benefit over a strategy of observation and salvage radiation at initial recurrence, if necessary, but results must be considered in the context of the limitations of the study design.

https://thejns.org/doi/abs/10.3171/2021.4.JNS21559

KEYWORDS adjuvant radiation; salvage radiation; gross-total resection; atypical meningiomas; recurrence; oncology

ABBREVIATIONS CTCAE = Common Terminology Criteria for Adverse Events; GTR = gross-total resection; HR = hazard ratio; IMRT = intensity-modulated radiation therapy; IPTW = inverse probability of treatment weighted; IQR = interquartile range; KPS = Karnofsky Performance Status; PFS = progression-free survival; PS = propensity score; RFFS = radiation failure-free survival; RTOG = Radiation Therapy Oncology Group; SG = Simpson grade; SRS = stereotactic radiosurgery; STR = subtotal resection.

SUBMITTED March 3, 2021. **ACCEPTED** April 28, 2021.
INCLUDE WHEN CITING Published online October 8, 2021; DOI: 10.3171/2021.4.JNS21559.

World Health Organization (WHO) grade II meningiomas have higher rates of recurrence and a worse prognosis than WHO grade I meningiomas.[1–3] Given the quality-of-life detriment and lower life expectancy associated with disease recurrence, many studies have explored the role of postoperative radiation following resection.[4–9] Adjuvant radiation after subtotal resection (STR) of a WHO grade II meningioma is widely accepted, but the benefit after gross-total resection (GTR) is still under debate.[9–16]

The NRG Oncology group is currently conducting a randomized controlled clinical trial (NCT03180268) to compare progression-free survival (PFS) after adjuvant radiation versus observation after GTR of newly diagnosed WHO grade II meningiomas. However, studies of this design fail to account for the potential success of salvage radiation at first recurrence in patients who are initially observed. Additionally, prior studies comparing adjuvant and salvage radiation are hampered by strong selection bias against salvage radiation cohorts, in which observed but disease-free patients are excluded, and only growing—and therefore more biologically aggressive—tumors are included in the salvage cohort.[5,17]

After GTR of WHO grade II meningiomas, patients and clinicians typically weigh the options of giving radiation upfront or at initial recurrence. Patients frequently perceive the risk and drawbacks of radiation therapy to be similar whether upfront or at first recurrence. In this setting, failure of first radiation, whether adjuvant or salvage, may be a more clinically relevant outcome for patients. A patient-centric outcome must account for the success rate of observation in addition to the success rate of both adjuvant and salvage radiation therapies.

In this study, in order to account for the limitations of historical narrowly focused outcomes, we introduced a novel outcome: radiation failure-free survival (RFFS). We evaluated traditional PFS associated with adjuvant radiation, observation, and salvage radiation after GTR of newly diagnosed WHO grade II meningiomas and also compared RFFS between two treatment strategies after GTR: adjuvant radiation versus observation with salvage radiation, if necessary, after initial recurrence.

Methods

Patient Population

We performed an IRB-approved retrospective review of all patients who underwent GTR of newly diagnosed WHO grade II meningiomas between 1996 and 2019 at our institution. Patients who received radiation prior to resection were excluded. Pathology reports were reviewed, and all of the included tumors met criteria for WHO grade II meningioma according to 2016 WHO diagnostic criteria.[18] The decision to receive adjuvant radiation or undergo serial observation after resection was determined by the preference of the treating neurosurgeon, radiation oncologist, and patient. Adjuvant intensity-modulated radiation therapy (IMRT) was given to the entire resection cavity with a 0.5- to 1.5-cm margin. Salvage IMRT was given to the area of recurrence and the resection cavity with a variable margin. Salvage stereotactic radiosurgery (SRS) was given to only the area of tumor recurrence with no margin. All patients were followed with either MRI or CT if MRI was contraindicated.

Data Collection

Patient demographics, extent of resection, tumor location and pathology, radiation modality and dosing, and treatment failure were collected from the electronic medical record. Tumor location was dichotomized into skull base (clinoid, sphenoid wing, petroclival, cavernous sinus, olfactory groove, planum sphenoidale, tuberculum sellae, spheno-orbital, lateral petrous, foramen magnum) and non–skull base (falcine, parasagittal, convexity, intraventricular, tentorial, calvarial). GTR was defined as Simpson grade (SG) I–III, which was confirmed with postoperative MRI, and extent of resection was reclassified as STR and excluded from analysis if residual tumor was identified radiographically. Preoperative tumor volumes were collected using volumetric MRI scans and Brainlab planning software (Brainlab). Radiation adverse events were collected and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://ctep.cancer.gov).

Statistical Methodology

Descriptive statistics were reported as counts (percentages), means (SD), or median (interquartile range [IQR]). Demographic variables were compared between the two treatment groups by using parametric Student t-test or nonparametric Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. For Kaplan-Meier analysis, log-rank testing was used to compare RFFS between groups.

In order to facilitate comparison with the literature, we evaluated PFS in patients who did not undergo adjuvant radiation by using two traditional definitions: 1) from the time of initial surgery to initial recurrence (observation alone), and 2) from the time of salvage radiation completion to subsequent tumor recurrence (salvage radiation alone). Additionally, we wanted to compare RFFS between two postoperative treatment strategies: 1) adjuvant radiation, and 2) observation with salvage radiation. Adjuvant radiation was defined as patients receiving radiation prior to tumor recurrence. For the adjuvant radiation cohort, RFFS and PFS were equivalent, and were measured from the date of initial resection to failure of adjuvant radiation. For the observation with salvage radiation cohort, RFFS was measured from the date of initial resection to failure of salvage radiation. In this cohort, recurrence after surgery was not considered a failure, because the clinical decision was to wait for recurrence before giving radiation. Patients who did not receive radiation (adjuvant or salvage) after surgery and those in whom the first radiation treatment did not fail were censored at time of last follow-up. Recurrence was defined as radiographic evidence of tumor recurrence by analysis of both imaging and clinical reports.

In order to account for selection bias in patients referred for adjuvant radiation, we estimated a propensity score (PS) for undergoing adjuvant radiation from a mul-

TABLE 1. Baseline characteristics of patients undergoing adjuvant radiation versus observation after initial GTR of a WHO grade II meningioma

Characteristic	Adjuvant Radiation, n = 39	Observation, n = 121	p Value
Baseline demographics			
Age in yrs, mean (SD)	58.4 (12.0)	59.4 (15.2)	0.72
Female, no. (%)	18 (46.2%)	72 (59.5%)	0.14
Race, no. (%)			0.82
Black	7 (17.9%)	17 (14.0%)	
White	31 (79.5%)	101 (83.5%)	
Other	1 (2.6%)	3 (2.5%)	
FU in mos, median (IQR)	33 (18–49)	47 (14–86)	0.21
Clinical frailty index, median (IQR)	4 (3–4)	3 (3–4)	0.57
Preop KPS score, median (IQR)	80 (70–90)	80 (70–80)	0.34
Tumor characteristics			
Histology, no. (%)			0.17
Atypical	31 (79.5%)	99 (81.8%)	
Chordoid	1 (2.6%)	12 (9.9%)	
Clear cell	7 (17.9%)	10 (8.3%)	
Tumor location: skull base, no. (%)	8 (20.5%)	34 (28.1%)	0.27
Simpson grade, no. (%)			**0.002**
I	19 (48.7%)	59 (48.8%)	
II	11 (28.2%)	56 (46.3%)	
III	9 (23.1%)	6 (4.9%)	
Preop tumor vol in cm^3, median (IQR)	29.3 (13.6–75.2)	35.8 (12.6–53.1)	0.86
Multiple meningiomas, no. (%)	2 (5.1%)	8 (6.6%)	0.89

Radiation Modality	Adjuvant Radiation w/ IMRT, n = 39	Recurrence, Salvage Radiation		p Value
		IMRT, n = 18	SRS, n = 14	
Radiation dosimetry				
Radiation dose in Gy, median (IQR)	54.0 (54.0–59.4)	59.4 (55–60)	14.5 (13–18)*	**0.006†**
Fractions, median (IQR)	30 (30–33)	30 (30–33)	1 (1)*	NA

FU = follow-up; NA = not applicable.
Boldface type indicates statistical significance.
* One patient received 25 Gy of SRS in 5 fractions.
† Comparison of adjuvant IMRT versus salvage IMRT radiation dose.

tivariable logistic regression model containing the following: age at diagnosis; sex; preoperative Karnofsky Performance Status (KPS); tumor histology (atypical, clear cell, chordoid); tumor location (skull base vs non–skull base); SG resection (grade I, II, or III); and the presence of multiple meningiomas. The inverse probability of treatment weighted (IPTW) method was then applied; patients who received adjuvant radiation were weighted by the reciprocal of their PS, and patients who received serial observation with salvage radiation, if necessary, were weighted by one minus the reciprocal of their PS.[19] We used three techniques to account for potential confounders: 1) multivariable Cox proportional hazards regression; 2) multivariable Cox regression adjusted for the (continuous) PS; and 3) IPTW Cox regression. All three Cox proportional hazards regression models investigated the association between postoperative treatment strategy and RFFS. These three techniques were selected to demonstrate the robustness of our results while addressing potential confounding variables.

All statistical analyses were performed using SAS version 9.4 (SAS Institute). The p values were 2-sided, with a significance threshold of 0.05.

Results

A total of 160 patients underwent GTR as initial treatment of WHO grade II meningiomas and were included in this study. Of these, 39 patients received adjuvant fractionated radiation therapy and 121 patients were observed. Baseline demographics, tumor characteristics, and radiation dosimetry for all patients are presented in Table 1. Patient age, sex, preoperative clinical frailty index, KPS, and tumor histology, location, and preoperative size were not significantly different between cohorts. There was a significantly lower proportion of SG II resections (28.2%

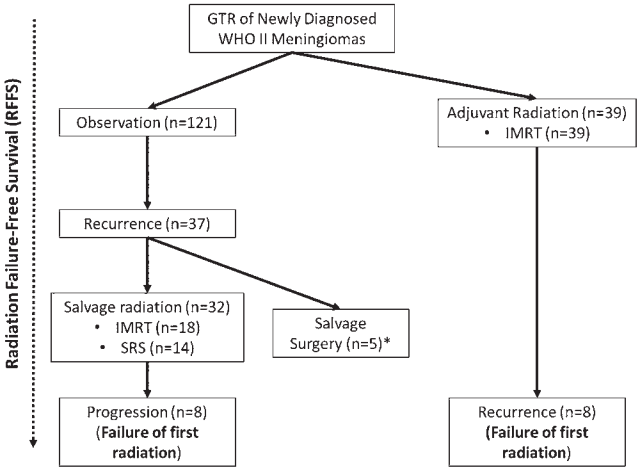

FIG. 1. Flow diagram of patients treated using different strategies after GTR of a newly diagnosed WHO grade II meningioma. The RFFS time was defined from initial surgery to failure of first radiation. *Patients who underwent salvage surgery were excluded from the RFFS analysis.

TABLE 2. Adverse events after adjuvant or salvage radiation

CTCAE	Adjuvant Radiation, n = 39	Salvage Radiation, n = 32
Grade 1, no. (%)*		
Fatigue	22 (56.4)	7 (21.9)
Alopecia	13 (33.3)	7 (21.9)
Radiation dermatitis	11 (28.2)	6 (18.8)
Radiation necrosis	4 (10.3)	1 (3.1)
Nausea	8 (20.5)	3 (9.4)
Headache	8 (20.5)	3 (9.4)
Amnesia	1 (2.6)	1 (3.1)
Grade 2, no. (%)*		
Fatigue	2 (5.1)	3 (9.4)
Alopecia	5 (12.8)	0 (0.0)
Radiation dermatitis	4 (10.3)	0 (0.0)
Radiation necrosis	1 (2.6)	2 (6.3)

* Percentages do not add up to 100% due to multiple adverse events occurring in a single patient.

vs 46.3%; p = 0.01) and a significantly higher proportion of SG III resections (23.1% vs 4.9%; p = 0.001) in the adjuvant radiation cohort than in the observation alone cohort.

Failure of adjuvant radiation occurred in 8 (20.5%) patients. Of 121 observed patients, 37 (30.6%) developed recurrence. Of these, 32 (86.5%) were treated with salvage radiation (IMRT or SRS) and 5 (13.5%) were treated with salvage surgery. Of 32 patients, 8 (25.0%) experienced failure of salvage radiation. The median follow-up was 42 months (IQR 16–76 months). A flow diagram of patients is shown in Fig. 1.

Of the patients who received adjuvant radiation, 19 (48.7%) had CTCAE grade 1, 4 (10.3%) had CTCAE grade 2, and 7 (17.9%) had both CTCAE grade 1 and 2 adverse events from radiation. Of the patients who received salvage radiation, 10 (31.3%) had CTCAE grade 1, 3 (9.4%) had CTCAE grade 2, and 2 (6.3%) had both CTCAE grade 1 and 2 adverse events from radiation. No patient experienced any adverse event beyond grade 2. The most common adverse events included alopecia, dermatitis, fatigue, nausea, and headache (Table 2).

Traditional PFS Outcomes

In the adjuvant radiation cohort, PFS and RFFS at 3 and 5 years was 86.1% (95% CI 68.0%–94.8%) and 59.2% (95% CI 29.4%–83.5%), respectively. In patients who underwent observation alone, PFS at 3, 5, and 10 years was 75.1% (95% CI 65.4%–82.8%), 65.6% (95% CI 54.5%–75.2%), and 45.5% (95% CI 30.8%–61.0%), respectively. When using the salvage radiation alone definition, PFS at 3 and 5 years was 81.7% (95% CI 59.1%–93.2%) and 61.3% (95% CI 36.8%–81.1%), respectively. The median tumor volume at the time of salvage radiation was 2.2 cm^3 (IQR 1.1–10.2 cm^3). There was no significant difference in PFS between the adjuvant radiation and observation alone (p = 0.39; Fig. 2A) or salvage radiation alone (p = 0.94; Fig. 2B) cohorts.

Patient-Centric Definition: RFFS

In the observation with salvage radiation cohort, 3-, 5-, and 10-year RFFS was 97.7% (95% CI 91.3%–99.4%), 90.3% (95% CI 79.5%–95.7%), and 87.9% (95% CI 76.3%–94.3%), respectively. The observation with salvage radiation cohort achieved a significantly longer RFFS than the adjuvant radiation cohort (p < 0.001; Fig. 3A). Of note, the median follow-up was 33 months (IQR 18–52 months) for the adjuvant radiation cohort compared with 45 months (IQR 13–85 months) for the observation with salvage radiation cohort (p = 0.32).

In subgroup analysis, patients who underwent SG I resection had 3- and 5-year RFFS of 100% in the observation with salvage radiation cohort and 88.2% (95% CI 62.8%–97.0%) in the adjuvant radiation cohort. In patients who underwent SG II or III resection, those in the observation with salvage radiation cohort had 3- and 5-year RFFS of 95.8% (95% CI 84.5%–98.9%) and 83.5% (95% CI 67.4%–92.6%), whereas the adjuvant radiation cohort had a 3-year RFFS of 82.1% (95% CI 49.1%–95.6%). RFFS was significantly longer in the observation with salvage radiation cohort than in the adjuvant radiation cohort after SG I (p = 0.04; Fig. 3B) and SG II or III resection (p < 0.001; Fig. 3C).

Multivariable Analysis

In multivariable Cox regression analysis, patients in the observation with salvage radiation cohort had significantly longer RFFS, after controlling for the difference in follow-up duration (hazard ratio [HR] 0.22, 95% CI 0.07–0.68). PS distributions for patients who received adjuvant radiation versus those in the observation with salvage radiation cohort are shown in Fig. 4. Patients in the observation with salvage radiation cohort had significantly longer RFFS even after adjusting for the PS (i.e., age at diagnosis, sex, preoperative KPS, tumor histology, tumor location, SG resection,

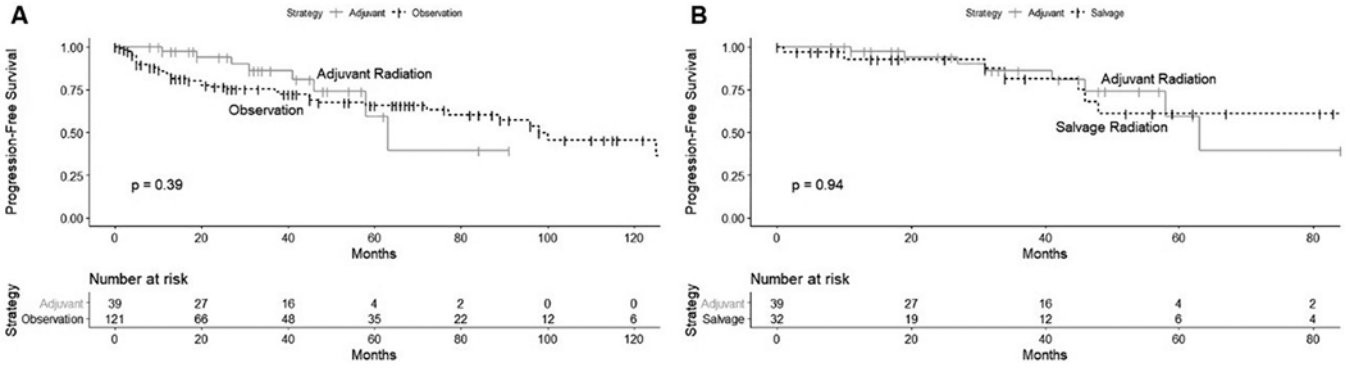

FIG. 2. Comparison of traditional definitions of PFS in patients undergoing GTR, stratified by adjuvant radiation versus observation alone (**A**) and salvage radiation alone (**B**).

and the presence of multiple meningiomas) and follow-up duration (HR 0.21, 95% CI 0.07–0.70). To demonstrate the robustness of these results, an IPTW multivariable Cox regression analysis was conducted, which also demonstrated that patients in the observation with salvage radiation cohort had significantly longer RFFS than patients in the adjuvant radiation cohort after controlling for follow-up duration (HR 0.21, 95% CI 0.07–0.58). Results of the three multivariable models are presented in Table 3.

Overall Survival

Overall survival did not differ significantly when comparing adjuvant radiation and observation alone (p = 0.19), salvage radiation alone (p = 0.25), or observation with salvage radiation (p = 0.23) cohorts. Of note, only 18 (11.3%) patients had known or documented deaths; all others were censored at last follow-up.

Sensitivity Analysis of Patients Who Received Salvage Surgery

Five (4.2%) patients who underwent observation followed by salvage surgery were qualitatively analyzed to understand why salvage surgery was chosen. In retrospect, 3 of these cases were also good candidates for salvage radiation, but surgery was chosen due to surgeon preference (2 patients) and patient preference (1 patient). Conversely,

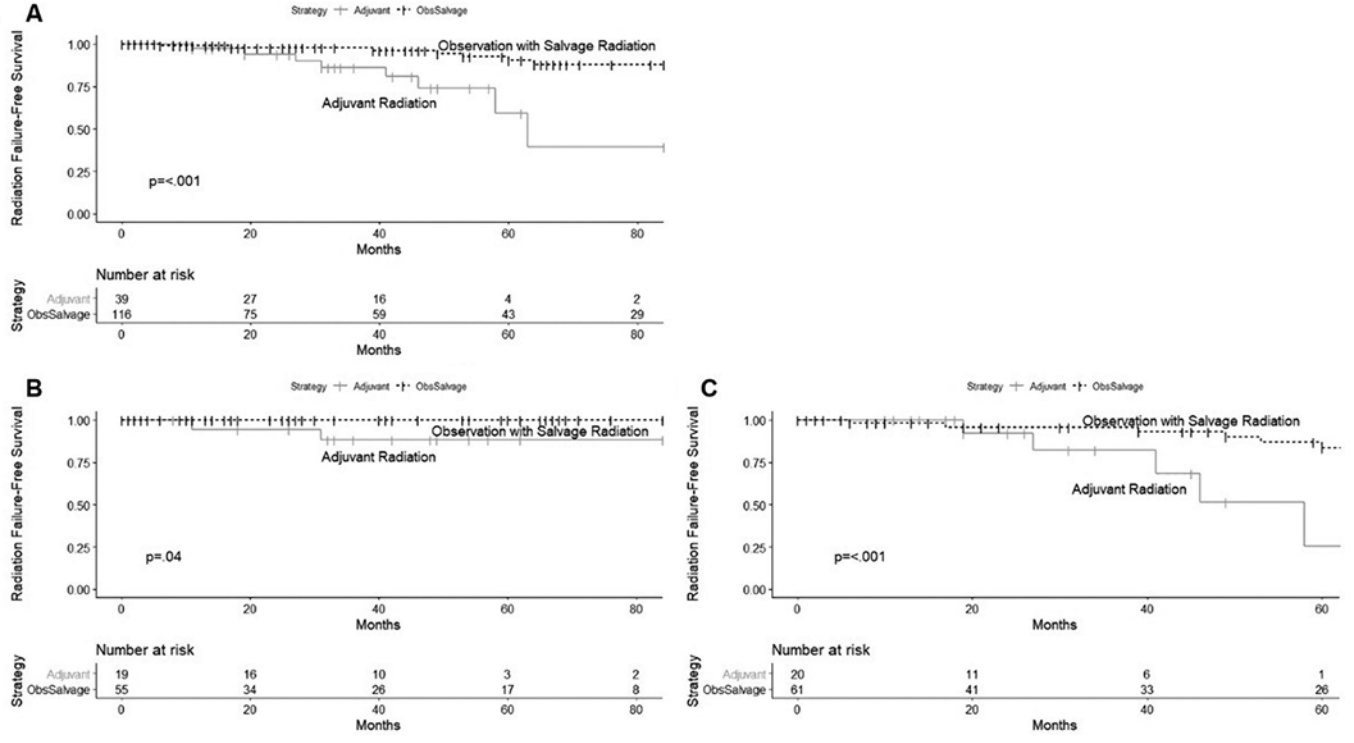

FIG. 3. Comparison of RFFS between adjuvant radiation versus observation with salvage radiation for entire cohort (**A**), only those undergoing SG I resection (**B**), or SG II/III resection (**C**). ObsSalvage = observation with salvage radiation.

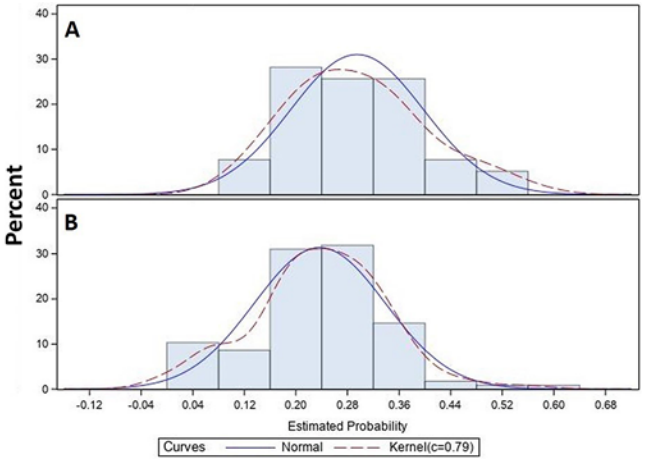

FIG. 4. Distribution of PSs stratified by treatment strategy: adjuvant radiation (**A**) versus observation with salvage radiation (**B**). Figure is available in color online only.

2 patients declined adjuvant radiation, were lost to follow-up, and subsequently returned with compressive symptoms necessitating re-resection.

If these 5 patients are included as experiencing treatment failures in the observation with salvage radiation cohort, the 3-, 5-, and 10-year RFFS rates in this cohort would be 93.1% (95% CI 85.5%–96.9%), 86.2% (95% CI 75.7%–92.6%), and 80.0% (95% CI 66.1%–89.2%), respectively. RFFS is still significantly longer in the observation with salvage radiation cohort as compared with the adjuvant radiation cohort ($p = 0.01$).

Discussion

Interpretation of Study Results

In our study, we found no significant difference in PFS between adjuvant and salvage radiation when using traditional definitions of PFS. A postoperative treatment strategy of observation with salvage radiation, if necessary, was associated with significantly longer RFFS compared with adjuvant radiation in patients who underwent initial GTR of a newly diagnosed WHO grade II meningioma. Of note, differences in RFFS between treatment strategies were significant even when controlling for Simpson grade within the PS and IPTW Cox regression analyses.

In our cohort of 121 patients who underwent observation, the 10-year actuarial PFS was 45.5%. This suggests that nearly half of the patients who undergo GTR will remain free of recurrent disease in the long term and may otherwise receive unnecessary radiation if routine postoperative radiation were the standard of care. Observation has the advantage of avoiding potential risks of radiation therapy including fatigue, alopecia, cognitive impairment, radiation necrosis with focal neurological deficits and/or seizures, and breakdown of overlying soft tissues.[20,21] Of the patients who experienced recurrence, it appears from our data that salvage radiation in this setting (smaller tumors, no prior radiation history) can be very effective. However, observation requires close follow-up and carries the risk of loss to follow-up, with recurrence only being discovered at onset of compressive symptoms requiring reoperation. In our series of 121 patients undergoing observation, this only occurred in 2 (1.7%) patients.

Comparison to the Literature

Similarly to our study, Lee et al. defined and compared two postoperative treatment strategies after GTR of WHO grade II meningiomas and they used a similar definition of RFFS.[22] Our 5-year (90%) and 10-year (88%) RFFS rates after observation with salvage radiation were similar to their reported 5- and 10-year RFFS rates of 92% and 87%. These authors found no significant difference comparing adjuvant radiation versus observation with salvage radiation at initial recurrence, if necessary. Their study was limited by a small adjuvant radiation cohort of only 18 patients.

In our study, patients treated with SG I–III resection followed by adjuvant radiation had 3- and 5-year PFS rates of 86.1% and 59.2%, respectively. This 3-year control rate is similar to the 93.8% control rate reported in the Radiation Therapy Oncology Group (RTOG) 0539 intermediate-risk cohort. This intermediate-risk cohort was a heterogeneous group that included patients who received adjuvant radiation after GTR of new WHO grade II meningiomas, adjuvant radiation of re-resected (GTR or STR) recurrent WHO grade I meningiomas, or salvage radiation of recurrent WHO grade I meningiomas.[23] The slightly higher control rate in RTOG 0539 may be accounted for by the fact that nearly one-third of patients in the intermediate-risk cohort had recurrent WHO grade I tumors, which may not have the same biological aggressiveness as WHO grade II tumors.

There was a considerable drop in our 5-year control rate

TABLE 3. Multivariable Cox proportional hazards models for comparing RFFS between treatment strategies

Predictors	Model Type, Adjusted HR (95% CI)		
	Multivariable*	PS†	IPTW‡
Observation w/ salvage radiation vs adjuvant radiation	0.22 (0.07–0.68)§	0.21 (0.07–0.70)§	0.21 (0.07–0.58)§
Length of FU	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.01)

* Multivariable Cox regression model adjusted for length of follow-up.
† Multivariable Cox regression model adjusted for the (continuous) PS and length of follow-up. The PS model contained age at diagnosis, sex, preoperative KPS score, tumor histology, tumor location, Simpson grade of resection, and the presence of multiple meningiomas.
‡ IPTW multivariable Cox regression model adjusted for length of follow-up.
§ Statistically significant.

after adjuvant radiation, a similar finding to a larger study by Park et al., in which the 5-year control rate fell to 53%. Of note, Park et al. only included SG I and II in order to be transparent in our comparison.[14] However, some studies (although many with smaller sample sizes) have reported 5-year adjuvant radiation PFS rates as high as 77%–89%.[6,24–26] Differences in adjuvant radiation PFS may be explained by several factors: differences in radiation dosing, radiation margins, and definition of GTR. Our median adjuvant IMRT dose was 54 Gy (IQR 54.0–59.4 Gy) to the resection cavity with 0.5- to 1.5-cm margins. This was similar to the RTOG 0539 intermediate-risk cohort, who received 54 Gy with 0.5- to 1.0-cm margins.[23] However, some prior studies report a median adjuvant IMRT dose of 60 Gy with 1- to 2-cm margins.[6,14,25] An ongoing clinical trial (NRG BN003) evaluating the utility of adjuvant radiation after GTR (SG I–III) of newly diagnosed WHO grade II meningiomas uses 59.4 Gy with 0.3- to 0.5-cm margins (NCT03180268).

Although higher doses of radiation may achieve better PFS, we did not observe a significant difference in PFS in patients receiving adjuvant IMRT ≤ 54 Gy compared to those receiving > 54 Gy, but this subgroup analysis was underpowered. Additionally, we defined GTR as SG I–III, whereas some other studies have defined GTR as SG I and II.[9,14,25,27] Inclusion of SG III resections may result in lower overall PFS with or without adjuvant radiation. In our study, when comparing adjuvant radiation in patients undergoing SG I versus SG II/III resections, there was a significantly lower control rate in the latter. It is possible that SG II/III may need to be treated at higher radiation doses. Another source of selection bias in our study is that a significantly higher proportion of SG III resections received adjuvant radiation versus observation, which may have negatively impacted the results of adjuvant radiation. However, in univariate subgroup analyses, RFFS was significantly longer for the observation with salvage radiation cohort after stratifying by SG I resection and SG II/III resection. Also, in multivariable analyses, when we controlled for Simpson grade in the PS analysis, patients in the observation with salvage radiation cohort had a significantly better RFFS compared with those in the adjuvant radiation cohort.

The 5-year PFS rate in our study for patients who underwent observation following GTR (65.6%) was comparable to the rate in a previously reported study[6] (67.8%) that also defined GTR as SG I–III, but was lower than in a study by Choi et al. in which the authors limited GTR to SG I and II (76.4%).[25] The 5-year PFS rate after salvage radiation in our study was 61.3%. This result is in the higher range of previously reported 5-year PFS rates after salvage radiation (45%–60%), but may be explained by two factors: 1) tumors are generally smaller at first recurrence after GTR, and 2) these tumors were not previously treated with radiation.[5,17] In the literature, prior radiation treatment (e.g., retreatments) and larger tumors are associated with lower control rates after salvage radiation.[5,17,28,29] In addition, our patients receiving salvage IMRT had a significantly higher median dose than those receiving adjuvant IMRT (59.4 vs 54.0 Gy, p = 0.01), which could partly explain the lack of difference in PFS between adjuvant and salvage radiation cohorts.

Limitations

The primary limitation of this study is its retrospective, nonrandomized design. To account for this limitation and to show the robustness of our results, we constructed three separate multivariable models: a multivariable Cox proportional hazards model, a PS-adjusted multivariable Cox model, and an IPTW multivariable Cox model. Despite this, there may be unknown confounders that led clinicians to select certain patients for adjuvant radiation as opposed to observation.

Of note, preoperative tumor volume was missing for approximately 25% of the patients in this cohort; these data are only reported descriptively and were not included in the PS and IPTW analysis. Given that all patients underwent GTR, we believed that preoperative tumor volume would probably not be a source of selection bias between cohorts. Additionally, there was a difference in length of follow-up between our two primary treatment strategies; however, this was not significantly different. To mitigate this potential confounder, we adjusted for follow-up duration in all of our multivariable models. The relatively shorter follow-up time in the adjuvant radiation group is probably due to trends in institutional practice patterns; patients in the latter part of the study period routinely underwent consultation with a radiation oncologist to discuss the option of adjuvant radiation after GTR of newly diagnosed WHO grade II meningiomas.

The study period spanned 2 decades, with changing WHO classifications of meningioma. To ensure standardized WHO grade II diagnostic criteria within our cohort, all meningiomas were reviewed to ensure that they met the 2016 WHO grade II diagnostic criteria.[18] Newer evidence suggests that DNA methylation and other genetic signatures such as cyclin-dependent kinase inhibitor 2A (CDKN2A) or telomerase reverse transcriptase promoter (TERTp) may further predict meningioma behavior, and in the future, these may impact the decision of when to treat with radiation.[30–33] Our study did not compare complications, radiation toxicities, patterns of failure, or quality-of-life measures between the two treatment strategies.

Conclusions

In this retrospective, nonrandomized study, adjuvant radiation after GTR of a newly diagnosed WHO grade II meningioma did not add any benefit over observation with salvage radiation at first recurrence, if necessary. In PS analyses, patients who underwent observation with salvage radiation at first recurrence had a significantly longer RFFS than those who underwent adjuvant radiation, even when controlling for age, sex, tumor histology, tumor location, Simpson grade, and follow-up duration. These results must be taken in the context of the limitations of the study design.

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Disclosures

Dr. Barnett is a consultant for Monteris Medical, Inc. Dr. Suh is a consultant for NovoCure, Neutron Therapeutics, and Philips. Dr. Chao received an honorarium from Varian Medical Systems. Dr. Recinos is a consultant for Stryker. Dr. Kshettry is a consultant for Integra and Stryker.

Author Contributions

Conception and design: Kshettry, Momin, Soni, Shao, Recinos. Acquisition of data: Momin, Soni, Shao. Analysis and interpretation of data: Kshettry, Momin, Soni, Recinos. Drafting the article: Kshettry, Momin, Soni, Recinos. Critically revising the article: Kshettry, Momin, Soni, Nowacki, Suh, Murphy, Chao, Angelov, Mohammadi, Barnett, Recinos. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kshettry. Statistical analysis: Momin, Soni, Nowacki. Study supervision: Momin.

Supplemental Information

Previous Presentations

This work was presented in part at the annual meeting of the North American Skull Base Society, held February 13, 2021 (virtual conference).

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