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Adjuvant radiation therapy, local recurrence, and the need for salvage therapy in atypical meningioma

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Background. The impact of adjuvant radiation in patients with atypical meningioma remains poorly defined. We sought to determine the impact of adjuvant radiation therapy in this population.

Methods. We identified 91 patients with World Health Organization grade II (atypical) meningioma managed at Dana-Farber/Brigham and Women's Cancer Center between 1997 and 2011. A propensity score model incorporating age at diagnosis, gender, Karnofsky performance status, tumor location, tumor size, reason for diagnosis, and era of treatment was constructed using logistic regression for the outcome of receipt versus nonreceipt of radiation therapy. Propensity scores were then used as continuous covariates in a Cox proportional hazards model to determine the adjusted impact of adjuvant radiation therapy on both local recurrence and the combined endpoint of use of salvage therapy and death due to progressive meningioma.

Results. The median follow-up in patients without recurrent disease was 4.9 years. After adjustment for pertinent confounding variables, radiation therapy was associated with decreased local recurrence in those undergoing gross total resection (hazard ratio, 0.25; 95% CI, 0.07–0.96; $P = .04$). No differences in overall survival were seen in patients who did and did not receive radiation therapy.

Conclusion. Patients who have had a gross total resection of an atypical meningioma should be considered for adjuvant radiation therapy given the improvement in local control. Multicenter, prospective trials are required to definitively evaluate the potential impact of radiation therapy on survival in patients with atypical meningioma.

Keywords: atypical meningioma, radiation, recurrence, salvage.

Meningioma is the most common intracranial tumor in the United States.[1] Historical series suggest that ~7% of patients presenting with meningioma have World Health Organization (WHO) grade II (ie, atypical) lesions,[2] while more modern series, which incorporate the 2000 and 2007 WHO pathologic reclassification systems for meningioma, suggest that an even higher proportion may be atypical.[3,4] Although atypical meningioma recurs more frequently than WHO grade I (ie, benign) meningioma,[5] it remains unclear whether adjuvant radiation should be routinely employed following maximal safe resection, particularly in those who have a gross total resection (GTR).[6] Given that disease recurrence has been linked with mortality in patients with atypical meningioma and that local progression can be associated with significant morbidity,[7] local control is considered to be an important therapeutic goal. The impact of immediate postoperative radiation therapy on long-term survival following GTR of atypical meningioma is

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unknown, and practice patterns vary widely.[2,7,8] The omission of radiation therapy must be related to either confidence in the efficacy of salvage options at recurrence or lack of faith in the ability of radiation to improve local control. The purpose of this study was to examine the impact of radiation therapy on local recurrence and need for salvage therapy among a relatively large series of patients with atypical meningioma.

Materials and Methods

Patient Population and Study Design

The Dana-Farber/Harvard Cancer Center Institutional Review Board approved this study. We used a search engine at our institution to identify a consecutive sample of 91 patients with an atypical (WHO grade II) meningioma managed at Dana-Farber/Brigham and Women's Cancer Center between 1997 and 2011. All patients underwent surgical resection as an initial management strategy. Extent of resection was deemed either GTR (Simpson grades I–III)[9] or subtotal resection (STR; Simpson grade >III) by the physician performing the operation. Extent of resection was also assessed radiographically. Thereafter, some patients received adjuvant external beam radiation therapy, as determined by the preferences of the treating neurosurgeon, radiation oncologist, and patient. No patient received brachytherapy. Of patients receiving adjuvant radiation, all but one received fractionated external beam radiation (median dose, 60.0 Gy; interquartile range, 55.8–64.0 Gy). The sole patient treated with stereotactic radiosurgery (SRS) received 16 Gy to a subtotally resected lesion. All patients were followed with either MRI or CT. Patients undergoing STR were included in the study in order to provide the percentage of patients receiving GTR versus STR and so that the impact of radiation therapy on the entire cohort of patients could be described.

Statistical Analysis

The predictor of interest in this study was employment of adjuvant radiation therapy versus no additional treatment. Baseline patient characteristics in patients who did and did not receive adjuvant radiation were compared using the *t*-test for continuous variables (all were normally distributed) and Fisher's exact test for categorical variables. Propensity scores derived from a logistic regression model for receipt versus nonreceipt of radiation therapy were generated, using the following covariates: age at diagnosis (continuous), gender, KPS $\geq$90 versus $<$90, tumor location (convexity vs base of skull), one-dimensional tumor size (continuous), reason for diagnosis (incidental finding vs symptom-initiated), and era of treatment (1997–2001, 2002–2006, 2007–2011). The covariates included in the propensity score model were selected prior to analysis and targeted during the chart abstraction process given their clinical relevance. Propensity scores were then used as continuous covariates in a Cox proportional hazards model to assess the impact of radiation therapy on the following endpoints: (i) local recurrence, defined radiographically, among patients who underwent radiographic GTR, and (ii) combined endpoint of salvage surgical or radiotherapeutic treatment (due to recurrence or progressive disease) or death due to progressive meningioma, as determined for patients in the entire cohort and among the subset that underwent GTR, with extent of resection assessed by the operating surgeon. The latter endpoint was used in addition to radiographic progression both as a potentially more clinically meaningful endpoint and to mitigate potential ambiguity with assigning radiographic progression. The latter endpoint was combined given the concern that patients treated with adjuvant radiation therapy initially may not be candidates for salvage therapy in the event of a recurrence because surgery and radiation had both been employed. Confounding variables (covariates that, when added to the Cox model already containing the propensity score, changed the hazard ratio [HR] for the radiation therapy variable by at least 10%) were included in the final Cox model along with the propensity score. To ensure the robustness of the propensity score model, univariable and multivariable Cox regressions for both outcomes of interest were performed with adjustment for the covariates included in the propensity score model. For both endpoints, the multivariable HR for the radiation covariate was similar to that obtained from the propensity score approach. Kaplan–Meier curves were used to graphically display the time to each of the above endpoints among patients who underwent GTR. Outcomes in patients who did and did not receive radiation therapy after undergoing STR were described qualitatively given the small sample size of this subset of patients. Outcomes in patients following recurrence were also described qualitatively. No failures occurred within the first 3 months, negating the utility of a landmark analysis.[10] The median follow-up in patients who did not experience a local recurrence was 4.9 years. All *P*-values are 2-sided. The threshold of .05 was used to determine significance. All statistical analyses were performed using SAS version 9.3.

Results

Patient Characteristics

Demographic and clinical characteristics for patients who did and did not receive radiation therapy are displayed in Table 1. No significant differences in age, gender, race, marital status, KPS, reason for diagnosis, and tumor site were observed between patients who did and did not receive radiation therapy. Patients who received radiation therapy had larger tumors at diagnosis (maximal one-dimensional size, 5.3 cm vs 4.2 cm, respectively, $P = .007$) and were more likely to have undergone STR than those who did not ($P = .004$).

Local Recurrence in Patients Who Underwent Gross Total Resection

Kaplan–Meier curves displaying time to local recurrence in patients who underwent radiographic GTR, stratified by receipt versus nonreceipt of adjuvant radiation therapy, are displayed in Fig. 1. Five-year freedom from local recurrence rates were 82.6% (95% CI, 55.2%–94.1%) and 67.8% (95% CI, 50.3%–80.2%) in patients who did and did not receive radiation therapy, respectively. After adjustment for confounding variables using a propensity score model, receipt of radiation therapy was associated with decreased local recurrence among patients undergoing GTR (HR, 0.25; 95% CI, 0.07–0.96; $P = .04$). On univariable Cox regression, radiation therapy was not significantly associated with decreased local recurrence (HR, 0.36; 95% CI, 0.11–1.23; $P = .10$). Era of diagnosis was the only confounder of the association

Table 1. Baseline characteristics in patients who did and did not receive radiation therapy

Variable	No Radiation[a] (n = 57)	Radiation[a] (n = 34)	P
Age, mean y (SD)	58 (17)	55 (14)	.46
Gender, n (%)			.83
Male	25 (44)	16 (47)	
Female	32 (56)	18 (53)	
Race, n (%)			.20[b]
White	47 (82)	26 (76)	
Other	5 (9)	7 (21)	
Unknown	5 (9)	1 (3)	
Marital status, n (%)			.10[b]
Unmarried	22 (39)	7 (21)	
Married	34 (60)	27 (79)	
Unknown	1 (2)	0 (0)	
KPS, n (%)			.50
≥90	19 (33)	14 (41)	
<90	38 (67)	20 (59)	
Reason for diagnosis, n (%)			.71
Symptoms	51 (89)	32 (94)	
Incidentally discovered	6 (11)	2 (6)	
Era of treatment, n (%)			.73
1997–2001	5 (9)	3 (9)	
2002–2006	25 (44)	12 (35)	
2007–2011	27 (47)	19 (56)	
Tumor size, mean cm (SD)	4.2 (1.9)	5.3 (1.9)	.007
Site, n (%)			1.0
Convexity	50 (88)	30 (88)	
Nonconvexity	7 (12)	4 (12)	
Extent of resection, n (%)			.004
GTR	52 (91)	22 (65)	
STR	5 (9)	12 (35)	

Abbreviations: KPS, Karnofsky Performance Status; N, Number; SD, Standard Deviation.
[a]Percentages may not add to 100 due to rounding.
[b]Excludes patients with unknown status.

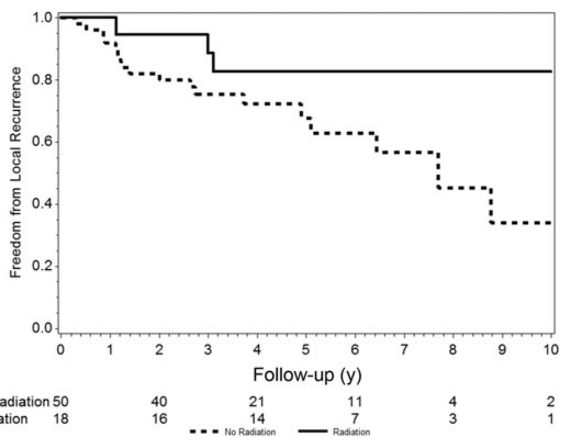

Fig. 1. Local recurrence in patients undergoing GTR, as stratified by receipt versus nonreceipt of radiation.

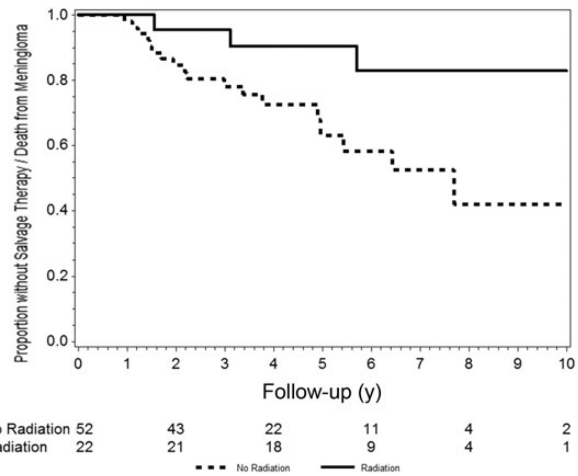

Fig. 2. Salvage therapy/death due to progressive meningioma in patients undergoing GTR, as stratified by receipt versus nonreceipt of radiation.

Table 2. Multivariable Cox regression for additional treatment or death secondary to meningioma using propensity score for receipt versus nonreceipt of radiation as a covariate

Variable	Multivariable HR*	95% CI	P
Radiation			
No	Ref	–	–
Yes	0.21	0.06–0.68	.009
KPS			
<90	Ref	–	–
≥90	0.42	0.17–1.00	.05

*Adjusted for propensity score for receipt versus nonreceipt of radiation therapy.

between radiation therapy and local recurrence. After adjustment of the Cox model by the same covariates used to adjust the propensity score model, the association between radiation therapy and local recurrence achieved statistical significance (HR, 0.24; 95% CI, 0.06–0.91; $P = .04$). No differences in overall survival were seen between patients who did and did not receive radiation therapy.

Salvage Treatment/Death Due to Progressive Meningioma

Kaplan–Meier curves displaying time to the combined endpoint of salvage treatment/death due to progressive meningioma in patients who underwent a radiographic GTR, as stratified by receipt versus nonreceipt of radiation therapy, are displayed in Fig. 2. After adjustment for confounding variables using a propensity score model, receipt of radiation therapy was associated with decreased need for salvage treatment or death due to meningioma (HR, 0.21; 95% CI, 0.06–0.68; $P = .009$; Table 2). Among the whole cohort (including patients who underwent an STR), this association remained significant (HR, 0.26; 95% CI, 0.10–0.69; $P = .007$). Among patients who underwent an STR, 2/12 and 1/5

Table 3. Outcome after surgical or radiotherapeutic treatment of locally recurrent disease

Patient Number	Age/Gender	Location/Size (mm)	Initial Treatment	Interval to Recurrence (y)	Treatment/Size (mm) at Recurrence	Interval to Failure or Last Follow-up (y)	Failure After Treatment for Recurrence[a]
1	50/female	R frontal/80	Surgery (STR)	1.9	Surgery (GTR)/10	1.3	Yes
2	63/female	R frontal/57	Surgery (STR)	3.2	Surgery (GTR)/44	1.1	Yes
3	72/male	L temporal/33	Surgery (STR)	1.5	Surgery (GTR)/20	0.0	No
4	45/female	L frontal/80	Surgery (GTR)	3.0	RT (64.0 Gy)/10	2.4	Yes
5	49/male	R frontal/25	Surgery (GTR)	1.2	RT (59.4 Gy)/10	1.1	Yes
6	70/male	L base of skull/20	Surgery (GTR)	1.4	RT (61.2 Gy)/23	3.4	Yes
7	22/female	R frontal/60	Surgery (STR)	1.7	RT (59.4 Gy)/17	4.3	No
8	48/female	R frontal/70	Surgery (GTR)	4.9	RT (57.6 Gy)/9	2.2	No
9	61/female	R frontal/19	Surgery (STR)	1.5	RT (59.4 Gy)/21	1.3	No
10	69/female	L frontal/48	Surgery (GTR)	3.4	RT (59 Gy)/21	1.6	No
11	69/male	R parietal/70	Surgery (GTR)	6.4	RT (45 Gy)/41	3.6	No
12	76/female	L frontal/27	Surgery (GTR)	5.0	RT (13 Gy, SRS)/12	7.2	No
13	88/male	R frontal/46	Surgery (GTR)	2.2	RT (15 Gy, SRS)/21	4.1	No
14	37/female	L frontal/65	Surgery (GTR)	7.7	Surgery (GTR) plus RT (18 Gy, SRS)/50	5.5	Yes
15	57/female	R frontal/35	Surgery (GTR)	3.8	Surgery (GTR) plus RT (66 Gy)/10	4.0	Yes
16	80/female	L frontal/47	Surgery (GTR)	0.9	Surgery (GTR) plus RT (60 Gy)/50	1.1	Yes
17	55/female	L frontal/70	Surgery (GTR)	2.2	Surgery (GTR) plus RT (54 Gy)/11	2.6	No
18	56/male	R frontal/12	Surgery (GTR)	5.4	Surgery (GTR) plus RT (64 Gy)/32	0.0	No
19	72/male	L frontal/58	Surgery (GTR)	1.1	Surgery (STR) plus RT (60 Gy)/43	2.8	No
20	45/female	L base of skull/35	Surgery (STR) plus RT (64.0)	5.6	Surgery (STR)/22	1.3	Yes
21	47/female	R parietal/49	Surgery (STR) plus RT (59.4)	3.7	Surgery (STR)/32	0.7	Yes
22	48/male	R frontal/70	Surgery (GTR) plus RT (68.0)	3.1	Surgery (STR)/5	0.6	Yes
23	62/male	R parietal/46	Surgery (STR) plus RT (61.2 Gy)	5.7	Surgery (GTR)/31	0.2	No

Abbreviations: GTR, gross total resection; L, left; mm, millimeters; R, right; RT, radiation therapy; SRS, stereotactic radiosurgery; STR, subtotal resection; y, years.
[a]Failure defined as need for additional surgical or radiotherapeutic treatment/death due to progressive disease.

who did and did not receive adjuvant radiation therapy, respectively, required salvage therapy (not statistically significant).

Outcome After First Recurrence

Patient outcomes after treatment for first local recurrence for all patients are displayed in Table 3. As shown in Table 3, of 23 patients treated for locally recurrent disease, 19 were initially treated with surgery alone and 4 were initially treated with surgery plus radiation. Of the 19 patients who developed a recurrence after receiving surgery alone as initial management, 8 later developed a second recurrence in spite of salvage treatment and required a third course of local therapy, including 2/3 patients treated with surgery alone, 3/10 patients treated with radiation alone, and 3/6 patients treated with surgery plus radiation for their first recurrent tumor. Of the 4 patients with recurrences who had received surgery and radiation as initial management, all were treated with surgery alone as salvage, and 3 developed a recurrence after their salvage therapy, requiring additional treatment thereafter. Particularly relevant to decision-making regarding the use of radiation after GTR is the clinical course following the initial treatment decision. Patient outcomes for patients following GTR based on radiographic progression are depicted in Figure 3.

Among patients who were treated with surgery alone as initial therapy ($n = 57$), 6 patients died (2 of progressive meningioma). Among patients treated with surgery and radiation as initial therapy ($n = 34$), 4 patients died (2 of progressive meningioma). Two patients with atypical meningioma at initial diagnosis (both managed with surgery as monotherapy) experienced transformation to WHO grade III (malignant) meningioma. Serious long-term adverse events in patients undergoing radiation were uncommon, although 1 patient developed an in-field glioblastoma 6 years after treatment for the meningioma.

Discussion

In this study of patients with atypical meningioma, we found that adjuvant radiation is associated with decreased local recurrence following GTR. We also noted decreased occurrence of the combined endpoint of salvage treatment or death due to meningioma among the whole cohort and those undergoing GTR.

Atypical meningioma recurs more frequently than benign (WHO grade I) lesions.[11–13] Extent of resection is a key predictor of recurrence among patients with atypical meningioma, and given that patients treated with STR are at very high risk of locally progressive disease, adjuvant radiation therapy is likely warranted

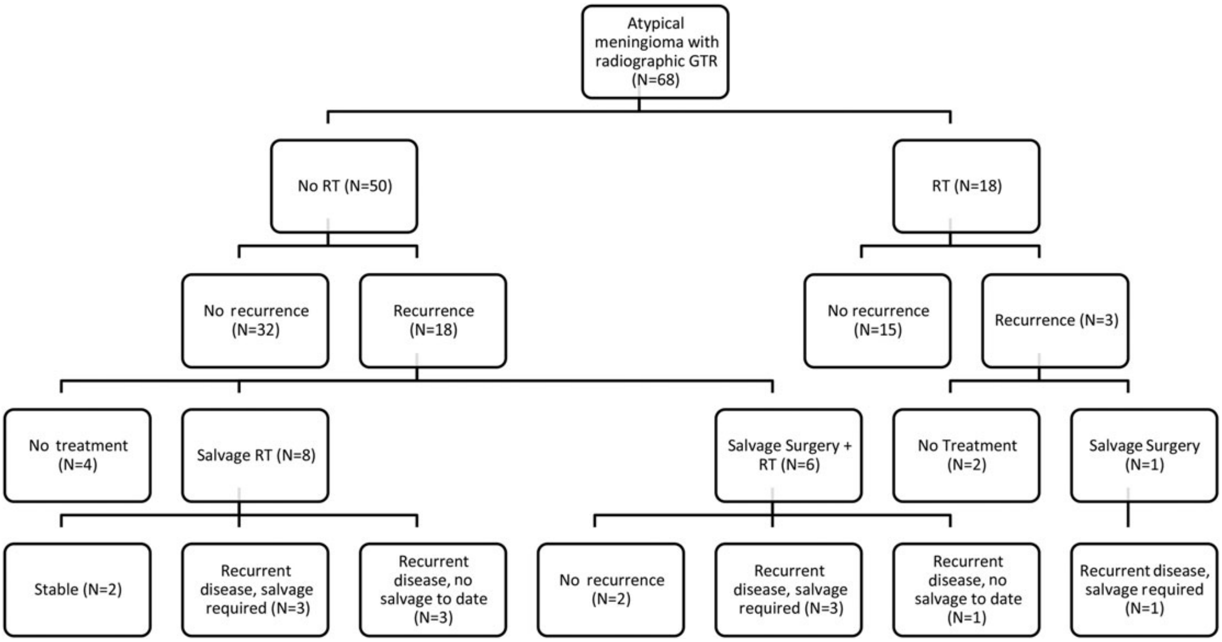

Fig. 3. Patient outcome, as stratified by receipt versus nonreceipt of radiotherapy (RT), in patients undergoing radiographic GTR.

in this population.[2,12,14] Whether to offer radiation after GTR remains controversial. The results of the current study suggest that adjuvant radiation therapy improves local control and should be considered in patients following GTR. Some investigators have called for employment of radiation therapy in patients with atypical meningioma given the possibility that recurrent tumors may be more aggressive than the original primary.[15] Notably, in the present series, 2/13 patients treated surgically for recurrence progressed to malignant (WHO grade III) histology.

Radiation may be especially useful in patients for whom the viability of repeat resection (in the event of a local recurrence) would be limited due to technical/anatomical constraints or unacceptably high levels of morbidity. What is unknown, however, is whether this improvement in local control translates to a potential survival benefit given the long time course of the disease and low overall numbers in any patient series. One could accept the proposition that radiation improves local control in the adjuvant setting but reasonably argue for the omission of radiation based on a belief that salvage is possible. We have attempted to describe the events following recurrence qualitatively, but the numbers of events are too small to make any firm conclusions. A large, prospectively randomized study with overall survival as a primary endpoint will be needed to better define the role of adjuvant radiation in the treatment of atypical meningioma. Of note, the European Organisation for Research and Treatment of Cancer is conducting a phase II trial (NCT00626730) randomizing patients with WHO grade II meningiomas to radiation versus observation, stratified by receipt versus nonreceipt of GTR, with progression-free survival as the primary endpoint. The toxicity of radiation therapy must also be considered. In the short term, adverse effects, including fatigue, nausea, hair loss, discomfort, and edema, can occur, while in the long term, radiation necrosis, focal neurologic deficits, visual/auditory decline, seizures, second malignancies, and vascular compromise, among other toxicities, are possible.

A positive impact of radiation on local control for atypical meningioma following GTR is not universally accepted or clearly supported by the literature. Aghi et al.[7] found that adjuvant radiation therapy was associated with a trend toward decreased local recurrence ($P = .10$) in patients who underwent GTR. More recently, Kotomar et al.[16] also found that the use of adjuvant radiation therapy was associated with a trend toward decreased local recurrence ($P = .09$); their study included 45 patients, and limited power may have prevented the group from finding a significant association. Notably, Mair et al.[17] and Park et al.[18] did not find a significant local recurrence benefit to radiation in patients with atypical meningioma who underwent GTR.

More recently, outcomes following SRS in the management of atypical meningioma have been reported by several investigators.[19,20] Hardesty et al.[21] evaluated the efficacy of SRS and intensity modulation radiation therapy in the adjuvant management of 149 patients with atypical meningioma who had undergone GTR. Rates of recurrence in those who were observed, received SRS, and received intensity modulation radiation therapy, were similar. Of note, this study did not involve a multivariable analysis, possibly due to the limited number of events, and the results may have been confounded by an association of adjuvant radiation with tumors that were more likely to recur following surgery. In our study, patients who received radiation likely had more advanced/aggressive disease than those who did not, as suggested by the shift in *P*-value, from univariable to multivariable analysis, for the association between radiation therapy and both outcomes evaluated. Pollock et al.[22] recently evaluated risk factors for tumor progression following SRS (median dose, 15 Gy) for WHO grades II–III meningioma and found that prior use of external beam radiation therapy and larger tumor volumes were associated with local recurrence, highlighting the importance of using multivariable models, where possible, when analyzing outcomes in patients with atypical meningioma.[22]

Our study should be considered in the context of its potential limitations. Although our series is one of the largest describing outcomes among patients with atypical meningioma, the sample size of 91 significantly limits the power of our statistical analysis. As a result, it was not possible to conduct analyses for overall survival or disease-specific survival as solitary endpoints. Despite this limitation, however, we did find a significant benefit associated with radiation and the outcomes that we were able to assess. Second, the follow-up of our study is relatively short. Third, our data are retrospective in nature, and it is possible that an unidentified confounding variable is, at least in part, the true driver of the results we observed. We tried to account for this limitation by using a propensity score model to account for the impact of potential patient- and tumor-related confounders, without overfitting our final Cox regression model. Lastly, our data include patients diagnosed over a period of 13 years. The WHO classification of meningioma changed over this period,[4] and it is possible that surgical and radiotherapeutic techniques/practices varied as well. There may be patients with grade I tumors under older WHO grading schemes who would be considered to have grade II tumors by the current scheme. We tried to account for this limitation by controlling for era of diagnosis in the propensity score model that was ultimately incorporated into the Cox regression. In doing so, we found that era of diagnosis was indeed a confounder of the relationship between use of radiation and outcome.

In conclusion, our study suggests that radiation therapy reduces local recurrence and the need for additional treatment among patients with atypical meningioma. Multicenter, prospective trials with overall or disease-specific survival, rather than local control or progression-free survival, as the primary endpoint are required to further evaluate the role of adjuvant radiation therapy in patients with this condition. Furthermore, identifying potential additional molecular characteristics associated with recurrence following GTR would help in personalizing the decision of whether to treat with adjuvant radiation therapy.

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