The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 226-235

Factors Affecting the Outcome of Surgical Management of Atypical Meningiomas

Shawky A. Elmeleigy*, Ahmed M. Deabes, Mohammed H. Eltantawy
Department of Neurosurgery, Faculty of Medicine, Benha University, Benha, Egypt
*** Corresponding author:** Shawky A. Elmeleigy, **Mobile:** (+20)1003495755, **Email:** elmelegyshawkey@gmail.com

ABSTRACT
Background: Atypical meningiomas differ from Grade I meningiomas in aspects of the higher rate of recurrence, more postoperative complications, and shorter life expectancy postoperatively.
Objective: This study was aimed to evaluate the clinical course of atypical meningioma and prognostic factors affecting its surgical outcomes.
Patients and Method: This retrospective study investigated the medical records of 45 patients who had surgical removal of atypical meningiomas at Benha University Hospitals between January 2010 and December 2021. Patients average age was (56.69± 11.11) ranged from 29 to 74 years. The follow-up period was 60 months. Analysis included multiple factors such as patient age, gender, tumor size, location, and the extent of surgical resection based on (Simpson Grading System).
Results: There was significant relationship between recurrence and Simpson grade, size, and side. There was a significant relationship between rate of recurrence and type of radiation used. The mean survival time was significantly longer in Gamma knife group compared to radiotherapy. Rate of mortality was significantly higher in group radiotherapy compared to gamma knife with hazard ratio (95% CI) (5.33(0.79-36.75%). Rate of recurrence was significantly higher in group radiotherapy compared to gamma knife with hazard ratio (95% CI) (3.03(0.89-10.31%).
Conclusion: It could be concluded that atypical meningiomas in elderly patients with a large size especially more than 60cc, incomplete surgical resection; frequently have poorer prognosis following surgical intervention. Postoperative radiotherapy could provide accepted local tumor control in patients with incompletely resected atypical meningioma.
Keywords: Atypical meningioma, Prognostic factors, Simpson grade, Recurrence, Cranial base, Stereotactic gamma knife.

INTRODUCTION

Meningioma is an intracranial tumor that arises from the meninges of the brain. It is the most common tumor of the central nervous system, accounting for around thirty percent of CNS neoplasms. Meningioma subtypes with aggressive and malignant features have been found. The term (atypical meningioma of grade II) was created in 1985 [1].

In its most recent classification methods, the WHO classified meningiomas based on histological criteria as atypical (Grade II) and anaplastic (Grade III) [2].

Since the adoption of the 2000 and 2007 WHO classifications, the percentage of atypical meningiomas has increased [3]. Recent figures indicate that 20–30% of meningioma patients are now diagnosed with atypical meningioma [4, 5].

According to a recent study, atypical meningiomas are linked with a greater risk of recurrence and shorter overall survival lengths than benign meningiomas (Grade I). Atypical meningioma is linked with a 7–8-fold higher risk of recurrence and a 2-fold greater risk of death 3–6 years after diagnosis [5, 6].

In addition, prior research identified the following potential prognostic markers for the recurrence of atypical meningioma: cellular proliferating index, age, tumor site, preoperative tumor size, degree of surgical resection, and early postoperative irradiation [7-9]. However, these studies are debated, and the appropriate treatment technique for atypical meningioma has not yet been found.

This study was aimed to evaluate the clinical course of atypical meningioma and prognostic factors affecting its surgical outcomes.

PATIENTS AND METHOD

This retrospective study investigated the medical records of 45 patients who had surgical removal of atypical meningiomas at Benha University Hospitals between January 2010 and December 2021. Patients average age was (56.69± 11.11) ranged from 29 to 74 years. The follow-up period was 60 months.

We collected demographic information, including the patient's age and gender. Patients had a pre-operative contrast-enhanced MRI; with a definitive radiological description of extra-axial brain SOL as regard site, size, side, focal pathological edema and the midline shift of the brain. The tumor size was determined in cubic centimeters based on the largest tumor length in all three dimensions.

According to the tumor location, meningiomas are classified anatomically into four categories. **Convexity meningioma** including (frontal, parietal temporal, occipital and that extending into more than one lobe of them), p**arasagittal meningioma** including (falcine and parasagittal), **sphenoid meningioma** (lateral sphenoidal, mid sphenoidal and

Received: 06/09/2022
Accepted: 05/11/2022

medial or clinoidal) and **Tentorial and olfactory groove meningioma**.

Exclusion criteria:

Patients with history of any other spinal or intracranial tumors, patients with multiple intracranial meningiomas (neurofibromatosis) and meningiomas associated with venous sinus thrombosis.

All patients were evaluated preoperatively, beginning with a review of their medical history and medical morbidity, such as diabetes, hypertension, ischemic heart disease, and other medical conditions, as well as their surgical history, date of their last general anesthesia, complete laboratory tests, ECG, echocardiography, and chest X-ray. The data of surgical technique and intraoperative steps documented including early interruption of the blood supply to the tumor, internal decompression using ultrasonic aspirator, dissection of the tumor capsule and possibility of removal of attached bone and dura.

After surgically verifying the diagnosis of atypical meningioma based on WHO histological criteria, forty-five individuals were identified.

The degree of tumor resection was estimated using the recorded operating notes and postoperative imaging by enhanced MRI brain to conclude the Simpson Grading system, which was utilized to classify the extent of surgical resection [10] as follow:

- **Grade I:** macroscopic complete removal of the tumor with excision of involved Dural attachment and abnormal bone reaction.
- **Grade II:** macroscopic complete removal of the tumor with endothermy coagulation of Dural attachment. **Grade III:** macroscopic complete removal of the tumor without excision or coagulation of involved Dural attachment.
- **Grade IV:** partial removal leaving tumor in situ.
- **Grade V:** simple decompression with biopsy.

Gross total resection (GTR) is defined as occurring in patients with Simpson Grade (I–II) resection, in whom no radiation therapy is required. For Simpson grades three or above, conventional radiation or gamma knife stereotactic radiosurgery was advised when tumors were not entirely eradicated (III, IV, V). Immediately after surgical treatment, the Department of Radiation Therapy at the International Medical Center, Cairo gave either conventional radiation or gamma knife radiosurgery. The decision making as regard the radiation modalities underwent the discussion of multidisciplinary team (neurosurgeon, pathologist, and radiotherapist). Stereotactic radiosurgery was done for residual less than 3 cm or residual in eloquent brain. While conventional radiation was indicated for large residual more than 3 cm when large radiological doses were needed so fractionation was a must.

After surgery and radiation therapy patients were followed-up in regular visits at 6 months, one year,3 years and 5 years postoperatively, using successive enhanced brain MRI. With regular data collection about radiological follow up and progress of the clinical conditions of the patients.

Overall survival and recurrence-free survival were computed from the date of surgery. The probability of death or recurrence was evaluated.

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

SPSS v27 was used to conduct statistical analysis (IBM, Armonk, NY, USA). Using the Shapiro-Wilks test and histograms, the normality of the data distribution was determined. The mean and standard deviation (SD) of the quantitative data tested using an unpaired student t-test were reported. When applicable, qualitative variables were reported in terms of frequency and percentage (percent) and analyzed using the Chi-square or Fisher's exact test. The Kaplan-Meier curve was used to illustrate the period until recurrence and death. A two tailed P value < 0.05 was considered statistically significant.

RESULTS

There were statisically insignificant differences between age, Gender, side, size, location, comorbidities, neurological deficit and mortality. There was statisically significant relationship between mortality and Simpson grade (Table 1).

Table (1): Relationship between mortality and different variables:

		Live (n=38)	Dead (n=7)	
Age (years)	<40	3 (7.9%)	0(0.0%)	0.077
	40-60	20 (52.6%)	1 (14.3%)	
	>60	15 (39.5%)	6 (85.7%)	
Gender	Male	12 (31.6%)	4 (57.1%)	0.194
	Female	26 (68.4%)	3 (42.9%)	
Side	Right	18 (47.4%0	2 (28.6%)	0.390
	Left	17 (44.7%)	5 (71.4%)	
	Medline	3 (7.9%)	0(0.0%)	
Size (cm)		49.05 ± 11.93	51.02±8.98	0.123
Location	Convexity	23 (60.5%)	6 (85.7%)	0.735
	Parasagittal	8 (21.1%)	1 (14.3%)	
	Sphenoidal	5 (13.2%)	0 (0.0%)	
	Tentorial	1 (2.6%)	0 (0.0%)	
	Olfactory groove	1 (2.6%)	0 (0.0%)	
Presentation	Seizures	10 (26.3%0	4 (57.1%)	0.429
	Weakness	14 (36.8%)	2 (28.6%)	
	Headaches	9 (23.7%)	0 (0.0%)	
	Visual diminution	4 (10.5%)	1 (14.3%)	
	Accidental discovered	1 (2.6%)	0 (0.0%)	
Neurological deficit	Not present	18 (47.4%)	4 (57.1%)	0.634
	Present	20 (52.6%)	3 (42.9%)	
Simpson grade	I	5 (13.2%)	0 (0.0%)	<0.001
	II	12 (31.6%)	0 (0.0%)	
	III	12 (31.6%)	0 (0.0%)	
	IV	9 (23.7%)	5 (71.4%)	
	V	0 (0.0%)	2 (28.6%)	

Data are presented as mean ± SD or frequency (%)

There were statisically insignificant differences between, location, comorbidities and recurrence. There was significant relationship between recurrence and Simpson grade and, size and side (Table 2).

Table (2): Relationship between recurrence and different variables:

		No recurrence (n=16)	Recurrence (n=29)	
Size (cm)		43.50 ±10.87	54.03 ±10.70	**0.003***
Side	Right	8 (50.0%)	12 (41.4%)	**0.027***
	Left	5 (31.3%)	17 (58.6%)	
	Medline	3 (18.8%)	0 (0.0%)	
Location	Convexity	7 (43.8%)	22 (75.9%)	0.142
	Parasagittal	4 (25.0%)	5 (17.2%)	
	Sphenoidal	3 (18.8%)	2 (6.9%)	
	Tentorial	1(6.3%)	0 (0.0%)	
	Olfactory groove	1(6.3%)	0 (0.0%)	
Presentation	Seizures	4 (25.0%)	10 (34.5%)	0.342
	Weakness	4 (25.0%)	12 (41.4%)	
	Headaches	5 (31.3%)	4 (13.8%)	
	Visual diminution	3 (18.8%)	2 (6.9%)	
	Accidental discovered	0 (0.0%)	1 (3.4%)	
Simpson grade	I	5 (31.3%)	0 (0.0%)	**<0.001***
	II	11 (68.8%)	1 (3.4%)	
	III	0 (0.0%)	12 (41.4%)	
	IV	0 (0.0%)	14 (48.3%)	
	V	0 (0.0%)	2 (6.9%)	

Data are presented as mean ± SD or frequency (%)

There was statisically significant relationship between rate of recurrence and type of radiation (Table 3).

Table (3): Relationship between mortality and different variables.

		No recurrence (n=16)	Recurrence (n=29)	
Type of radiation	None	16 (100.0%)	1(3.4%)	<0.001*
	Conventional Radiotherapy	0 (0.0%)	16 (55.2%)	
	Gamma knife	0 (0.0%)	12 (41.4%)	

Data are presented as frequency (%)

The mean survival time was significantly longer in Gamma knife group compared to radiotherapy. Rate of mortality was statisically significantly higher in group radiotherapy compared to gamma knife with hazard ratio (95% CI) (5.33(0.79-36.75%) (Table 4, Figure 1 and Figure 2).

Table (4): Mean survival rate according to different radiotherapy

Group	Mean	SE	95%CI	P value
None	60	0.00	60 -60	**0.0065***
Radiotherapy	38.375	6.98	24.68-52.06	
Gamma knife	55.08	3.096	46.816-64.018	

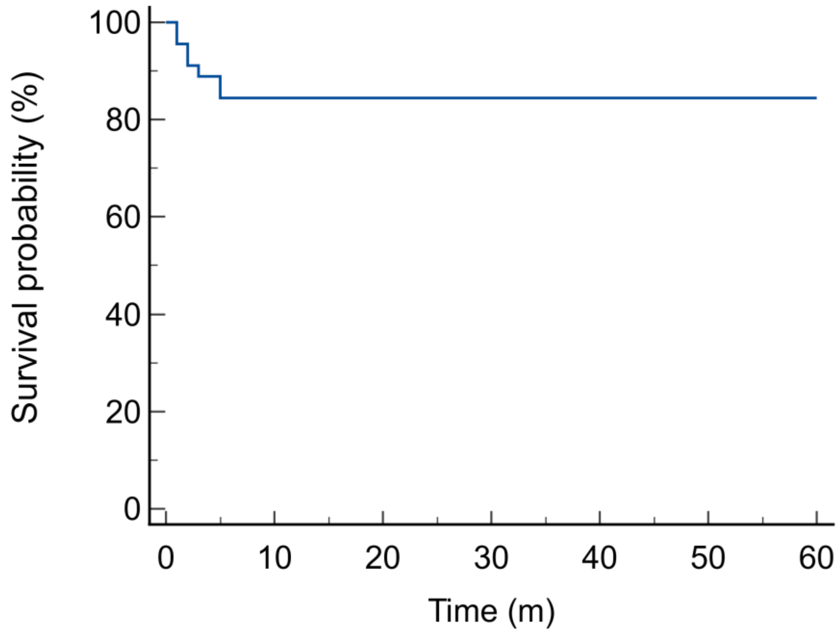

Figure (1): Kaplan Meier curve for mortality in all studied patients.

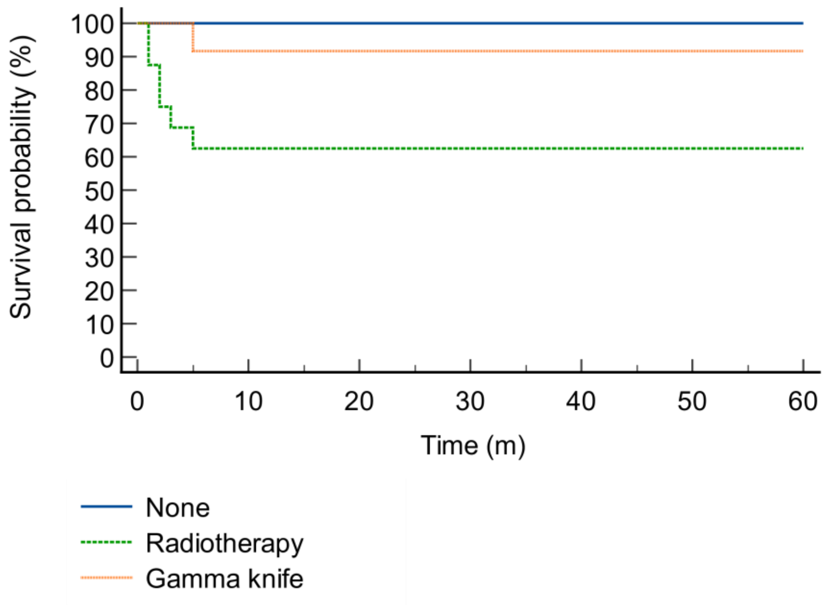

Figure (2): Kaplan Meier curve for mortality in different procedures.

Rate of recurrence was statisically significantly higher in group radiotherapy compared to gamma knife with hazard ratio (95% CI) (3.03(0.89-10.31%) (Table 5 and Figure 3).

Table (5): Mean recurrence rate according to different radiotherapy

Group	Mean	SE	95%CI	P value
None	58.58	1.370	55.904-61.28	**<0.001***
Radiotherapy	17.68	1.087	15.55-19.81	
Gamma knife	32.25	1.638	29.03-42.41	

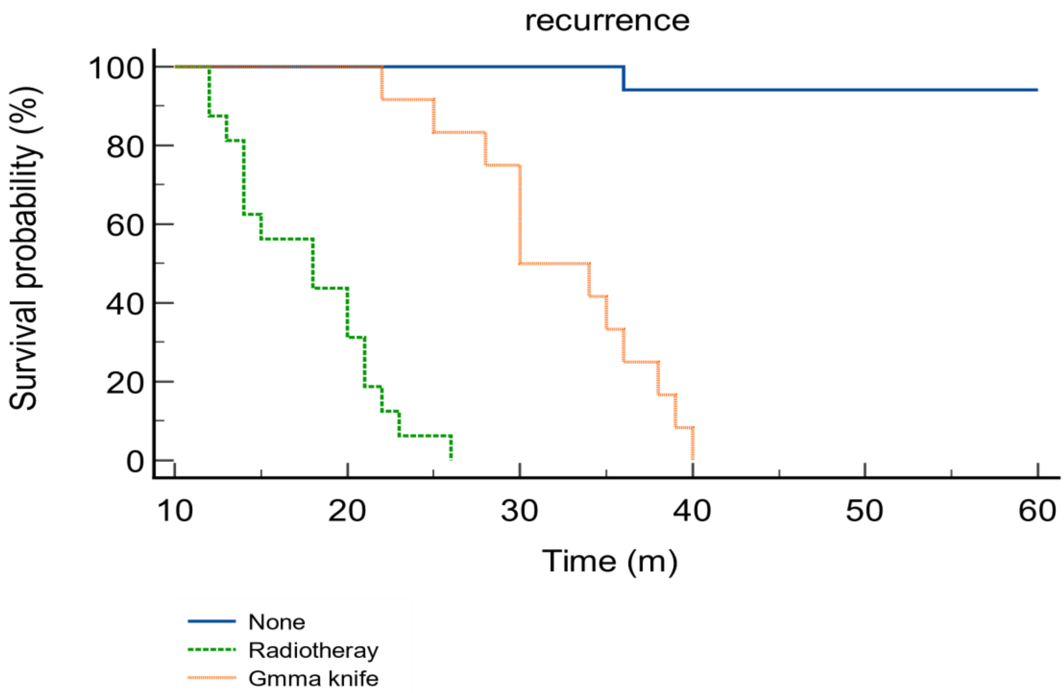

Figure (3): Kaplan Meier curve for recurrence in different procedures.

CASES

CASE NO. 1

Female patient, 53-year-old, presented with partial seizures, computerized tomography suggested Lt temporal SOL, enhanced M.R.I. brain concluded: tempropartial extra-axial mass mostly meningioma, operated upon by GTR. No postoperative residual or long-term recurrence up to 6 years postoperative without neurological deficit.

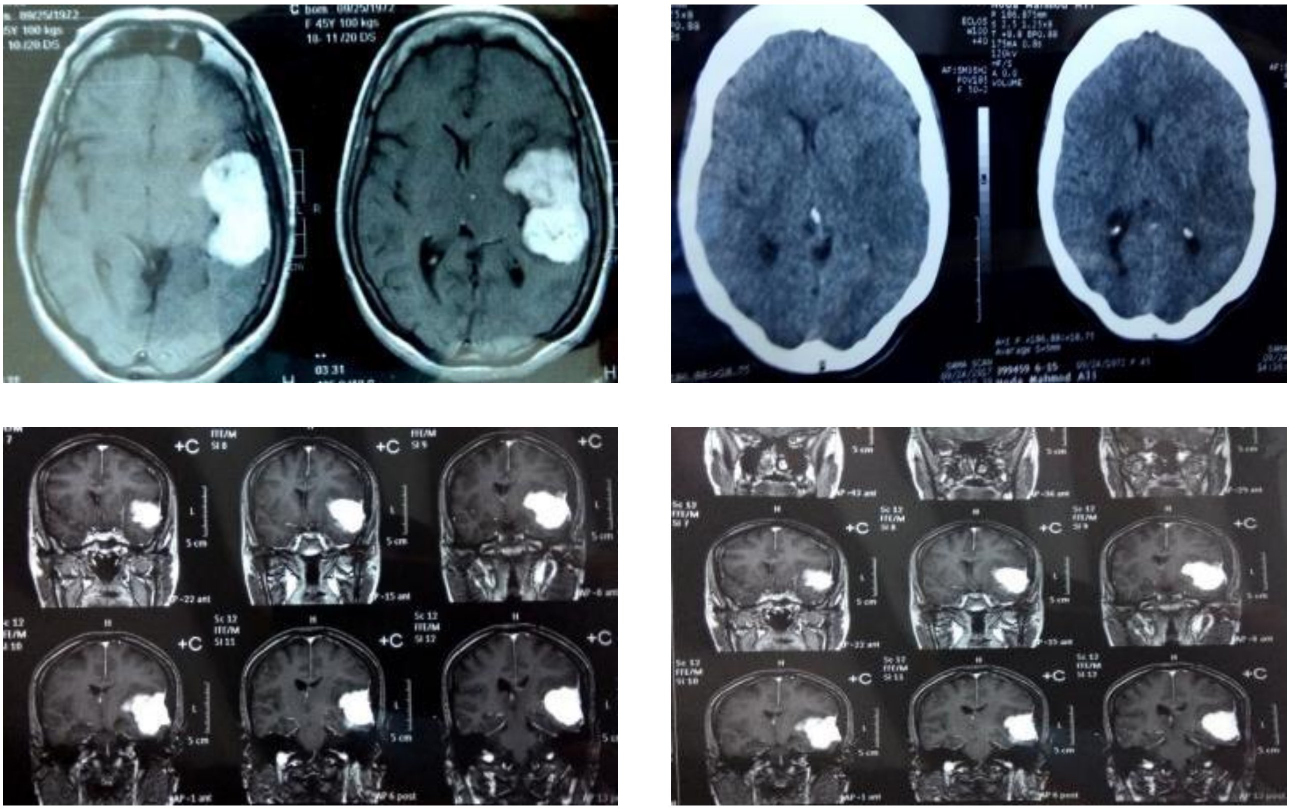

Figure (4): Preoperative CT brain axial cuts, and preoperative enhanced MRI brain axial and coronal cuts

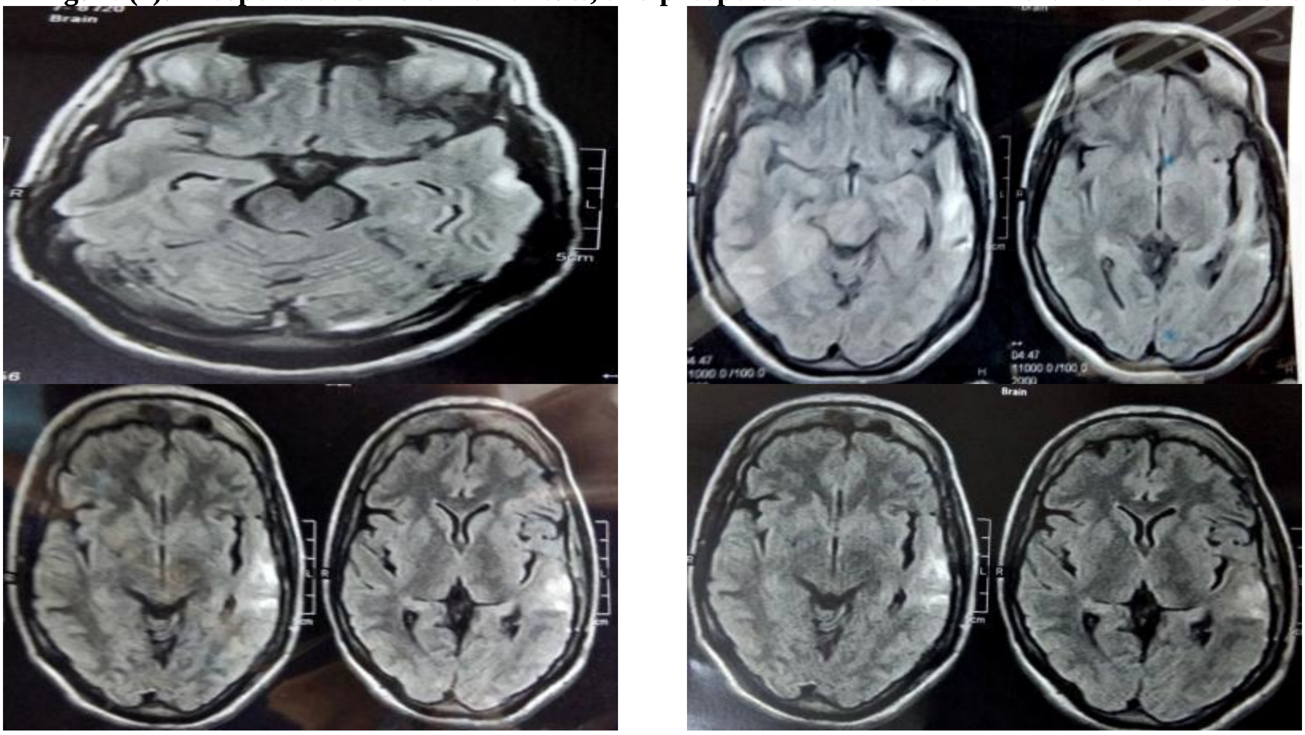

Figure (5): Post operative follow up 3 and 5 years after surgery enhanced MRI brain with no evidence of tumor residual or recurrence

CASE NO. 2

Male patient, 60 years old, presented with Lt foot drop of gradual onset & progressive courses, diagnosed as a spinal cause due to (L.D.P). MRI brain showed Rt falcine meningioma, operated upon by surgical excision postoperative enhanced MRI showed small tumor residual underwent radiotherapy by stereotactic gamma knife, with long term follow-up showed good tumor control.

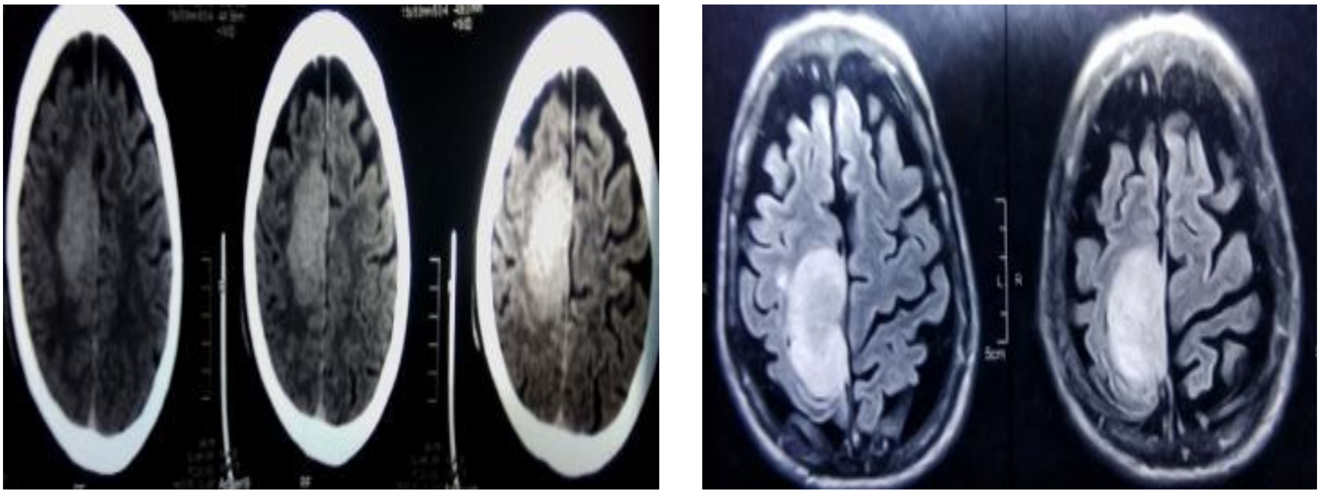

Figure (6): Preoperative axial CT and MRI brain with contrast showing RT falcine extra axial mass mostly meningioma

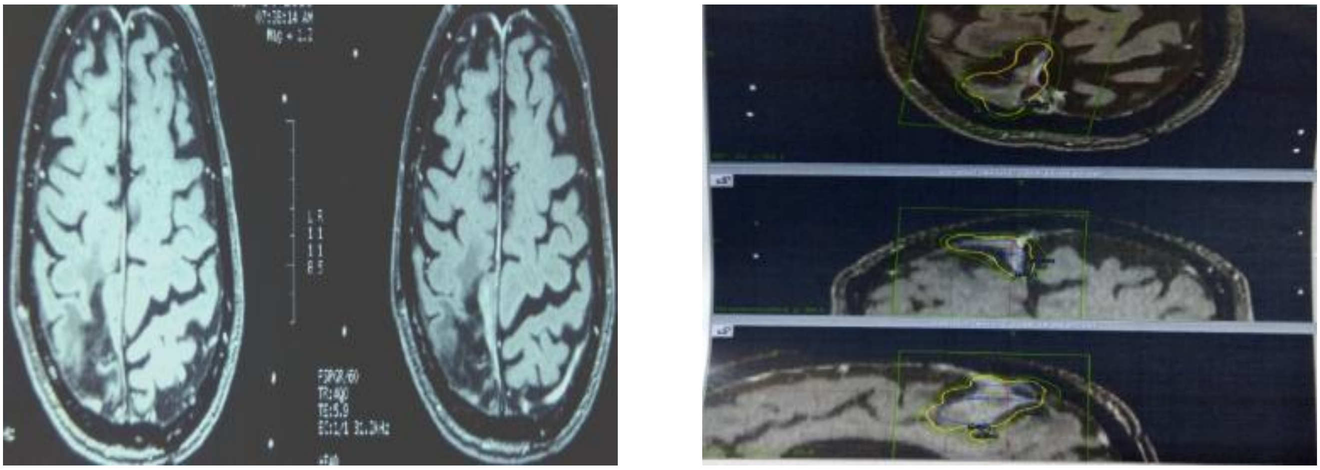

Figure (7): Postoperative enhanced images detected tumor residual needs post operative radiation by Gamma knife

CASE NO. 3

Female patients, 67 years old, presented with progressive Lt sided hemiparesis of progressive course CT brain, MRI brain with contrast showed Rt parietal parasagittal meningioma large size with mass effect surgical excision of the tumor done with postoperative large tumor residual that underwent conventional 3D radiotherapy follow up of the residual increased sized needing surgical Re- do, postoperative follow up detected large tumor recurrence.

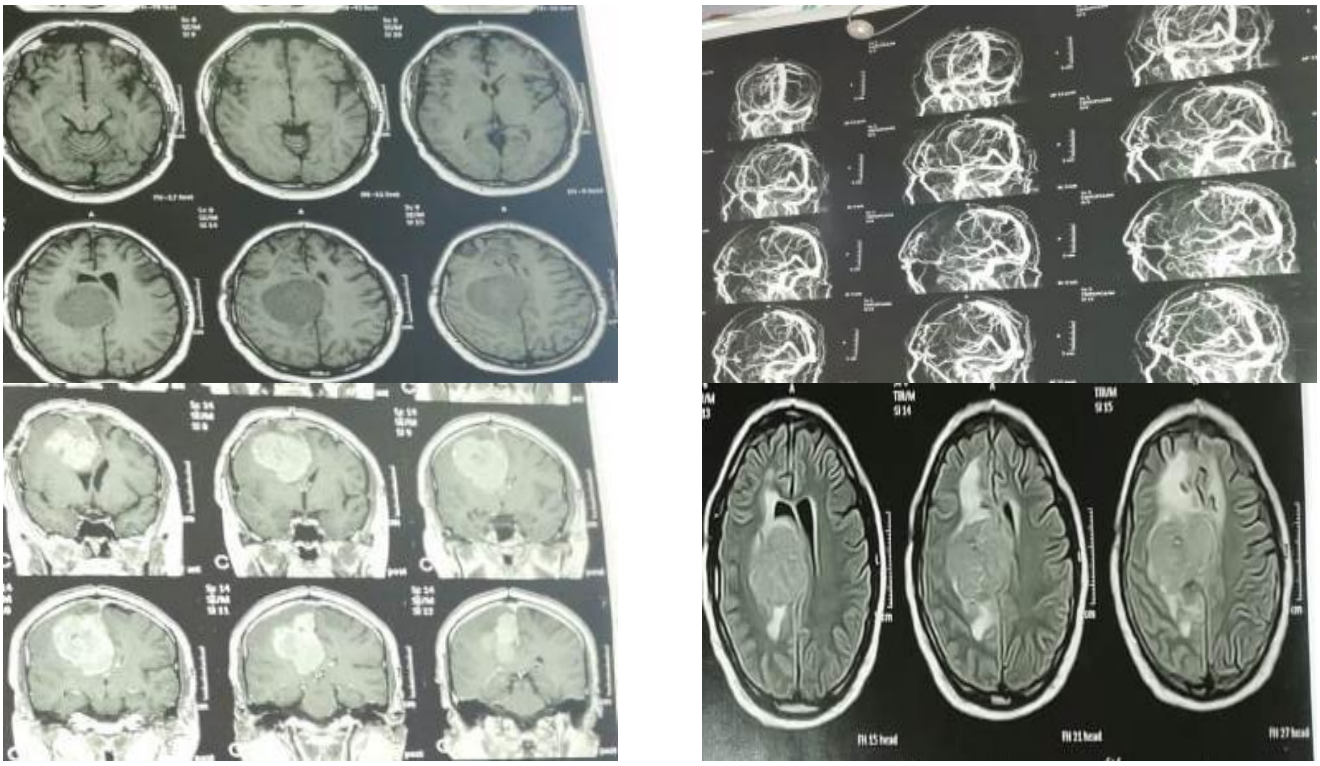

Figure (8): Preoperative.

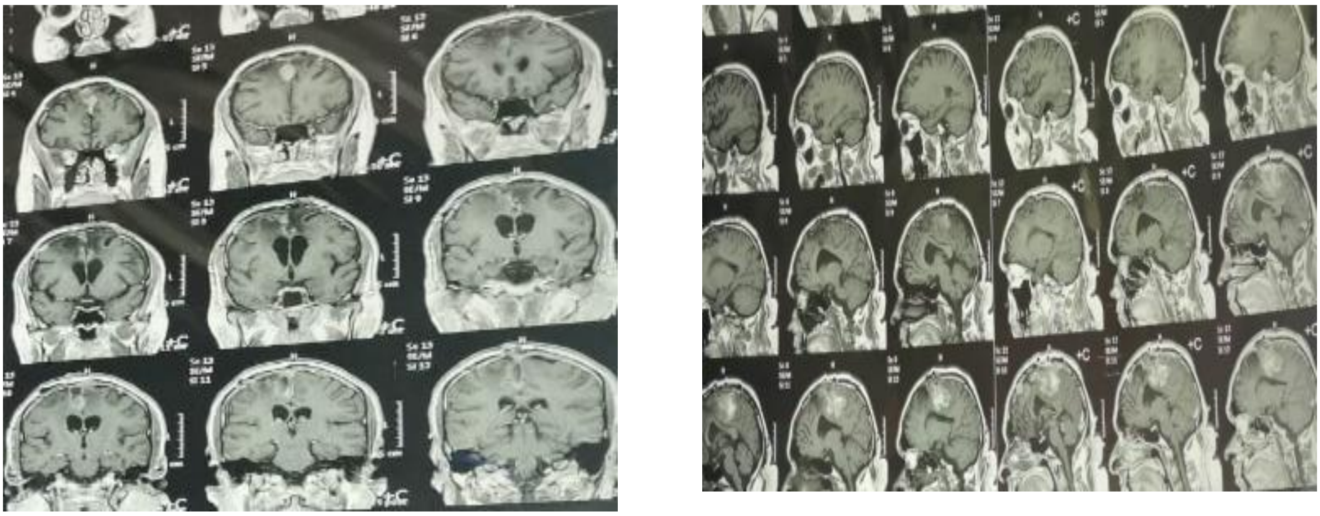

Figure (9): Postoperative

DISCUSSION

In this investigation, 45 individuals with atypical meningiomas were retrospectively evaluated for an average of 60 months. Comparable to previous trials in terms of clinical outcomes, including recurrence-free and overall survivals at 3 and 5 years post-operatively. Notably, our analysis comprised mostly female patients (63.3%), which was consistent with prior research revealing a comparable gender preponderance in benign and malignant meningiomas [11, 12]. Furthermore, in our analyses there was no gender significance in relation to risk of recurrence or mortality rate.

Our study actually indicated that the preoperative neurological deficit, local tumor control by radiation therapy and Simpson grade were related significantly to the recurrence rates; this conclusion similar to that of **Zaher *et al.***[13] series of 44 patients that proved the close relation between recurrence rates and the extent of tumor excision with paresis as a neurological deficit [13].

According to one research [14], male gender was a risk factor for poor survival in atypical meningioma. According to a study [15], female gender was a predictor of recurrences whereas male gender was not. Our limited cohort sample may have contributed to the discrepancy regarding gender as a risk factor for recurrence or death in our research. Our study also identified advanced age as a major prognostic factor, which is consistent with previous studies that identified advanced age as a substantial risk factor for disease recurrence and shorter survival.

In this study we concluded that; in addition to age, size of the tumor the gross total resection (GTR) evaluated by Simpson grade was very important factor in relation to the mortality rates; this conclusion similar to other studies by **Zaher *et al.***[13] **and Zhao *et al.***[15] who proved that the degree of resection of atypical meningioma was a single important factor related to mortality.

Surgical resection: In our case series, the degree of surgical resection had a significant influence on clinical outcomes. Concerning surgical resection, our findings corroborated those of other studies suggesting that complete surgical resection of a tumor was an important factor in reducing recurrence and predicting longer overall survival [14]. **Vranic *et al.*** stated that a parasagittal and falcine location was associated with a higher recurrence rate in their series of 76 cases of atypical meningiomas [14]. Even though the extent of surgical resection was not a significant prognostic factor in their study, the authors hypothesize that residual tumors along the superior sagittal sinus because of increased intraoperative risk contributed to the higher recurrence rate of atypical meningioma in this location. In the risk categorization of atypical meningiomas, our data indicate that a thorough resection should be of the utmost importance.

Postoperative radiotherapy: Even after subtotal resection, postoperative radiation is often useful in the long-term management of benign grade I meningiomas. In a study of 300 instances of benign meningioma, the recurrence rates of patients who had partial resection and postoperative irradiation improved, becoming equivalent to the recurrence rates of patients who underwent entire resection [16]. In the instance of an atypical meningioma, the circumstances are distinct. After partial resection, **Hardesty *et al.*** [17] **and Komotar *et al.*** [18] observed that irradiation was ineffective in controlling atypical meningiomas with irradiation. The usefulness of postoperative radiation remains debatable.

In the present study, patients with incomplete tumor resection underwent immediate postoperative radiotherapy with referral to studies that advocated early adjuvant radiotherapy for atypical meningioma. Radiotherapy succeeded to provide long-term control of tumor residual in our study with better control after stereotactic Gamma knife. This result must be re-evaluated on a large scale of cases for more confirmation in comparison of limited number of cases in current study.

The present study had limitations due to its retrospective design, small number of patients, and single center; another limitation is that our analyses primarily relied on the clinical data of the patients and the documented histological grade of the tumors, despite the fact that additional details of histological examinations, such as the Ki-67 proliferative index, add significant value to the prediction of the final outcome [19]. Recent gene sequence analysis has indicated distinct genetic origins for meningioma at different sites [20, 21]. For example, medial and lateral meningiomas showed distinct genetic bases while being histologically identical. Recognizing the significance of genetic changes in the development and progression of meningioma [22]. Future investigations should include genetic background analysis.

CONCLUSION

The prognosis of atypical meningioma remains not good as that of typical one (meningioma grade I) even with multimodal treatments. Based on our analyses, atypical meningioma in elderly patients with a large size especially more than 60cc, incomplete surgical resection; frequently have poorer prognosis following surgical intervention.

Postoperative radiotherapy could provide accepted local tumor control in patients with incompletely resected atypical meningioma, particularly if applied as early as possible. Our results emphasize the importance of pursuing complete surgical removal of atypical meningioma.

Conflict of interest: The authors declare no conflict of interest.
Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Author contribution: Authors contributed equally in the study.

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