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Clinical Efficacy of Adjuvant Radiotherapy for World Health Organization Grade II Intracranial Meningioma

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BACKGROUND: **Maximal surgical resection remains the treatment of choice for grade II meningiomas, and for some authors it is sufficient to guarantee a long indolent course even without postsurgical radiotherapy (RT), but there is no consensus on the use of RT in this patient population.**

METHODS: **We retrospectively compared clinical and radiologic outcomes between World Health Organization grade I (group A) and grade II (group B) surgically treated meningiomas, focusing on the role of adjuvant RT. We registered clinical, surgical, and radiologic data to detect differences in survival and functional outcome between the 2 groups.**

RESULTS: **The final cohort consisted of 284 patients for group A and 94 patients for group B. Group B showed a higher risk of developing recurrence independently of the extent of resection (7.75% for Group A vs. 27.7% for Group B, $P = 0.01$). Patients who did not undergo adjuvant RT documented recurrence in 50% of cases, compared with 19% of patients who underwent RT ($P = 0.024$). There is a weak difference in the risk of developing postoperative seizures in the group submitted to radiotherapy ($P = 0.08$). Performance status remained stable for both groups, but for Group B it tended to decrease significantly after 1 year with regard to extent of resection and RT.**

CONCLUSIONS: **Recurrence is more frequent for grade II meningiomas, even though there are no significant differences in terms of complications and functional outcome. Radiotherapy in grade II meningiomas does indeed lead to better control of recurrence but leads to an increased risk of seizures and reduced performance status.**

INTRODUCTION

Meningiomas are the most common primary central nervous system tumor in adults, having the highest incidence rate (37.6%)[1] and representing a third of brain lesions, with peak incidence in elderly patients and with a female-to-male ratio of approximately 2:1.[2] The World Health Organization (WHO) classification system describes 15 different meningioma subtypes, 9 of which are considered WHO grade 1 (benign), 3 WHO grade 2 (atypical), and 1 WHO grade 3 (malignant). Available data suggest that 94% of meningiomas are benign, 5% atypical, and 1% malignant.[1] After several modifications Simpson first defined atypical meningiomas features, and borderline between benign and malignant meningiomas were commonly identified. Finally in the classification of WHO 2007 atypical meningioma including brain invasion as the only criterion to define previously grade I lesions as grade II, and in the latest WHO 2021 classification, brain invasion remains an independent criterion for atypical meningioma. This, obviously, increased the percentage of meningiomas classified as atypical.[1] Although the management of benign and malignant tumors is widely approved, with gross

Key words
- Atypical meningioma
- Grade II meningioma
- Meningioma
- Neurosurgery
- Radiotherapy

Abbreviations and Acronyms
EOR: Extent of resection
GTR: Gross total resection
KPS: Karnofsky Performance Scale
MRI: Magnetic resonance imaging
OS: Overall survival
RT: Radiotherapy
WHO: World Health Organization

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total resection (GTR) considered curative and at low risk of recurrence rates for the former and maximal surgical resection with adjuvant radiotherapy (RT) for the latter,[1,3] only a few controlled clinical trials have been performed to guide clinical decision making. They have had variations in management modalities, particularly for atypical ones, possibly due to the low incidence of such lesions. This implies that prospective available data are limited, so the standardized treatment protocol for atypical meningioma is discussed, and the role of the adjuvant RT is still unclear.

In this study, we performed an institutional retrospective review of a consecutive series of surgically treated patients suffering from histologically confirmed intracranial meningiomas, operated on in our departments between January 2016 and December 2020, with the aim of analyzing differences in outcome between atypical meningiomas (WHO type II) and grade I meningiomas and verifying the efficacy and usefulness of preventive radiotherapy in grade II meningiomas.

METHODS

Participants and Eligibility

We collected a total of 378 patients suffering from intracranial meningioma. We adopted the following inclusion criteria:

1. Patients with confirmed histologic diagnosis of meningioma grade I or grade II performed according to the updated version of the 2021 WHO guidelines at their first surgery
2. Preoperative and postoperative magnetic resonance imaging (MRI) performed at our institution or available on the picture archiving and communication system for review
3. Patients who underwent a standard clinical and radiologic follow-up starting from the 30th day after surgery
4. Estimated target of the surgical procedure was the total or subtotal resection of the lesions

We excluded patients who met these exclusion criteria:

1. Patients with histologic diagnosis of malignant meningioma (WHO grade III)
2. Patients who underwent only biopsy
3. Patients with severe comorbidity such as to compromise evaluation in follow-up (intractable oncological, metabolic or cardiovascular diseases)
4. Incomplete or wrong data on clinical, radiologic, and surgical records and/or lost to follow-up

All the patients who met the aforementioned inclusion and exclusion criteria were assigned on the ground of the histologic diagnosis to the following subgroups: benign meningiomas, WHO I (Group A) and atypical meningiomas, WHO II (Group B).

For all the included patients we recorded age, sex, time of hospitalization, time of follow-up, clinical onset, presence of seizure on clinical debut, and performance status (measured using Karnofsky performance scale [KPS]) at the moment of radiologic diagnosis.

Regarding clinical onset, we considered as focal neurologic deficits the focal disorders of body motility and sensitivity, sphincter disorders, and disorders involving cranial nerves including visual disturbances. We also considered the presence of dizziness, alteration of mental status and memory loss, the presence of intractable headache, seizure, and the incidental diagnosis.

All the patients included underwent a preoperative brain MRI scan including a high-field 3 Tesla volumetric study. On radiologic evaluation we recorded the location of the lesion, presence of multiple meningiomas and/or meningiomatosis, involvement of subtentorial compartment, tumor major diameter (measured in cm), and tumor volumes (measured in cm^3) using isotropic volumetric T1-weighted sequences before and after intravenous administration of paramagnetic contrast agent (gadolinium). We used T2-weighted and fluid-attenuated inversion recovery sequences to obtain the edema volumes (measured in cm^3 before antiedemigen therapy).

Volume of the contrast-enhancing lesion and edema were calculated drawing a region of interest (ROI) in a volumetric-enhancing postcontrast study weighted in T1 (a multivoxel study) and T2, conforming to the margins of the contrast-enhancing lesion with software Horos[4] (more details are described in our previous study on meningiomas based on the same collection[5]) (**Figure 1**).

Every patient with Simpson grade >I and WHO type II and III was submitted to radiotherapy and oncologic evaluation.

On the basis of the histologic final diagnosis, we recorded WHO grading with subtypes. The mitotic index was measured using the count of mitosis on 10 high-power field. Immunohistochemistry with ki67 was routinely performed in our Department of Neuropathology. Ki67 was applied to frozen sections of fresh tissue using a standard immunoperoxidase technique.

Overall survival (OS) was recorded in months; it was measured from date of diagnosis to date of death or date of last contact if alive. Clinical information was obtained by the digital database of our institution, whereas OS data were obtained by telephone-interview. We recorded after surgical procedure the status of performance (using KPS) for each patient at 1 month, 6 months, and at last clinical evaluation. A special focus was on the KPS result: Such parameter was considered, as previously observed as predictive and associated to survival. We evaluated the presence of complications, recurrence, and consequent second treatment recording biological switch. We investigated whether the postsurgical radiotherapy treatment was indicative of different OS, grading, immunohistochemical characteristics, and clinical/neurologic outcome.

Statistical Methods

The sample was analyzed with SPSS version 18. Comparisons between nominal variables have been made with the chi^2 test. Extent of resection (EOR, measured with Simpson grade) means was compared with 1-way and multivariate analysis of variance analysis along with contrast analysis and post-hoc tests. Continuous variable correlations have been investigated with Pearson's bivariate correlation. Threshold of statistical significance was considered $P<.05$.

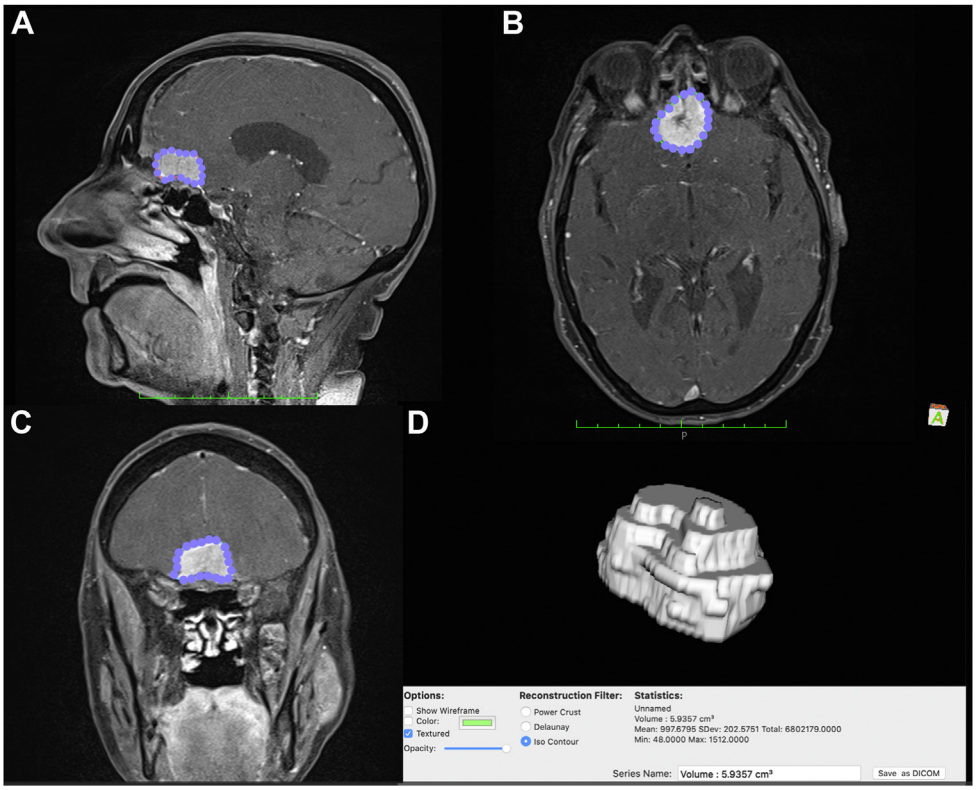

Figure 1. A typical case of atypical olfactory shower meningioma in contrast-enhanced T1-weighted magnetic resonance imaging (MRI) to which volume was measured using Horos software; with 3-Tesla high-field MRI, we collected for each patient the T1-weighted contrast-enhanced volumetric sequence in the sagittal (**A**), axial (**B**), and coronal (**C**) planes. Using Horos software, we drew with free-hand technique a region of interest and outlined the tumor at the edges of the contrast-enhancing signal for all slices in at least 2 of the 3 planes, obtaining the tumor reconstruction with automatic calculation of the volume expressed in cm^3 (**D**).

Potential Source of Bias and Study Size

We addressed no missing data since incomplete records were among the exclusion criteria. A potential source of bias is expected to derive from exiguity and asymmetry of the sample, which nevertheless, in regards to the endpoints selected, present an excellent post-hoc statistical estimated power (difference between 2 independent means; $1-\beta = 0.9488$ for α 0.05 and effect size 0.5), thus providing extremely reliable conclusions.

Informed consents were approved by the Institutional Review Board of our institution. Before their surgical procedures, all patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. This study is consistent with the Helsinki Declaration of Ethical Principles for medical research involving humans.

RESULTS

The final cohort consisted of 284 patients for Group A and 94 patients for Group B. The average age was 60.03 ± 13.56 years and 61.68 ± 12, respectively, for the 2 groups. Neither subgroup presented remarkable differences in age/sex (Table 1).

Radiologic and Histologic Comparison Analysis Between the Groups

The volume of contrast-enhancing lesion between the 2 groups was evaluated. Atypical meningiomas presented at radiologic diagnosis with a higher volume than the group of benign meningiomas (57.23 cm^3 vs. 32.56 cm^3, $P = 0.002$) with significant differences in major diameter (5.43 vs. 4.16, $P = 0.001$). The extent of cerebral edema in relation to tumor size was also evaluated. There was no significant difference in edema volume between the 2 groups (39.16 cm^3 vs. 25.7 cm^3), showing a direct proportional relationship between edema volume and tumor volume presented in both groups. These results were confirmed and evaluated by a previous study conducted on the same case series by our research group.[6]

There are no significantly different locations compared with others, neither a higher incidence of multiple lesions nor meningiomatosis between the 2 groups ($P = 0.16$). Biologically, Group B showed a higher mitotic index (mean <1 per 10 HPF vs. 3.35 per 10 HPF for Groups A and B, respectively, $P = 0.01$) and a higher proliferation index expressed as ki67% (mean 4.43 vs. 9, $P = 0.002$). There are no significant differences between

Table 1. Population Study

Patients 378	World Health Organization I (284)	World Health Organization II (94)	*P* Value
Age	60.03	61.68	1.000
Hospitalization	17.06	18.14	1
Diameter	4.16 SD = 1.69	5.43 SD = 1.5	**0.001**
Volume lesion	32.56	57.23	**0.002**
Volume edema	25.7	39.16	0.14
Subtentorial location	24	4	0.551
Multiple lesion	18	8	0.16
Seizure at debut	65	16	0.56
Mitotic index	<1	3.35	**0.001**
Ki-67	4.43	9	**0.002**
KPS pre	80	75–80	0.290
GTR	260	89	1
Recurrence	22	26	**0.01**
Complications	52	26	0.11
Seizure after surgery	32	18	0.08
KPS post	80	80	0.93
KPS after 1 year	85	75	**0.06**
Death after recurrence	50	10	0.59
Death without recurrence	4	7	0.18
Recurrence and RT		14/24 (50%) without RT	**0.024**
		12/62 (19%) with RT	

Bolded *P* values are statistically significant.
SD, standard deviation; KPS, Karnofsky Performance Scale; GTR, gross total resection; RT, radiotherapy.

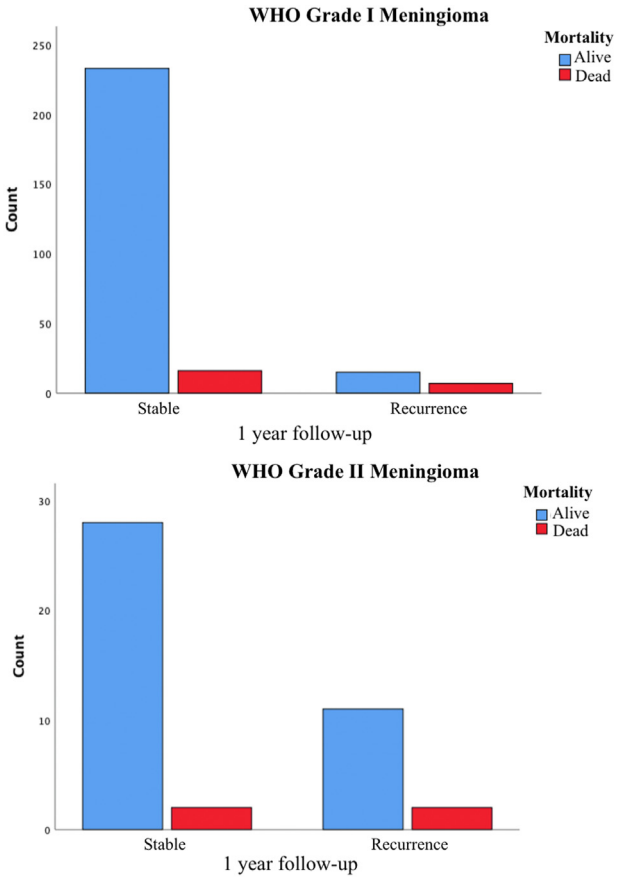

Figure 2. In the statistical analysis with chi-square test (22/284 7.75% for Group A vs. 26/94 27.7% for Group B, $P = 0.01$), it is found that the group of grade II meningiomas (bottom graph) shows a higher occurrence of recurrence at 1 year than grade I meningiomas in the face of no significantly different mortality.

the 2 groups on the ground clinical debut (P = 1), presence of seizure at diagnosis (P = 0.56), and preoperative KPS (P = 0.29).

Outcome Data and Main Results

Neurologic and clinical outcome was measured with KPS score for the entire collection and for the 2 subgroups. GTR measured as Simpson grade I was obtained in 260/284 patients (91.5%) in Group A and in 89/94 patients (94.7%) in Group B without any statistical difference (P = 1).

The rate of postoperative complications in the first 30 days was comparable between the 2 groups with no evidence of significant differences (52/289, 17.9% for Group A vs. 26/94 for Group B, 27% P = 0.11).

Patients with a histologic diagnosis of WHO type II have a higher risk of developing recurrence independently of the EOR (22/284 7.75% for Group A vs. 26/94 27.7% for Group B, P = 0.01) (Figure 2). Mortality is not affected by the diagnosis and radiotherapy treatment, and there is no significant difference between the 2 groups in case of recurrence (50/284 for Group A, 10/94 for Group B, P = 0.593) and in the case of normal postoperative controls (4/284 for Group A, 7/94 for Group B, P = 0.18).

Considering only the WHO type II meningioma group, 62/94 (65.9%) patients underwent adjuvant RT while 24/94 (25.5%) underwent only close radiologic follow-up (for 8 patients [8.5%], the data were not clear and well transcribed, so they were not considered in the final data-processing stage). Patients who did not undergo adjuvant RT experienced 50% more recurrence (vs. 19%) than patients who were treated with adjuvant RT (P = 0.024) (Figure 3).

Interestingly, there is a weak difference in the risk of developing postoperative seizures in the group submitted to radiotherapy (32/289, 11% for Group A vs. 18/94, 19% for Group B, P = 0.08) (Figure 4). Postoperative performance status remained stable for both groups, but for Group B it tended to decrease significantly at 1 year after the procedure with regard to EOR and RT (Figure 5).

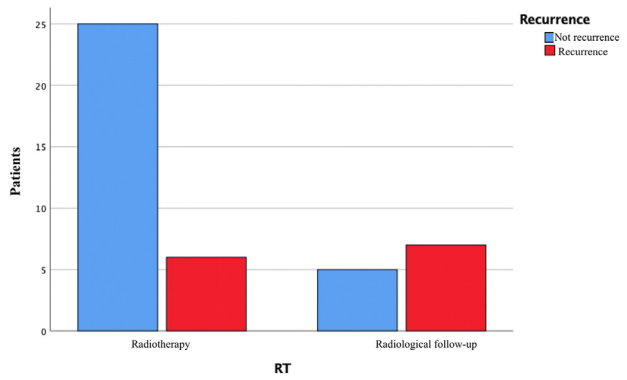

Figure 3. The bar chart shows a significant effectiveness of radiotherapy in controlling recurrence compared with the group that performed only radiologic follow-up.

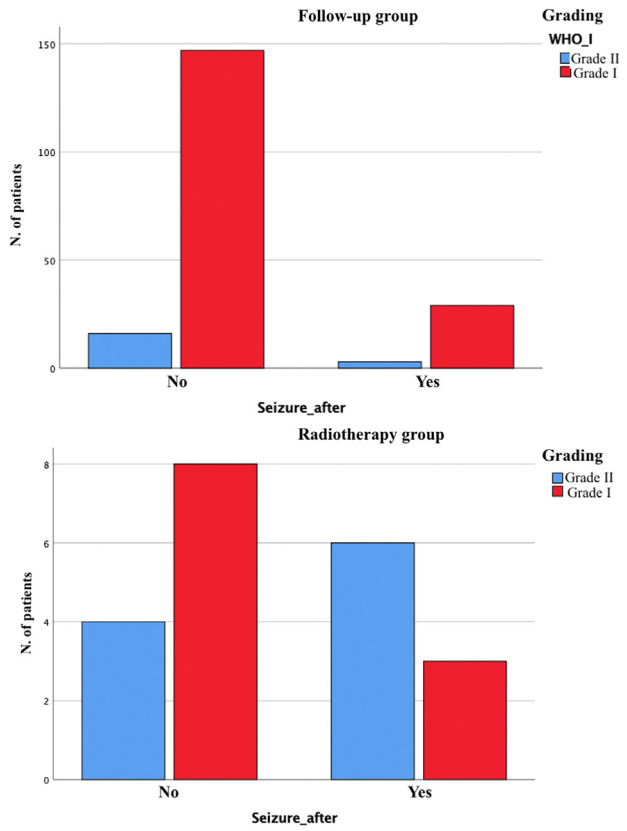

Figure 4. The bar graph shows that the group of patients who received radiotherapy presented more seizure episodes during follow-up than the control group with little significant evidence (32/289, 11% for Group A vs. 18/94, 19% for Group B, $P = 0.08$).

DISCUSSION

The standardized treatment protocol for grade II meningioma is still discussed in literature. Maximal surgical resection remains the treatment of choice for atypical meningiomas,[7] and for some authors it is sufficient to guarantee a long indolent course,[1] but there is no consensus on the use of adjuvant RT in this patient population, considering that residual meningioma can then be monitored or treated with postoperative conformal fractionated RT or stereotactic radiosurgery.

The extent of resection (EOR) is determined by tumor location, consistency, size, and proximity or involvement of critical neurovascular structures. Additionally, when grade II meningiomas occur at the convexities, they have lower recurrence rates and better overall prognosis than similar tumors found over the skull base.[5,8] Currently, in accordance with Simpson's classification, grades 1–3 constitute GTR, while grades 4–5 constitute subtotal resection (STR),[9] influencing the rate of recurrence and progression, but the impact on overall survival (OS) remains less clear.[10]

In our study, it is shown that although atypical meningiomas do not have a higher mortality and higher risk of complications than benign meningiomas, the risk of recurrence and reduced performance status is still higher.

According to literature, the recurrence rate at 5 years of benign meningiomas is relatively low (7.75% in our study), while the risk of recurrence is higher in atypical and malignant meningioma (29%–52% and 50%–94%, respectively).[2] It has been demonstrated that up to 70% of atypical meningiomas recur within the next few months after surgery.[11]

This leads to describing the use of postoperative radiation after GTR, but the question of whether early adjuvant RT reduces the risk of tumor recurrence remains unanswered.[1] Some authors demonstrated that patients undergoing subtotal resection could benefit from RT,[12] and others suggested that the role of radiation in atypical meningiomas was limited after documented recurrence.[13] Several retrospective studies reported no benefit in terms of local control with adjuvant RT compared with initial surveillance after GTR.[14-18]

In our collection, it was identified that although RT effectively provides a good outcome on recurrence control at 1 year independently of EOR, RT also results in an increased risk of long-term complications such as the presence of seizures that impact the patient's performance status as measured by the KPS.

A large patient series demonstrated the absence of significant OS or PFS benefit from adjuvant stereotactic radiosurgery even among patients whose tumors had been subtotally resected.[19,20] Conversely, other studies reported a higher 5-year freedom from local recurrence rates in patients who had received RT.[21-23] A recent study supported the use of postoperative RT for newly diagnosed gross totally resected tumors.[24] Cooperative group randomized controlled trials, including U.S.[24-26] and European trials,[9] suggested potential benefits of fractionated RT for patients with intermediate and high-risk meningiomas with acceptable toxicity, while in a recent analysis conducted by the Surveillance, Epidemiology, and End Results,[10] GTR improved survival, whereas this was not the same for radiotherapy.[27-31] In addition, many studies are performed on the basis of clinical data from

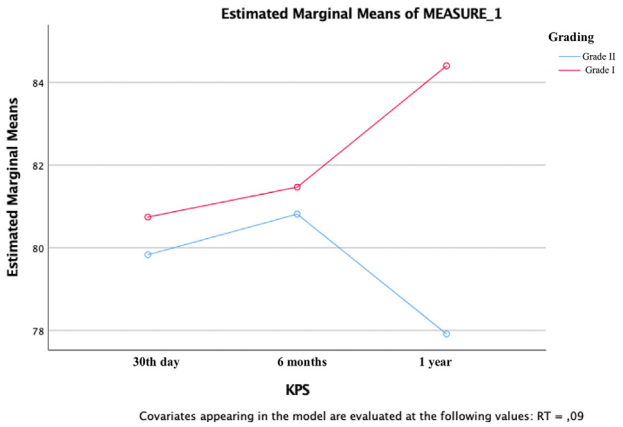

Figure 5. In the analysis of repeated measurements, it can be seen that in the group of patients with grade II meningioma, there is a greater reduction in performance status (expressed with Karnofsky Performance Scale) after 1 year with significant differences with regard to radiotreated patients.

national tumor databases, making direct multiparametric analysis and especially subjectivity of surgical choices impossible.[32]

According to some authors, adjuvant RT significantly improved progression-free survival (PFS)[15,25-27] but didn't translate into an OS benefit. Zeng et al[28] have reported that the OS in patients who underwent GTR alone was similar to those who received adjuvant RT, regardless of the EOR.

Only 1 study indicated lower PFS rates in patients who received adjuvant RT.[29] Therefore it remains controversial whether to use RT immediately after GTR or after recurrence.

To date there is no consensus in relation to this issue; currently, the therapeutic decision for the use of adjuvant radiotherapy depends on the preferences of the patient, neurosurgeon, and neurooncologist.[9]

The study of Byun et al[31] reported a significantly improved PFS and reduced recurrence in relation to radiologic parameters such as tumor size, cell replication index expressed by ki67%, and EOR. We partly confirm these data in our study with a multidimensional analysis regarding clinical (highlighting on the seizure debut of meningioma), radiologic, and surgical parameters of patients treated by the same surgical team.[31]

No studies analyzing the risk-benefit ratio in treating grade II meningiomas undergoing GTR with RT are reported in the literature. The use of RT, when a clear benefit is demonstrated, could be helpful in avoiding further surgical procedures, but potential long-term toxicity risks including radiation necrosis, neurocognitive deterioration, hypopituitarism, optic neuropathy, and radiation-induced secondary cancers should be considered.[30] The incidence of neurotoxicity ranges from 3.4% to 16.7% on the basis of the location of the lesion, radiation dose, and radiation pattern.[26]

This preliminary analysis highlights in our opinion that the choice to set adjuvant radiotherapy treatment should be contextualized to the patient's clinical status, age, degree of tumor excision, and presence of epileptic risk at debut.

The reasons why the patients treated with combined surgery + RT therapy are not entirely related to tumor site or biological status, while it appears that the presence of seizures in the postoperative phase greatly impacts the patient's functional recovery from any neurologic deficits.

CONCLUSIONS

The standardized treatment protocol for atypical meningioma is still discussed. Recurrence is more frequent for this kind of meningioma than a benign one, even though there are no significant differences in terms of postoperative complications and functional outcome. Our study shows that grade II meningiomas have a greater tendency to recur at 1 year regardless of EOR. RT in grade II meningiomas does indeed lead to better control of recurrence but also an increased risk of seizures and reduced performance status.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Mauro Palmieri: final editing, bibliography, and check analysis. **Daniele Armocida:** writing, research, surgical operator. **Raffaella De Pietro:** research and radiotherapy protocol application. **Giuseppina Chiarello:** research and radiotherapy protocol application. **Francesca Rizzo:** follow-up, data collection. **Diego Garbossa:** supervising. **Francesco Marampon:** project and radiotherapy supervising. **Antonio Santoro:** surgical operator, supervising. **Alessandro Frati:** ideation, project supervisor.

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