Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 25 (2021) 101201

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

journal homepage: www.elsevier.com/locate/inat

Research Article

Radiotherapy versus observation after surgical resection of atypical meningiomas

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ARTICLE INFO

Keywords:
Atypical Meningioma
Radiotherapy
Recurrence
Survival

ABSTRACT

Objectives: To describe the treatment and clinical results in patients diagnosed with atypical meningioma treated at the Donostia University Hospital. We evaluated recurrence, overall survival, and disease-free survival.
Methods: From 284 meningiomas treated in our center over 16 years, 32 cases of grade II atypical meningioma were selected. Clinical and surgical notes were retrospectively evaluated. Pre and postoperative clinical and radiological parameters, the modality of radiotherapeutic treatment and its clinical results were evaluated. The histological classification was consistent with the 2007 WHO (World Health Organization) classification. The Simpson classification system was used to assess the degree of surgical resection.
Results: we found 18 men and 14 women with a mean age of 60 years. Parasagittal location and convexity were the most frequent locations respectively (14 and 12 cases). The mean follow-up was 50 months. Simpson I-III resection was performed in 28 cases (87%). 22 patients (20 Simpson I-III and 2 Simpson IV) received post-operative radiotherapy (20 cases fractionated radiotherapy and radiosurgery in 2), while 10 patients (8 Simpson I-II and 2 Simpson IV) did not receive postoperative radiotherapy. The recurrence rate in patients who received radiotherapy was 45% and 60% in those who did not receive radiotherapy. Recurrence-free survival and overall survival in patients under radiotherapy was 36 and 48 months, respectively. On the contrary, in those who did not receive radiotherapy it was 44 and 56 months.
Conclusions: In this study, the most important prognostic factor related to survival was the degree of surgical resection. Therefore, adjuvant radiotherapy should be used in those cases without complete surgical resection. In addition, we recommend evaluating reoperation in recurrent symptomatic cases.

1. Introduction

Meningiomas represent 20% of all intracranial brain tumors. Although most meningiomas are benign, 5% to 15% are classified as atypical and are associated with an increased risk of recurrence [1,2,9,17]. Although the recognition and definition of this atypical subclass is in transition, the incidence is increasing [3,17]. The 2007 WHO guidelines classify atypical meningiomas by the following characteristics: increased mitotic activity (≥4 mitotic figures per high-power field) or 3 or more of the following histological features: 1) loss of lobular architecture (laminae), 2) prominent nucleoli, 3) hypercellularity, 4) small cells with high nuclear to cytoplasmic ratios, and 5) foci of spontaneous necrosis [4,5,20].

Regardless of tumor grade, resection is one of the main treatment options for all meningiomas. Benign meningiomas lack aggressive features and have a low mitotic rate and slow growth [6,12,13]. The low recurrence rates for grade I meningiomas after gross total resection (GTR) avoid the postoperative radiation therapy [4,7,16]. After subtotal

Abbreviations: GTR, Gross Total Resection; STR, Subtotal Resection; CSF, Cerebrospinal fluid; MRI, Magnetic Resonance Image; WHO, World Health Organization; DFS, Disease-free Survival; OS, Overall Survival; M, Male; F, Female.

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https://doi.org/10.1016/j.inat.2021.101201
Received 18 October 2020; Received in revised form 18 February 2021; Accepted 28 March 2021
Available online 1 April 2021

resection (STR), some authors recommend postoperative irradiation, even for the Grade I tumors [4,5], while others advocate a wait-and-see approach[5]. The higher recurrence rates for grade III anaplastic meningiomas lead most professionals to recommend radiation therapy after resection, regardless of whether GTR or STR has been performed [7]. However, the role of postoperative radiation therapy remains a controversial issue for grade II atypical meningiomas [8].

To better address this problem and develop a treatment paradigm for the postoperative management of atypical meningiomas, we retrospectively reviewed our 16-year surgical experience comparing tumor recurrence rates after STR or GTR and examined the role of postoperative radiation therapy in prevention of recurrence.

2. Methods

Patient selection

In this retrospective cohort study of 284 patients who underwent resection of intracranial meningiomas at the University Hospital of Donostia from 2002 to 2018, 32 cases had confirmed pathology of grade II atypical meningiomas and at least 1 year of follow-up (Fig. 1). The degree of resection was based both on the surgeon's impression during surgery (using the Simpson classification system) and on our review of postoperative magnetic resonance images. The pathological review confirmed in all cases the diagnosis of grade II atypical meningioma according to the 2007 WHO criteria. 22 patients received radiotherapy after the operation (fractional radiotherapy in 20 and radiosurgery in 2).

Evaluated parameters

Tumor locations were classified into one of 5 categories: convex, parasagittal / Falx, sphenoid wing, posterior fossa, or other. Tumor size resection was determined by evaluating preoperative MRI images and compared with a postoperative control MRI. Simpson Grade I-III resections were considered GTR, while Grade IV resections were considered STR.

Statistic analysis

All variables were tabulated and analyzed using IBM SPSS Statistics v25. Quantitative variables were described using the mean, median and range. Categorical variables were described using frequency and percentage. Recurrence-free survival was measured from the date of surgery to the date of recurrence for patients after GTR or progression after STR. Overall survival was measured from the date of surgery to death or last follow-up. Survival analysis was evaluated using Kaplan-Meier regression methodology and was calculated from the date of surgery. Finally, a multivariate analysis using model Cox regression was made.

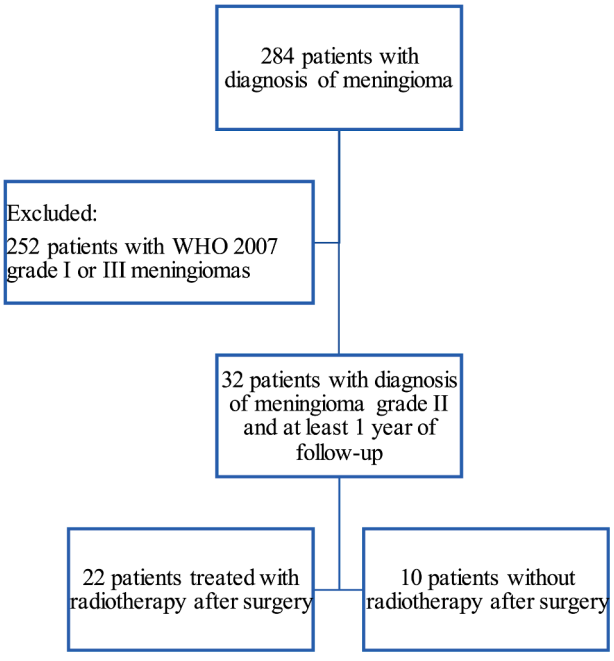


Fig. 1. Study subject flow.

3. Results

A total of 284 meningiomas were resected in our institution from January of 2002 to January of 2018. Thirty-two patients (18 men and 14 women; mean age of 60 years, with a range of 34 to 83 years) were confirmed with an atypical grade II meningioma (Tables 1 and 2).

GTR (simpson I-III) was performed in 28 patients (87.5%) and a STR in only 4 patients.

The most common tumor locations were convexity in 14 cases (44%) followed by parasagittal / falx in 12 cases (37%). Follow-up was carried out for a mean of 50 months (range 12–102 months). All 32 cases had at least 1 year of follow-up and more than half of the patients (56%) were followed either until recurrence or for at least 4 years after surgical resection.

The overall survival of our 32 patients after resection was 81% at 3 years, 56% at 4 years, and 50% at 5 years. 16 (50%) of these patients had tumor recurrence within the first 32 months (range 12–88 months). Recurrence-free survival rates were 81.25% at 1 year, 68.75% at 2 years, 62.5% at 4 years, 56.25% at 5 years, and 50% at 8 years (Fig. 2).

22 patients (68.7%, 14 Simpson I, 5 Simpson II, 1 Simpson III and 2 Simpson IV) received postoperative adjuvant radiotherapy (20 fractionated cases and radiosurgery in 2). In contrast, 10 patients did not receive postoperative radiotherapy (31%, 6 Simpson I, 2 Simpson II and 2 Simpson IV). Table 1 summarize the main characteristics for each group.

In the 4 patients in whom STR was performed, those who did not receive radiotherapy (2 patients), the recurrence was 100%. On the contrary, there was no recurrence in the 2 patients with STR that they did receive radiotherapy (table 2).

The dose that all patients with fractionated radiation therapy received was a mean of 59.4 Gy (range 50.4–60.0 Gy) delivered to the tumor bed in 2.0 Gy fractions. In those patients who used radiosurgery, the dose used was 15 Gy. Recurrences developed in 10 (45.5%) of these 22 patients and in 6 patients (60%) without radiotherapy (Table 2). The recurrence rate in patients who received radiotherapy was 45% and 60% in those who did not receive radiotherapy (Table 2). Median recurrence-free survival and overall survival in patients under radiotherapy was 38

Table 1
Clinical characteristics of meningioma cohorts. *SD: standard deviation, GTR: gross total resection, STR: subtotal resection.*

	Radiotherapy group(n = 22)	Observation group(n = 10)
Age (year), mean [SD]	60 [15]	64 [12]
Gender		
MaleFemale	12 [54,5%] 10 [45,5%]	6 [60%] 4 [40%]
Location		
Convexity	8 [36%]	6 [60%]
Parasagittal/falx	10 [46%]	2 [20%]
Sphenoid wing	4 [18%]	0 [0%]
Posterior fossae	0 [0%]	2 [20%]
Symtomps,		
Headache	8 [36%]	2 [20%]
Epilepsy	12 [55%]	4 [40%]
Paresis	6 [27%]	2 [20%]
Gate instability	2 [9%]	2 [20%]
Aphasia	2 [9%]	2 [20%]
Simpson Grade		
I-III (GTR)	20 [91%]	8 [80%]
IV (STR)	2 [9%]	2 [20%]

Table 2
RFS, OS and recurrence rates. *RFS: recurrence free survival, OS: overall survival.*

	Radiotherapy group (n = 22)	Observation group (n = 10)	*p* value
RFS (months), median [range]	38 [9–73]	51 [9–73]	0,555
OS, (months), median [range]	53 [2–103]	55 [12–114]	0,597
Recurrence			
Yes	10 [45,5%]	6 [60%]	
GTR	10	4	
STR	0	2	
No	12 [54,5%]	4 [40%]	
GTR	10	4	
STR	2	0	

and 53 months, respectively. On the other hand, in those who did not receive radiotherapy it was 51 and 55 months (Table 2). The median recurrence in the radiotherapy group was 38 months vs. 51 months in observation group, but there was not statistically significant difference (p = 0,555).

We analyze age and gender as prognostic factors, we found that the male gender presents a higher risk of recurrence when compared to women with a statistically significant result (Table 3). Age<50 years is also a risk of recurrence although there was no statistical significance.

In the Kaplan-Meier analysis, the median of RFS comparison by gender shows an early recurrence in men (20 months) against women (73 months) with statistically significant difference (p = 0.000). Similar comparison the median of RFS by age group was found, but there was not statistically significant difference (p = 0.105). Kaplan-Meier analysis shows a slight difference in the median of RFS for RT vs observation group (73 and 61 months, respectively), there was not statistically significant difference between both groups (p = 0.841) (Fig. 2).

4. Discussion

In our retrospective cohort study after atypical meningioma resection in 32 patients, postoperative radiation therapy effectively reduced the risk of recurrence after STR but not after GTR. This is in agreement with Hammouche et.al, in their series in 2014, they concluded that the most important prognostic factor to determine recurrence was the Simpson score[9,21]. Furthermore, there was no statistically significant impact of adjuvant radiotherapy on the recurrence of atypical meningiomas. In another more recent series from 2015, Sun S et al, concluded that the evidence mainly supports safe GTR or, if GTR is not feasible, performing STR with adjuvant radiation therapy[10,11,22,24,25].

The clinical care of patients with atypical meningiomas remains controversial and a challenge for neurosurgeons. Since the implementation of the WHO classification changes in 2000, the incidence of these tumors has increased. In our study of 284 meningiomas, 32 tumors (11.3%) were classified as atypical, a rate similar to the incidence data from other published series ranging from 5% to 15% [1,9,12,17,18]. As the classification of pathology continues to change, previous studies are less relevant. Our study is reinforced by the fact that all cases were reviewed by a single neuropathologist. In a retrospective meningioma staging study conducted in the United Kingdom using the pre and post 2000 WHO guidelines, Willis et al, observed an incidence rate of 20.4% for atypical meningiomas. Importantly, 38% of grade II meningiomas had originally been classified as grade I using the WHO guidelines prior to 2000[13,14,19]. In another retrospective series, Smith et al, he reported that the degree of atypical meningioma increased from 18% to 23%[15,16,17]. The limitations of the previous studies were the combination of atypical and anaplastic meningiomas and the combination of the WHO guidelines before and after 2000[5,6,10,11,18]. Based on these inconsistencies, it is difficult to draw concrete conclusions about the role of different therapies in tumor recurrence of atypical meningiomas.

5. Atypical meningioma recurrence

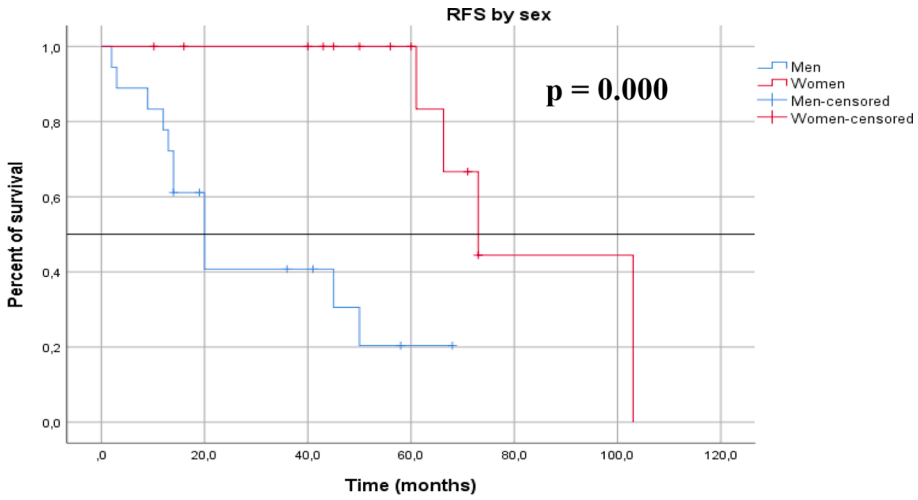
Resection has always been and continues to be one of the most important treatment modalities for meningiomas, whether they are WHO grade I, II, or III. This finding in our series coincided with other studies that indicate that the degree of resection is a strong prognostic factor for tumor recurrence in all grades of meningiomas[3,10,14,16]. The importance of the degree of resection is reinforced by the propensity for grade II meningiomas to occur in areas where GTR is often easier to achieve[19]. Most of the atypical meningiomas in our patients occurred in the parasagittal location (43.74%) and convexity (37.5%), a location where the majority (92%) could undergo complete resection. Although the importance of the degree of resection seems clear to reduce the risk of recurrence, even in the most recent reports, consensus is lacking on the role of adjuvant radiation after resection[19,20]. In a 2009 study, Aghi et al, found a high recurrence rate (41%) for atypical meningiomas 5 years after GTR. Although their data did not show a statistically significant effect, the authors ultimately found at least one benefit for postoperative radiation in tumors after GTR[1]. In a 2011 study evaluating the role of postoperative radiation therapy for 114 patients after resection of atypical meningiomas, Mair et al, found that neither radiotherapy nor the degree of resection statistically affected recurrence for the whole group; These authors then recommended against postoperative radiotherapy for patients after GTR[7].

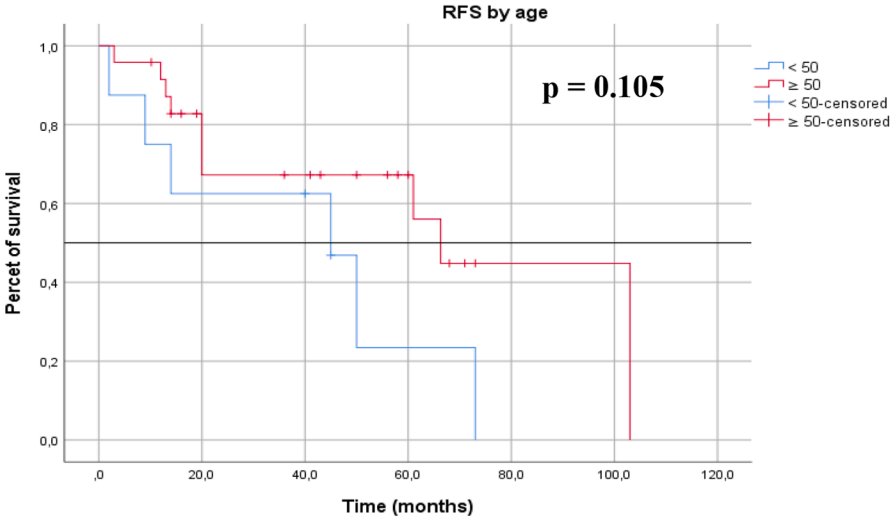
Along with the pathological anatomy, it is necessary to identify other parameters that may determine the tendency to relapse or aggressive biological behavior, such as the proliferation index such as Ki-67 > 2. Also, the number of mitoses is important, atypical menigiomas with Mitoses close to the anaplastic variant (20 or more) have shown a greater tendency to malignancy, therefore, a greater probability of relapse[21]. Tumors that present progesterone hormone receptors have a better prognosis and a lower relapse rate, and on the contrary, aggressive behavior has been seen in the absence of receptors or the presence of estrogen receptors. A subgroup of patients appears to have a higher risk of recurrence (those with a mitosis number close to 20, Ki-67 > 2, absence of progesterone receptors or presence of estrogen receptors). For these patients, given the high rate of tumor recurrence, postoperative radiation is recommended after total or subtotal resection. For all other patients, close observation after GTR using serial follow-up MRI is recommended and salvage therapy for symptomatic recurrence by surgery or additional fractionated radiation therapy or stereotactic radiosurgery. Cytogenetic analysis can probably become a predictor in aggressive meningiomas: normal karyotypes are associated with lower relapse and slow growth. Chromosome 22 monosomy is a common finding in benign meningiomas. The deletion of chromosome 1P or 14Q is associated with biological aggressiveness[22,23].

In our study population, adjuvant radiation was administered after initial surgery to 22 patients, a segment that represented a large proportion of our study population. Although radiation therapy significantly decreased the risk of recurrence among patients after STR, there was no beneficial effect after GTR. Although the recurrence decreased in the radiotherapy group, this fact does not affect the survival of the patients compared to the patients without adjuvant radiotherapy, therefore we recommend that, instead of routine radiotherapy, close observation after GTR for atypical meningiomas it may be a possible therapeutic option. This also reserves the potential for other modalities, such as stereotactic radiosurgery, in the event of a recurrence.

6. Limitations

As a retrospective review without a formal prospective treatment plan to define which patients were treated and / or underwent radiotherapy, selection bias may have played a role in patients receiving





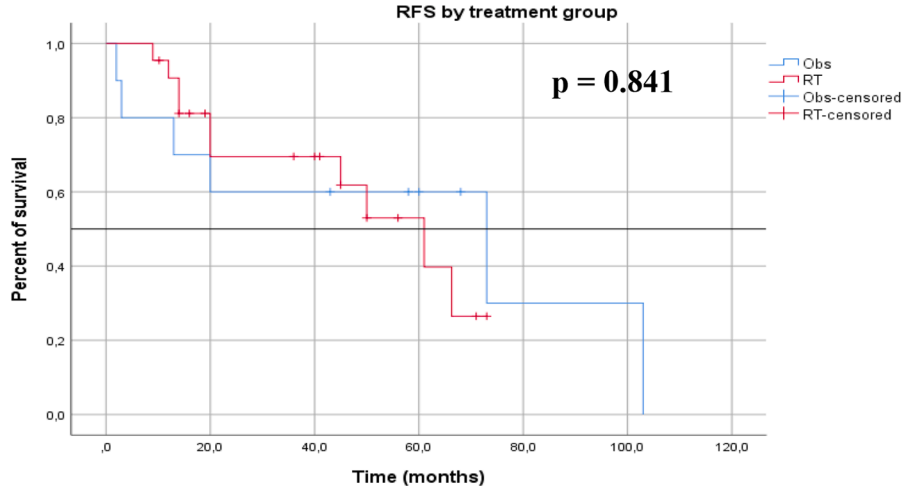


Fig. 2. Survival analysis. Kaplan-Meier comparison of RFS by sex **(A)**, age **(B)** and in radiotherapy vs observation groups **(C)**. Horizontal line is the median. *RFS: recurrence-free survival, GTR: gross-total resection, STR: subtotal resection, RT: radiotherapy, Obs: observation.*

Table 3
Recurrence related to age and gender.

Variable	RR	IC 95%	p-value	
Age (<50y)	2,1	1,22 – 3,78	0,083	In patients age < 50 increases 2,1 times the recurrence risk
Male	2,3	0,96–5,68	0,033*	In men, increase 2,3 times the recurrence risk

*Statistical significance; RR: Relative risk.

radiotherapy, especially in the GTR group.

Although a significant proportion (68.5%) of our patients underwent postoperative radiotherapy, there was no consistent protocol regarding the criteria and timing of radiotherapy. Most patients received radiation therapy in a similar manner, that is, fractionated radiation (mean dose 59.4 Gy, range 50.4–60.0 Gy) administered in 2.0 Gy fractions to the tumor bed. Our data suggest that radiation therapy may be delayed after GTR; however, given the limitations of a retrospective study, we definitely support the importance of a prospective randomized trial to answer this problem. Until there are guidelines based on prospective randomized trials, we suggest that radiotherapy can be delayed until the time of recurrence for patients undergoing GTR for an atypical meningioma and who do not have high-risk criteria as discussed above (any activity mitotic, hormone receptors, altered cytogenetic analyzes).

Sample size difficult a robust statistical analysis. A study which include a greater number of patients is needed.

In the future, more important than developing a general paradigm is to identify the factors that predispose patients to recurrence. More studies and research have the potential to allow the identification of molecular markers that could better indicate an increased risk of recurrence and the need for radiation therapy, thus facilitating a more personalized approach to these tumors.

7. Conclusions

The results of this study show that atypical meningiomas have a high recurrence rate after STR and that radiotherapy is beneficial in terms of reducing this risk of recurrence. However, after GTR, the role of radiation is unclear. In this study, the most important prognostic factor related to survival was the degree of surgical resection. Therefore, we consider that adjuvant radiotherapy should be used in those cases without complete surgical resection. More studies are needed to define the usefulness of the number of mitoses, the Ki-67 proliferation index, and progesterone receptors.

8. Financial disclosure

The authors report that there is no conflict of interest with respect to the materials or methods used in this study or the findings specified in this document.

CRediT authorship contribution statement

Sergio Torres-Bayona: Conceptualization, Data curation, Writing - original draft, Investigation, Methodology, Resources, Funding acquisition, Writing - review & editing. **Melissa Gil-Durán:** Investigation, Methodology, Resources, Funding acquisition, Writing - review & editing. **Pablo Rodríguez-Hernández:** Investigation, Methodology, Resources, Funding acquisition, Writing - review & editing. **Julián Monroy:** Investigation, Methodology, Resources, Funding acquisition, Writing - review & editing. **Paula Africano:** Software, Validation, Visualization, Funding acquisition, Writing - review & editing. **Yeiris Miranda-Acosta:** Formal analysis, Funding acquisition, Writing - review & editing. **Nicolás Samprón:** Project administration, Supervision, main surgeons, Funding acquisition, Writing - review & editing. **Enrique Úrculo:** Project administration, Supervision, main surgeons, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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