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Impact of Adjuvant Radiotherapy on Recurrence of Surgically Treated Atypical Meningiomas and Retrospective Analysis of Prognostic Factors

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ABSTRACT

AIM: To investigate the recurrence rate of atypical meningiomas after surgery (with or without adjuvant radiotherapy), and to determine which factors were related with recurrence.

MATERIAL and METHODS: Data obtained from 83 patients who underwent surgery and histopathologically diagnosed with atypical meningioma at a single institution between January 2009 and June 2019 were retrospectively reviewed. Then, the patients were divided into two groups: the surgery-only (n=43) and surgery + adjuvant radiotherapy (n = 40) groups.

RESULTS: The mean age of the patients was 53.5 ± 14.6 years. Among them, 51 (61.4%) were female and 32 (38.6%) were male. The recurrence rates were 30.2% (n=13) in the surgery-only group and 17.5% (n=7) in the surgery + adjuvant radiotherapy group. A statistically significant decrease in the recurrence rate was observed after adjuvant radiotherapy application (p=0.046). Moreover, adjuvant radiotherapy significantly increased progression-free survival (p=0.042). Peritumoral edema, sinus invasion, brain invasion, subtotal tumor resection, and complications were significant predictors of tumor recurrence, and the main risk factors for the recurrence of atypical meningiomas were brain invasion (p=0.019) and subtotal tumor resection (p=0.006). Progression-free survival and overall survival of the study group were 45.50 ± 27.56 and 56.69 ± 28.17 months, respectively. The parameters examined in the study, except for tumor recurrence, did not show a statistically significant influence on overall survival.

CONCLUSION: This study revealed that the important prognostic factors for tumor recurrence are subtotal tumor resection and brain invasion. Moreover, adjuvant radiotherapy in addition to surgical resection reduces the recurrence rate of atypical meningiomas and improves progression-free survival of the patients. However, adjuvant radiotherapy did not show a significant influence on overall survival.

KEYWORDS: Atypical meningioma, Radiotherapy, Recurrence, Surgical resection, Brain invasion

INTRODUCTION

Meningiomas are the most common primary brain tumors in adults. In studies, it has been determined that meningiomas constitute approximately 33.8%–36.4% of primary central nervous system tumors (1,23,33). It has been determined that the incidence of meningioma increases in older patients. Moreover, the incidence of meningiomas is doubled in individuals aged 65 years and above (1,4) and decreases in pediatric patients, accounting for only 1%–4% of childhood central nervous system tumors (31). It is found that the female-to-male ratio is approximately 2 in all age groups (4,33).

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Meningiomas are divided into three subgroups according to their histopathological features: benign meningiomas (grade I), atypical meningiomas (grade II), and anaplastic-malignant meningiomas (grade III). The term "atypical meningioma" was first described by the World Health Organization (WHO) in 1993 and was used for meningiomas with a behavioral pattern between benign and malignant meningiomas (4,22). Histopathological features were determined in the WHO classifications in 2000 and 2007, and the features of grade II meningiomas were clarified in the last revision of the WHO classification in 2016 (4,19). Thus, WHO grade II meningiomas currently include atypical meningiomas, chordoid meningiomas, and clear cell meningiomas (19).

While the rate of atypical meningiomas in all meningiomas in previous periods was between 5% and 7%, it increased up to 20%–25% after the 2016 WHO classification revision (7,14). In recent clinical series, the rates of atypical meningiomas were in the range of 10%–20% (16,26). There is no definite consensus yet on the treatment of atypical meningiomas. Various approaches are available in the literature, such as surgical resection only, adjuvant radiotherapy (RT) with surgical resection, and RT after recurrence (7,11–18,26–30). This study was designed to assess the results of patients with atypical meningiomas who had surgery with and without adjuvant RT.

MATERIAL and METHODS

The present study was performed according to the principles of the World Medical Association's Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013), and Institutional Review Board approval was obtained (24/05/2022-00013). This study included 83 patients who underwent surgery and histopathologically diagnosed with atypical meningioma at a single institution between January 2009 and June 2019. Patients who had multiple meningiomas, spinal column meningiomas, radiation induced tumors, or neurofibromatosis type II were excluded from this study. The patients with chordoid meningiomas (n=3), and clear cell meningiomas (n=2) were excluded from the study not to break the homogeneity of the study group. Among the included patients, 40 underwent adjuvant RT following surgical resection, whereas 43 did not undergo any adjuvant treatment.

After obtaining written consent from each patient, patient data, including patient demographics (i.e., age, gender, comorbidities, and symptoms), radiological parameters (i.e., tumor location, tumor volume, peritumoral edema, and recurrence), histopathological parameters (i.e., histopathological diagnosis, and brain invasion), and surgical parameters (i.e., extent of resection, sinus invasion, bone involvement, and complications), were retrospectively collected. Systemic diseases, including diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, malignancy, thyroid disease, and chronic kidney disease, were defined as comorbidities. The Simpson grading was used to define the extent of tumor resection. The ellipsoid volume measurement method was used to calculate the tumor volumes. Follow-up and tumor volume measurements of the patients were conducted by performing contrast-enhanced brain magnetic resonance imaging (MRI) scans (Figure 1). The patients underwent MRI scans 3 months after surgery for the first follow-up and 1 year after surgery for the second follow-up. Then, they underwent MRI scans once in a year in the absence of recurrence. Peritumoral edema was determined by examining T2-weighted and fluid-attenuated inversion recovery (FLAIR) brain MRI scans (Figures 2A, B). Brain invasion was determined by histopathological examination (Figure 2C). All specimens of the patients were re-evaluated, and atypical meningioma diagnoses were confirmed according to the current 2016 WHO classification. The advantages and disadvantages of adjuvant RT was discussed with all patients, and adjuvant RT following surgical resection was applied to patients who agreed to undergo this treatment modality. Conventional RT was performed in all patients who underwent adjuvant RT following surgical resection. Other adjuvant treatment modalities, such as stereotactic radiosurgery, were not performed.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software version 23.0 (IBM Corporation, Armonk, New York, United States) was used to analyze the variables. The quantitative variables were presented as mean ± SD (standard deviation) and the range (maximum-minimum) and categorical variables as n (%). The Kolmogorov–Smirnova test was used to determine whether the parameters in the study showed normal distribution. Data conformance to normal distribution was evaluated by independent student t-test, and Mann-Whitney U test was used for parameters not showing normal distribution. The logistic regression test was used with the backward stepwise (Wald) method to determine the main risk factors for recurrence of atypical meningiomas. Multiple linear regression modeling was used to examine factors affecting progression-free survival (PFS) and overall survival (OS). The variables were investigated at a 95% confidence level and differences with p values of less than 0.05 were evaluated statistically significant.

RESULTS

In this study, 83 patients were enrolled with 43 (51.8%) patients classified into the surgery-only group and 40 (48.2%) patients classified into the surgery + adjuvant RT group. The mean age of the patients was 53.5 ± 14.6 years. Among the 83 patients, 51 (61.4%) were females and 32 (38.6%) were males. Hypertension (22.9%), diabetes mellitus (22.9%), and coronary artery disease (12%) were the most common comorbidities in the study group. The most common symptoms were headache (81.9%), consciousness disorder (22.9%), seizure (18.1%), hemiparesis (14.5%), and dizziness (12%). The patients' demographic data, and radiological, histopathological, and surgical parameters, were examined between the two groups and are shown in Table I. There were no statistically significant demographic differences between the surgery-only and surgery + adjuvant RT groups (Table I). The recurrence rates were 30.2% (13 patients) and 17.5% (seven patients) in the surgery-only and surgery + adjuvant RT groups, respectively. A statistically significant decrease in the recurrence rates was

observed with adjuvant RT application (p=0.046). Moreover, adjuvant RT improved PFS of the patients (p=0.042) (Table I).

The features of the patients with recurrent and non-recurrent tumors were compared. It was identified that characteristics, including age, gender, comorbidities, tumor location, and tumor volume, did not affect the recurrence rates (Table II). Peritumoral edema (p=0.004), sinus invasion (p=0.002), brain invasion (p<0.001), subtotal tumor resection (p<0.001), and complications (p=0.020) were significant predictors of tumor

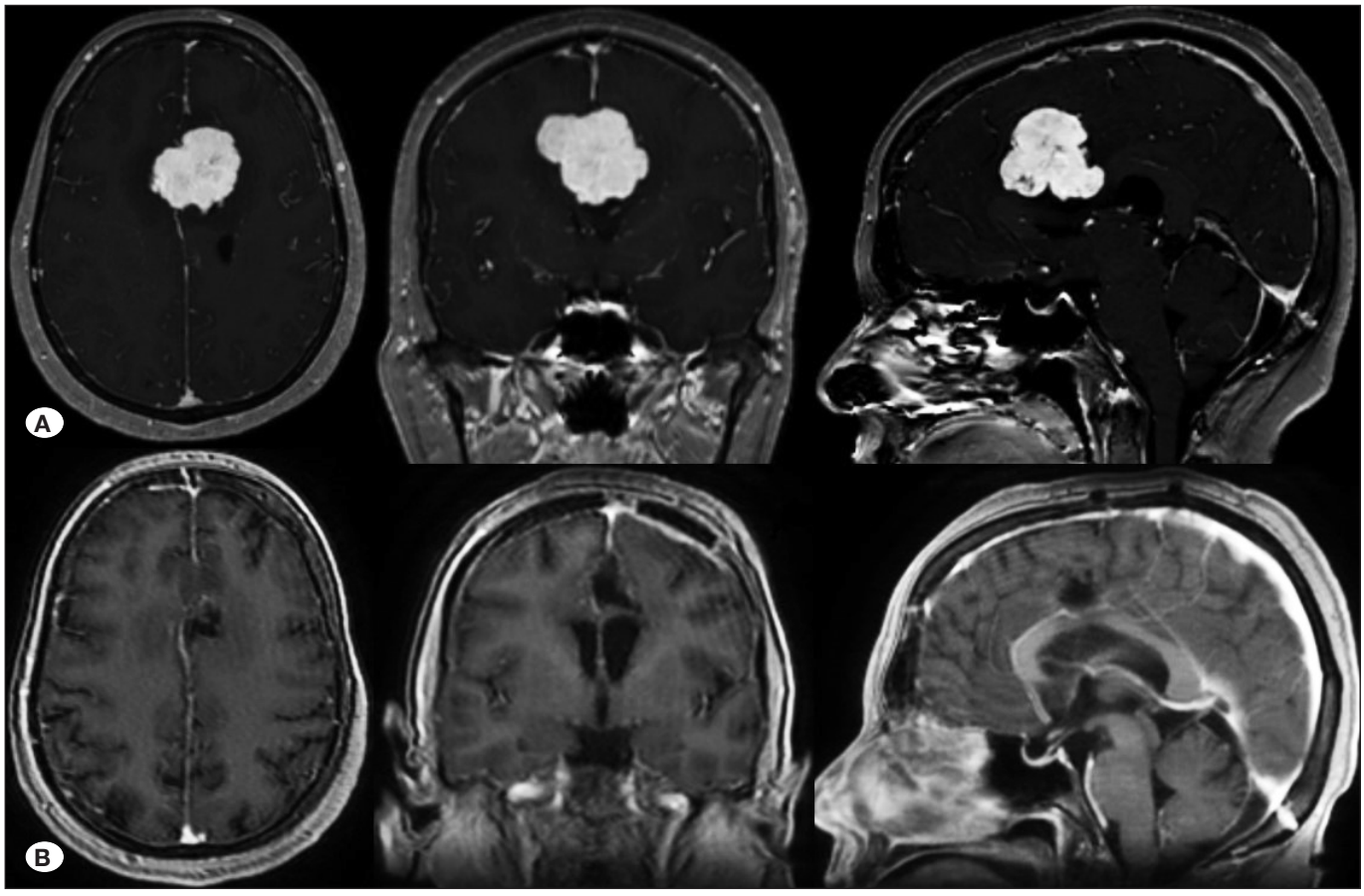

Figure 1: Preoperative axial (left), coronal (middle) and sagittal (right) contrast enhanced magnetic resonance imaging scans revealing bifrontal falx meningioma **(A)**. Postoperative axial (left), coronal (middle) and sagittal (right) contrast enhanced magnetic resonance imaging scans revealing Simpson grade 1 resection of the tumor **(B)**.

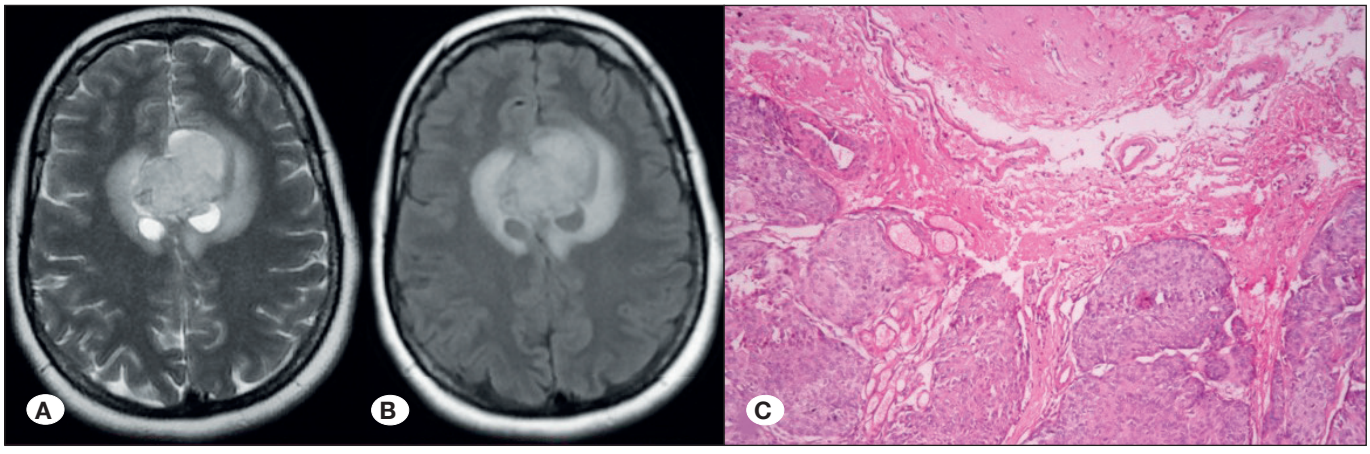

Figure 2: Preoperative axial T2-weighted **(A)** and FLAIR **(B)** magnetic resonance imaging scans revealing peritumoral edema of the bifrontal falx meningioma. Tumor islands invading the glial tissue of the surrounding brain parenchyma revealing brain invasion of the tumor (H&E, x200 magnification) **(C)**.

Table I: Demographic Data of the Patient Groups

Characteristics		Radiotherapy (+) n=40 (%)	Radiotherapy (-) n=43 (%)	Total n=83 (%)	p
Age (mean)		54.4 ± 16.4	52.5 ± 12.8	53.5 ± 14.6	0.564
Gender	Female	21 (52.5)	30 (69.8)	51 (61.4)	0.120
	Male	19 (47.5)	13 (30.2)	32 (38.6)	
Symptoms					
Headache		34 (85)	34 (79.1)	68 (81.9)	0.574
Consciousness disorder		11 (27.5)	8 (18.6)	19 (22.9)	0.435
Seizure		6 (15)	9 (20.9)	15 (18.1)	0.574
Hemiparesis		6 (15)	6 (14)	12 (14.5)	0.284
Dizziness		5 (12.5)	5 (11.6)	10 (12)	0.146
Comorbidities					
Hypertension		8 (20)	11 (25.6)	19 (22.9)	0.608
Diabetes mellitus		11 (27.5)	8 (18.6)	19 (22.9)	0.435
Coronary artery disease		5 (12.5)	5 (11.6)	10 (12)	0.168
Others*		7 (17.5)	7 (16.3)	14 (16.9)	0.238
Location					
Convexity		9 (22.5)	16 (37.2)	25 (30.1)	0.748
Parasagittal		10 (25)	10 (23.3)	20 (24.1)	
Falx		7 (17.5)	6 (14)	13 (15.7)	
Sphenoid ridge		6 (15)	5 (11.6)	11 (13.3)	
Midline anterior fossa		4 (10)	4 (9.3)	8 (9.6)	
Cerebellopontine angle/tentorial		4 (10)	2 (4.7)	6 (7.2)	
Tumor volume (cm^3)		36.9 (4.8-157.8)	20.9 (4.9-109)	26.3 (4.8-157.8)	0.068
Peritumoral edema (+)		30 (75)	34 (79.1)	64 (77.1)	0.795
Sinus invasion (+)		7 (17.5)	12 (27.9)	19 (22.9)	0.304
Bone involvement (+)		9 (22.5)	14 (32.6)	23 (27.7)	0.337
Brain invasion (+)		20 (50)	20 (46.5)	40 (48.2)	0.827
Simpson grade	1	24 (60)	20 (46.5)	44 (53)	0.640
	2	9 (22.5)	12 (27.9)	21 (25.3)	
	3	5 (12.5)	7 (16.3)	12 (14.5)	
	4	2 (5)	4 (9.3)	6 (7.2)	
Complication (+)		5 (12.5)	6 (14)	11 (13.3)	0.164
Recurrence (+)		7 (17.5)	13 (30.2)	20 (24.1)	**0.046**
Follow-up (years)		4.5 (2-9)	4 (2-11)	4 (2-11)	0.691
Progression-free survival (months)		54.87 ± 26.08	37.23 ± 29.12	45.50 ± 27.56	**0.042**
Overall survival (months)		56.37 ± 23.44	57 ± 32.23	56.69 ± 28.17	0.207

** Chronic obstructive pulmonary disease, chronic kidney disease, malignancy, thyroid disease.*

recurrence (Table II). The multiple logistic regression method was performed for these predictors, and the main risk factors for the recurrence of atypical meningiomas were brain invasion (p=0.019) and subtotal tumor resection (p=0.006) (Table III). PFS and OS of the study group were 45.50 ± 27.56 and 56.69 ± 28.17 months, respectively. The parameters examined in the study, except for tumor recurrence, did not show a statistically significant influence on OS (Table IV).

DISCUSSION

The term "high-grade meningioma" was first used by Cushing and Eisenhardt in 1938 (6). This histopathological grading has undergone many changes over the years and has been finalized with the WHO classification in 2016. In the current classification, the criteria determined for diagnosing atypical meningioma are as follows: mitotic hyperactivity (4 or more mitoses per high-power field), histopathological brain invasion, and 3 or more of the subsequent characteristics; loss of sheeting architecture, spontaneous necrosis, increased cellularity, prominent nucleoli, and small cells (high nuclear to cytoplasmic ratio) (4,14,19).

Risk factors for the recurrence of atypical meningiomas are histopathological features of the tumors (i.e., increased mitoses, necrosis, and brain invasion), tumor location, invasion of adjacent structures, patient-related factors (e.g., age and comorbidities), and surgery-related factors (e.g., extent of resection and complications) in previously published literature. Budohoski et al. have investigated the factors that predict the risk of early tumor progression of atypical meningiomas (3). They defined that patients with tumor recurrence within 24 months after surgery comprised the early recurrence group. They found that subtotal tumor resection,

Table II: Comparison of Characteristics of the Patients with Recurrent and Non-Recurrent Tumors

Characteristics		Recurrence (-) n=63 (%)	Recurrence (+) n=20 (%)	p
Age (mean)		53.0 ± 13.7	54.6 ± 17.3	0.691
Gender	Female	40 (63.5)	11 (55)	0.600
	Male	23 (36.5)	9 (45)	
Comorbidities (+)		33 (52.4)	6 (30)	0.122
Location				
Convexity		20 (31.7)	5 (25)	0.142
Parasagittal		11 (17.5)	9 (45)	
Falx		10 (15.9)	3 (15)	
Sphenoid ridge		10 (15.9)	1 (5)	
Midline anterior fossa		6 (9.5)	2 (10)	
Cerebellopontine angle/tentorial		6 (9.5)	0 (0)	
Tumor volume (cm^3)		24.5 (4.8-157.8)	47.6 (5.7-109.2)	0.056
Peritumoral edema (+)		44 (69.8)	20 (100)	**0.004**
Sinus invasion (+)		9 (14.3)	10 (50)	**0.002**
Bone involvement (+)		15 (23.8)	8 (40)	0.250
Brain invasion (+)		21 (33.3)	19 (95)	**<0.001**
Simpson grade	1	41 (65)	3 (15)	**<0.001**
	2	18 (28.6)	3 (15)	
	3	3 (4.8)	9 (45)	
	4	1 (1.6)	5 (25)	
Complication		5 (7.9)	6 (30)	**0.020**
Radiotherapy (+)		33 (52.4)	7 (35)	**0.046**
Progression-free survival (months)		55.66 ± 27.62	34.25 ± 20.56	**0.036**
Overall survival (months)		55.66 ± 27.62	59.95 ± 30.35	0.186

Table III: Main Risk Factors for Recurrence of Atypical Meningiomas

	B	S.E.	Wald	p	Odds Ratio	95% CI	
						Lower	Upper
Peritumoral edema	16.035	1.856	0.000	0.999	9.177	3.147	10.586
Brain invasion	3.941	1.685	5.467	**0.019**	**51.463**	1.892	1400.005
Sinus invasion	-0.626	1.268	0.243	0.622	0.535	0.045	6.421
Gross total resection (Simpson grade 1-3)	0.963	0.998	0.930	0.335	2.618	0.370	18.524
Subtotal resection (Simpson grade 4)	4.002	1.467	7.448	**0.006**	**54.733**	3.090	969.597
Complication	1.251	1.073	1.358	0.244	3.493	0.426	28.625
Constant	-9.214	1.928	0.000	0.998	0.000		

*Multiple Logistic Regression Method = Backward Stepwise (Wald), **CI:** Confidence interval, **SE:** Standard Error, **B:** Regression Coefficient, *p<0.05*

Table IV: Comparing the Effects of the Parameters on Overall Survival of the Patients

Model	Non-standardized coefficients		Standardized coefficients	T	p
	B	Std Error	Beta		
Constant	1.247	2.073		0.602	0.549
Age	-0.032	0.027	-0.016	-1.165	0.248
Gender	0.320	0.736	0.006	0.434	0.665
Symptoms	0.264	0.615	0.006	0.430	0.669
Comorbidities	0.668	0.798	0.012	0.837	0.405
Tumor volume	0.012	0.011	0.015	1.112	0.270
Peritumoral edema	0.251	0.964	0.004	0.261	0.795
Brain invasion	0.787	0.932	0.014	0.845	0.401
Sinus invasion	0.546	0.999	0.008	0.546	0.587
Bone involvement	-0.386	0.806	-0.006	-0.479	0.633
Simpson grade	0.105	0.518	0.004	0.203	0.840
Complication	0.893	1.083	0.011	0.825	0.413
Radiotherapy	0.160	0.728	0.003	0.220	0.827
Recurrence	-3.222	1.115	-0.049	-2.890	**0.005**
Model 1: R= 0.995; R^2= 0.991; Adjusted R= 0.989; F= 510.231; p=0.001***, Durbin-Watson=1.818					

***p<0.05, Multiple Linear Regression Method.*

parafalcine/parasagittal location, peritumoral edema, and a mitotic index of more than 7 were all independently associated with early recurrence (3). Chen et al. have examined the histopathological features of atypical meningiomas in 182 patients and identified predictive factors for recurrence (5). They concluded that a mitotic index of more than 10, brain invasion, and bone invasion were risk factors for recurrence of the tumors (5). Moreover, Li et al. have found that brain invasion, bone invasion, and peritumoral edema were risk factors for tumor recurrence (17). They also identified that a low Karnofsky Performance Status Scale score, infratentorial location, and subtotal tumor resection were poor prognostic factors for these patients (17). Garcia-Segura et al. have found that the combination of brain invasion and necrosis is a strong predictor of tumor recurrence (9).

The main treatment objective for meningiomas is gross total tumor resection. The Simpson grading, in which the extent of tumor excision is defined, remains up-to-date and is considered the key criterion affecting the success rate in meningioma surgery (27). Simpson grade I–III resections are defined as gross total resection. Gross total tumor resection

is detected as one of the most important prognostic factors in most studies in the literature (11,15,17,18,29). Keric et al. have examined the prognostic factors of atypical meningiomas in one of the largest series involving 258 patients and concluded that the most important prognostic factor was the extent of tumor resection (15). It was found that gross total tumor resection decreases the recurrence rates and improves PFS in most studies in the literature (10,11,15,21,27,29,30).

Adjuvant RT application in treating atypical meningiomas remains a controversial issue, and there is no consensus on this issue in the literature. Adjuvant RT application is the most controversial issue in cases where gross total resection can be achieved. Some studies have reported that gross total resection and adjuvant RT application decrease the recurrence rates and improve PFS (2,5,8,12,13,20,25,26). Hasan et al. performed a meta-analysis involving 757 patients to evaluate the benefits of adjuvant RT after gross total resection of atypical meningiomas (12). They showed that the recurrence rate of the patients who did not undergo adjuvant RT was twice as high (33.7% vs. 15%). The local control rate in the first year was 90% for gross total resection and 97% for gross total resection + RT. The median 5-year local control rate was 62% for gross total resection and 73% for gross total resection + RT (12). In a study, Bagshaw et al. concluded that the addition of adjuvant RT following even a Simpson grade I, II, or III resection conferred a local control benefit. Moreover, they emphasized that it is difficult to control the recurrent disease and underlined the significance of aggressive primary treatment (2).

Furthermore, some studies in the literature have reported that adjuvant RT application has no benefit on the recurrence rate or PFS (10,11,15,18,21,24,25). Pereira et al. have conducted a literature review including 17 studies and 1,761 patients (24). According to this review, among the 1,761 patients, 573 underwent RT (32.5%) with a recurrence rate of 26% (149 patients). Of the 1,188 patients who were primarily treated with surgery only, 299 had tumor recurrence (25.16%). The difference between the two groups was statistically insignificant (24). Liu et al. and Graffeo et al. have published clinical series and concluded that observation following gross total resection may be a safe alternative to adjuvant RT (10,18).

Although adjuvant RT application after gross total resection is a controversial issue, adjuvant RT application following subtotal resection is an accepted treatment protocol in the literature (7,14,16,32,34). Wang et al. conducted a study to compare OS with or without adjuvant RT after subtotal resection or gross total resection in patients with atypical meningioma (32). This study included 2,515 patients and revealed significantly improved OS with adjuvant RT compared with that without adjuvant RT after subtotal resection. However, adjuvant RT was not associated with improved OS in patients who underwent gross total resection (32). In their studies, Zhi et al. and Lee et al. concluded that patients who undergo subtotal resection for newly diagnosed atypical meningiomas should receive adjuvant RT based on improvements in local control and PFS (16,34). Delgado-López and Corrales-Garcia, and Kaur et al. published systematic reviews confirming the benefit of adjuvant RT on PFS in patients with atypical meningioma who underwent subtotal resection (7,14).

There are certain limitations of this study. The retrospective nature of the study and the relatively small sample size (83 patients) are the main limitations. The lack of 5 year follow-up of all patients is also another limitation of the study. Nonetheless, this study also has several strengths. For instance, demographic data of the patients groups are similar, and there is no statistically significant difference between the patient groups (Table I). All histopathological diagnoses of the patients were made according to the current 2016 WHO classification. This study is one of the studies in the literature with the highest number of patients diagnosed with atypical meningioma and applied adjuvant RT.

CONCLUSION

According to the updated 2016 WHO classification of central nervous system tumors, atypical meningiomas account for a larger proportion of all meningiomas, and treatment strategies have become more important. This study demonstrates that adjuvant RT in addition to surgical resection reduces the recurrence rates of atypical meningiomas and improves PFS of patients. The recurrence rate was 30.2% in the surgery-only group and was reduced to 17.5% in the surgery + adjuvant RT group. However, adjuvant RT did not show a significant influence on OS. Brain invasion and subtotal tumor resection were major risk factors for the recurrence of atypical meningiomas.

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AUTHORSHIP CONTRIBUTION

Study conception and design: KO, KMO

Data collection: KO, NEC, DCY, OBE

Analysis and interpretation of results: KO, SE, TE

Draft manuscript preparation: KO, KMO, NEC

Critical revision of the article: KO, KMO, TE

Study supervision: KO, KMO

All authors (KMO, KO, NEC, DCY, OBE, SE, TE) reviewed the results and approved the final version of the manuscript.

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