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Early Postoperative Adjuvant Radiotherapy Versus Active Monitoring After Gross Total Resection for Atypical Meningiomas: Factors Associated with Early Recurrence

Muhammet Enes GURSES[1], Hatice Yagmur ZENGIN[2], Aysel SHIKHALIYEVA[1], Cengiz Savas ASKUN[3], Melike MUT[1,4]

[1]Hacettepe University, School of Medicine, Department of Neurosurgery, Ankara, Turkey
[2]Hacettepe University, School of Medicine, Department of Biostatistics, Ankara, Turkey
[3]Middle East Technical University, Department of Computer Education and Instructional Technology, Ankara, Turkey
[4]University of Virginia, School of Medicine, Department of Neurosurgery, Charlottesville, VA, U.S.A.

Corresponding author: Melike MUT ✉ mm2ee@virginia.edu

ABSTRACT

AIM: To investigate the predictors of recurrence after gross total resection (GTR) that require early adjuvant radiotherapy upfront rather than at initial recurrence of atypical meningiomas (AMs).

MATERIAL and METHODS: A retrospective study of gross totally resected AMs was conducted in a tertiary care center within ten years. The clinical, radiological, and pathological parameters were analyzed statistically, and the factors associated with recurrence after GTR were determined with univariate analysis.

RESULTS: Among 23 AMs with GTR, 34.8% showed recurrence in a median follow-up of 40 months after the surgery. Preoperative tumor volume, tumor location in the skull base or tentorium, and lack of progesterone expression were associated with the higher recurrence rate. AMs with a preoperative volume of 27.5 cm^3 were the most significant risk factor for the recurrence (a 9.3-fold increase) than those with <27.5 cm^3 (66.7% vs. 14.3%, respectively).

CONCLUSION: Patients diagnosed with larger AMs (> 27.5 cm^3) might have higher recurrence rates after GTR and, therefore, would benefit from early adjuvant radiotherapy without waiting for a recurrence. AMs located in the skull base or tentorium and AMs having no progesterone expression might also be potential predictors for recurrence.

KEYWORDS: Meningioma, Resection, Radiotherapy, Recurrence, Atypical

INTRODUCTION

Meningioma is the most common tumor, constituting 39% of brain and other CNS tumors in adults. Atypical meningiomas (WHO Grade II) are less frequent than benign meningiomas, approximately 18% of all meningiomas (22). Atypical meningiomas (AMs) are complex neoplasms with various clinical presentations and morphologies. Histological review of grade II Meningiomas are defined by one or more of the following four criteria according to 2016 WHO classification: 1) 4–19 mitotic figures/10 HPF or brain invasion. 2) Chordoid or clear cell histological subtype, 3) brain infiltration, and 4) three or more of the following five histological features: increased cellularity, a small cell with high N/C ratio, large and prominent nucleoli, patternless or sheet-like growth, foci of 'spontaneous' or geographic necrosis. The WHO Classification for CNS Tumors, revised in 2016, now includes brain invasion as a single criterion for classifying these tumors as AMs (18,30). AMs have more aggressive

Muhammet Enes GURSES : 0000-0001-7141-0654
Hatice Yagmur ZENGIN : 0000-0002-9855-2449
Aysel SHIKHALIYEVA : 0000-0002-0309-8862
Cengiz Savas ASKUN : 0000-0002-4805-9381
Melike MUT : 0000-0002-9601-9907

behavior and tend to recur around 41-47% in a 5-year follow-up (7). Surgery and radiotherapy (RT) are the main therapeutic approaches for AMs (32). Predictors of recurrence are still indeterminate for AMs; likewise, treatment approaches may differ after surgical resection (29). In case of recurrence, a modality of RT is unequivocally undertaken, accompanied by another surgical intervention if feasible. Moreover, gross total resection (GTR) of AMs raises questions regarding the timing of RT; whether to treat with radiation upfront or at initial recurrence remains controversial.

Early postop RT may help reduce tumor regrowth with side effects like hair loss, fatigue, lethargy, and late toxicities like memory deficits, difficulty concentrating, and other neurocognitive dysfunction. On the other hand, only surgical treatment with active monitoring may carry a higher risk of recurrence, resulting in more aggressive treatment with radiotherapy, surgery, or both. Clinical trials addressing the question had inherent difficulties in randomization due to the heterogeneity of both tumor and therapeutic approaches in AMs (13,35,36).

A clinical trial, the RTOG 0539 study, classified meningiomas into three risk groups: The low-risk group with new WHO grade 1 meningioma after GTR or STR, the intermediate-risk group with recurrent WHO grade 1 meningioma after GTR or STR, and WHO grade 2 meningiomas after GTR, and the high-risk group with WHO grade 3 meningioma and any recurrent WHO grade 2 meningioma, or a new WHO grade 2 meningioma after STR resection (28,31). The role of early postoperative adjuvant RT is still being debated in the intermediate group of AMs with GTR. Several studies reflected conflicting conclusions on whether adjuvant radiotherapy reduces recurrence and leads to overall survival benefits (1,2,8,15,25,39).The RTOG 0539 proposed using postoperative RT for newly diagnosed AM regardless of the extent of resection, but surgical series do not necessarily agree with this conclusion (3,6,14,23,25, 26,28,31,33,40).

Our study retrospectively analyzed the atypical (WHO Grade II) meningiomas after GTR. The main objective of the present study was to find “predictors of recurrence” in AMs. We also sought to determine the factors to justify active monitoring of AMs and delaying RT after the GTR of AMs.

MATERIAL and METHODS

We conducted a retrospective analysis of patients harboring AM treated at Hacettepe University Department of Neurosurgery between 2010-2019 and collected the data of 57 patients diagnosed with AM. Hacettepe University Ethics Committee permission was obtained (GO 20/505-09.06.2020, Decision No: 2020/12-60). Patients who did not meet the criteria (patients who received RT at recurrence, any incomplete data sets regarding radiological and pathological work-up, patients lost to follow-up, spinal AMs) were excluded (Figure 1). Each patient’s treatment characteristics, such as the extent of resection, histopathological findings, follow-up outpatient visits, and adjuvant treatment information, were reported, including sex, age at diagnosis, tumor diameters and location, operative characteristics, molecular findings, postoperative radiotherapy, if any, and duration of follow-up. In the end, 23 patients were included in the study for analysis.

According to their anatomical location, the tumors were divided into the following categories: convexity, parasagittal skull base, and tentorial. The extent of resection was described as GTR if no residual tumor was detected in early postoperative magnetic resonance imaging (MRI) report per neuroradiologist report.

Tumors were histopathologically diagnosed as AM per diagnostic criteria of the WHO 2016 classification. The criteria used were being clear cell, or chordoid in morphology; or 4–19 mitotic figures/10 HPF; or brain invasion; or 3 of the following minor criteria: increased cellularity, small cell with high N/C ratio, large and prominent nucleoli, patternless or sheet-like growth, foci of ‘spontaneous’ or geographic necrosis.

The recurrence was described as radiological evidence of tumor regrowth after GTR. Follow-up time was calculated from the time of the first surgical intervention to the last clinic visit. For each patient, an interdisciplinary tumor board was conducted to obtain the postoperative care recommendations.

Statistical Analysis

Independent groups were compared in terms of numeric parameters by using the independent samples t-test when the parametric test assumptions were satisfied. In addition, mean ± standard deviation was represented as descriptive

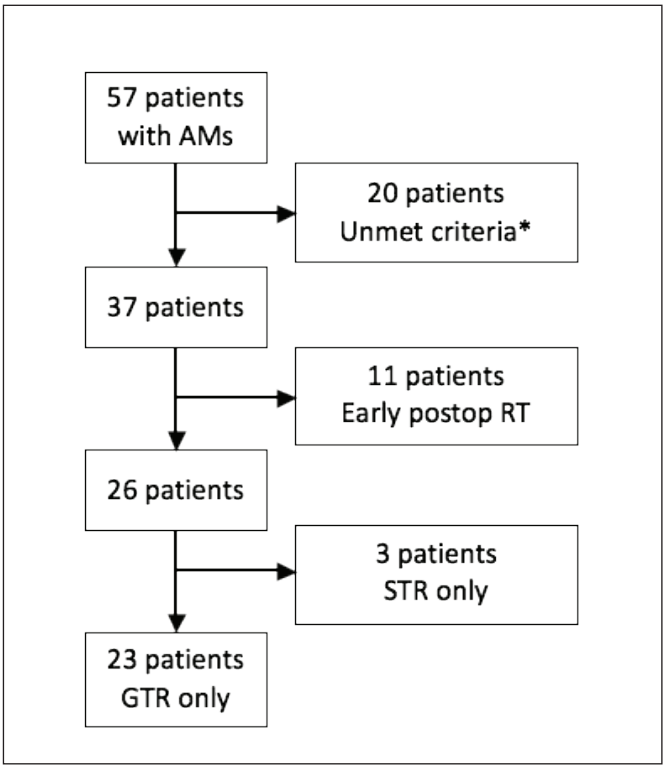

Figure 1: Flowsheet for patient selection (*18 patients had no early postop MRI done in 48 hours after surgery; among them, 5 patients were lost to follow-up and 2 patients had spinal AMs).

statistics. Otherwise, the Mann-Whitney U test was used with the median (minimum value-maximum value) as descriptive statistics. Normality assumption was evaluated using the Shapiro-Wilk normality test. The assumption of homogeneity of group variances was assessed using the Levene test. The independence of the categorical variables was assessed by Fisher's Exact test or Fisher-Freeman-Halton's (Generalized Fisher's) Exact test. The exact test choice depended on the size of the contingency table. In addition, the one-sample chi-square test was used for evaluating homogeneity in distributions of categorical variables such as progesterone positivity. Univariable Firth's logistic regression analyses were applied to estimate odds ratios with 95% confidence intervals to predict the risk of recurrence in general and in patients who did not receive radiotherapy treatment after GTR. Linearity in logit assumption for continuous predictors was evaluated using the Box-Tidwell test. All continuous predictors were satisfied with this assumption. In addition, Receiver Operating Characteristics (ROC) Curve Analysis was performed to estimate the Area Under the Curve (AUC) for meningioma volume to evaluate the predictive performance of the variable considering the patient's recurrence. Hence, Youden's J index was used to calculate the optimal cut-off point for meningioma volume. IBM SPSS Statistics version 23® for Windows (IBM Corp, Armonk, NY) was used for all statistical analyses. The level of significance was set at $p<0.05$.

RESULTS

Our study mainly addressed the predictors of recurrence for AMs to better indicate early adjuvant therapy after GTR. This analysis included 23 patients with AM after GTR; eight patients (34.8%) showed recurrence in a median follow-up of 40 months after surgery. It is worthy of note that all recurrences occurred within 24 months after the surgery, with a median of 18 months. Our analysis demonstrated that the preoperative volume was the only factor significantly affecting the recurrence after GTR was the preoperative volume (p=0.03) (Table I). A ROC analysis for determining a cut-off point of the volume associated with recurrence revealed 27.5 cm^3 (Figure 2). Patients harboring AM with a preoperative volume of 27.5 cm^3 or larger disclosed a significantly higher risk of recurrence than those with smaller ones, even though they had undergone a GTR for their tumors (66.7% vs. 14.3% recurrence rate). Even if a statistical significance of p=0.05 was not attained, probably due to the small sample size, skull base and tentorial AMs showed higher recurrence rates than parasagittal AMs (11.6 and 15 times, respectively). Similarly, progesterone negativity was associated with a higher recurrence rate. Tumor volume ≥ 27.5 cm^3 had an approximately 9.3-fold risk compared to small tumor volume for recurrence (Table I).

DISCUSSION

Our analysis of AMs after GTR showed that 2 out of 3 patients might remain recurrence-free with a median of 40 months. On the other hand, 1 out of 3 patients had a tumor recurrence even after GTR, primarily within 24 months, with a median of 18 months. The most crucial factor in predicting

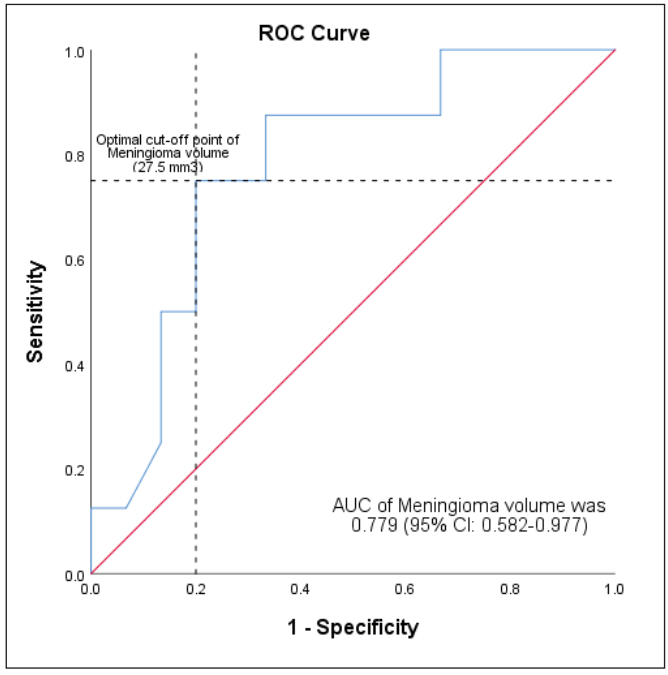

Figure 2: Determination of a cut-off value for preop tumor volume for predicting recurrence in the patients in GTR only group (ROC Curve analysis; Area under curve was estimated 77.9% (95% CI: 0.582-0.977) and it was significant at 0.05 (p=0.031). Cut-off of preop tumor volume was estimated at 27.5 cm^3 according to the maximum Youden's J Index with 75% sensitivity and 80% specificity with a positive and negative predictive value of 66.7% and 85.7%, respectively where the prevalence of the recurrence was 34.8%).

the recurrence was the preop tumor volume ≥ 27.5 cm^3. In addition to the preop volume, location in the skull base or tentorium and progesterone negativity was correlated with the higher recurrence rates after GTR of AMs. However, statistical significance was not reached due to our small sample size.

Atypical meningiomas carry a 7 to 8-fold increased risk of recurrence at five years compared to WHO grade I meningiomas (9). Surgical resection is the first step in the treatment algorithm for treating meningiomas. The impact of GTR on prognosis is well-grounded, given established literature revealing a GTR under relatively safe conditions remains an effective treatment technique and remains the mainstay of the approach to minimize the risk of recurrence and increase survival compared to STR in AMs (5,10-12,17,19,20). Studies advocating the active monitoring after GTR of AMs impose that early postoperative adjuvant RT has no significant impact on overall survival but a possible role on progression-free survival (PFS) (5,11,19,20,37). A recent study by Pan et al. evaluated the outcomes following upfront radiation versus monitoring in AMs, of which 71% of 32 GTR cases remained free of recurrence after the surgery for the rest of their follow-up, with a median follow-up of 41 months. Their study focused on the outcome; with RT, PFS was 100% at 12 and 36 months (compared to 84% and 63%, respectively, with observation); and there was no difference in overall survival (24). AMs are a

Table I: Clinical and Pathological Parameter Distributions in 23 Patients with GTR Only in Addition to Estimated Odds Ratios (a. Mann-Whitney U test p-value, b. Fisher's Exact Test p-value, c. Fisher-Freeman-Halton Exact Test p-value, d. One-sample Chi-square Test p-value, e. Independent Samples t-test p-value; ***p<0.05).** Odds Ratios and 95% Confidence Intervals were Obtained Using Firth's Penalized Logistic Regression Approach to Reduce Bias (**p <0.05**)

		Recurrence			Univariate	
		Absent (n=15)	**Exist (n=8)**	**p**	**OR with 95% CI [a]**	**p**
Age, (years)		58 (32-64)	48.5 (28-76)	0.78a	0.99 (0.9298-1.0521)	0.735
Gender, n (%)	Male	8 (80)	2 (20)	0.38b	-	-
	Female	7 (53.85)	6 (46.15)		1.855 (0.2197-27.9141)	0.214
Localization, n (%)	Parasagittal	4 (100)	0 (0)	0.152c	-	-
	Skullbase	3 (42.9)	4 (57.1)		11.571 (0.7844-1741.9277)	0.078
	Convexity	7 (77.8)	2 (22.2)		3 (0.1825-451.3395)	0.473
	Tentorial	1 (33.3)	2 (66.7)		15 (0.6915-2630.0251)	0.088
Headache, n (%)	Absent	10 (71.43)	4 (28.57)	0.66b	-	-
	Exist	5 (55.56)	4 (44.44)		1.909 (0.358-10.6052)	0.445
Seizure, n (%)	Absent	13 (72.22)	5 (27.78)	0.30b	-	-
	Exist	2 (40)	3 (60)		3.436 (0.5199-26.3895)	0.198
Meningioma volume		**16 (2-117)**	**50.5 (8-127)**	**0.03a ***	1.02 (0.9976-1.0474)	**0.082**
Meningioma volume	**< 27.5 mm³**	**12 (85.7)**	**2 (14.3)**	**0.02b ***	-	-
	≥ 27.5 mm³	**3 (33.3)**	**6 (66.7)**		**9.286 (1.5805-73.8899)**	**0.013***
Herniation, n (%)	Absent	10 (76.92)	3 (23.08)	0.22b	-	-
	Exist	5 (50)	5 (50)		3 (0.5712-17.9092)	0.195
MRI edema, n (%)	Absent	7 (77.78)	2 (22.22)	0.40b	-	-
	Exist	8 (57.14)	6 (42.86)		2.294 (0.421-15.7198)	0.344
Ki67		6.53 ± 3.720	5.38 ± 2.774	0.45d	0.914 (0.6827-1.1647)	0.480
Mitotic index		4.27 ± 1.223	3.50 ± 1.069	0.15e	0.603 (0.2663-1.2099)	0.158
4 - 19 mitotic figures/10 HPF, n (%)	Absent	0 (0)	1 (100)	0.35b	6.2 (0.2943-950.6894)	0.240
	Exist	15 (68.18)	7 (31.82)		-	-
Brain invasion, n (%)	Absent	10 (66.67)	5 (33.33)	1.00b	-	-
	Exist	5 (62.5)	3 (37.5)		1.215 (0.2107-6.6655)	0.822
Increased cellularity, n (%)	Absent	13 (72.22)	5 (27.78)	0.30b	-	-
	Exist	2 (40)	3 (60)		3.436 (0.5199-26.3895)	0.198
Small cells with high N/C ratio, n (%)	Absent	8 (72.73)	3 (27.27)	0.67b	-	-
	Exist	7 (58.33)	5 (41.67)		1.781 (0.344-10.1818)	0.493
Large and prominent nucleoli, n (%)	Absent	3 (75)	1 (25)	1.00b	-	-
	Exist	12 (63.16)	7 (36.84)		1.4 (0.1843-16.5248)	0.752
Patternless or sheet-like growth, n (%)	Absent	13 (68.42)	6 (31.58)	0.59b	-	-
	Exist	2 (50)	2 (50)		2.077 (0.2643-16.621)	0.472
Foci of necrosis, n (%)	Absent	8 (66.67)	4 (33.33)	1.00b	-	-
	Exist	7 (63.64)	4 (36.36)		1.133 (0.2156-5.9996)	0.881
Progesterone, n (%)	Positive	9 (75)	3 (25)	0.08d	0.435 (0.075-2.2592)	0.324
Follow-up time (months)		36 (5-108)	54 (2-84)	0.32a	1.011 (0.9806-1.0453)	0.470

troublesome situation for both neurosurgeons and radiation oncologists. Although surgical resection, particularly GTR, is unmistakable in managing AMs and late-term complications pertained to radiation-induced toxicity are known, patients with recurrence get multiple surgeries. For whom RT should be reserved is a persistent question. Moreover, the timing of RT remains a significant challenge for clinicians in managing AMs after GTR.

Clinicians tend to give early postop RT to patients with large tumors and after STR. The most important factors associated with recurrence in AMs are tumor location, STR, absence of postop RT, and negative progesterone expression. Several studies compared the patients who received early postop adjuvant RT with those with salvage RT at their recurrences after GTR. Momin et al. found that radiation naïve patients had significantly higher benefits from the salvage RT at their recurrences than the pretreated patients in the early postop period (21). Radiation naïve patients significantly prolonged radiation failure-free survival (3-, 5-, and 10-year radiation failure-free survival rates were 97.7%, 90.3%, and 87.9%, respectively) compared to pretreated patients (3-, 5-, and 10-year radiation failure-free survival rates were 67.5%, 45.4%, and 23.3%, respectively-p = 0.008) (21). The crucial question is what factors should be considered when planning the care of a patient with an AM with GTR. Even if GTR is achieved, some factors may cause meningiomas to recur. In a series of 108 patients, Aghi et al. found a 28% recurrence rate of AMs after GTR; most recurrences occurred within five years after resection (1). In their study, factors predicting worse prognosis were older age, sheeting, and prominent nucleoli (1). In Komotar' et al.'s series, 41% of patients who did not undergo postoperative radiotherapy after GTR showed recurrence. Residual tumor, parafalcine/parasagittal location, peritumoral edema, and a MI > 7 were all independently associated with early recurrence (16). In Budohoski et al.'s series, patients with early recurrence had worse neurological outcomes (4). Our intermediate-risk group, AMs with GTR, revealed 38.4% recurrence in a median of 39.65 months (Table I).

Volume

In our 23 patients, at statistical significance ($p<0.05$), preoperative tumor volume was associated with the recurrence after GTR. The ROC analysis revealed a cut-off point for the volume. Any tumor greater than 27.5 cm^3 had a higher recurrence rate (66.7%), and tumor volume ≥27.5 cm^3 had an approximately 9.3-fold risk of small tumor volume for recurrence. Recently, a study with case series of 565 meningioma patients of all grades evaluated the factors predicting the risk of postoperative recurrence. High-grade histology in patients with intracranial meningiomas and a large tumor volume increased the risk of recurrence with a cut-off volume of 11.32 cm^3. Associations between the tumor volume and recurrence were possibly attributed to increased proliferative activity in these lesions (38,41).

Tumor Location and Progesterone Expression

In our 23 patients, tumor location and progesterone expression were related to the early recurrence. Tumors located in the skull base or tentorium were associated with early recurrence after GTR. The progesterone negativity in the immunohistopathological staining was more common in tumors with early recurrence. The significance levels for both location and progesterone expression were $p<0.1$; nevertheless, $p<0.05$ significance was not attained, probably due to the small sample size. The skull base and tentorium location might have a higher recurrence rate due to the *en-plaque* nature of the skull base meningiomas and the bony invasiveness (34). The level of progesterone receptor expression has been related to the grade of meningioma, and a negative or low level of expression was associated with early recurrence and aggressive behavior (27).

Limitations

The primary limitation of this study is its retrospective, nonrandomized design. The present study is observational, with a level of evidence is C, and a level of recommendation is D. The possible selection bias by different clinicians may favor one treatment instead of the other. We only analyzed the radiological evidence of recurrence. We did not compare the treatment complications, quality of life measurements, neurocognitive evaluation, and failure patterns. Moreover, the median follow-up was 48 months for the whole cohort; however, when we looked at the subgroups of the GTR cohort, the recurrence-free group had a median of 36 (5-108) months follow-up in comparison to 54 (2-84) months for the recurrent group although this was not significantly different. We did not include any molecular or genetic signatures of meningiomas to predict the recurrence pattern. We wanted to develop a prognostic scale, but our number was limited for statistical validation of each parameter. Further validation will be possible through the results from the prospective, randomized trials with more significant numbers of patients.

CONCLUSION

Our results disclosed that patients diagnosed with larger AMs (> 27.5 cm^3) might have higher recurrence rates after GTR and would benefit from early adjuvant radiotherapy. Other factors, such as skull base, tentorium locations, and progesterone negativity, might also be considered a potential risk for recurrence. These decisions should be made with multidisciplinary neuro-oncology teams for each patient. Further prospective and multi-institutional studies need to be made to confirm our findings and develop a predictive scale for AMs.

AUTHORSHIP CONTRIBUTION

Study conception and design: MEG, MM
Data collection: MEG, AS
Analysis and interpretation of results: HYZ, CSA
Draft manuscript preparation: MEG, MM
Critical revision of the article: MEG, MM
Other (study supervision, fundings, materials, etc...): MM, MEG
All authors (MEG, HYZ, AS, CSA, MM) reviewed the results and approved the final version of the manuscript.

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