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<sup>1</sup>Neurosurgery Department, King Hussein Medical Center, Royal Medical Services, Amman, Jordan

<sup>2</sup>Endocrinology Department, King Hussein Medical Center, Royal Medical Services, Amman, Jordan

<sup>3</sup>Neurosurgery Department, Mafraq Hospital, Abu Dhabi, UAE

<sup>4</sup>Plastic Surgery Department at Farah Center, Royal Medical Services, Amman, Jordan

<sup>5</sup>Pathology Department at Princess Iman Research and Laboratory Sciences Center, Amman, Jordan

**Corresponding author:** Rami Y. Alqroom, MD, FACS. Neurosurgery Department, King Hussein Medical Center, Royal Medical Services, Amman, Jordan. ORCID ID: <http://www.orcid.org/0000-0001-7338-8243>. E-mail: [dr.alqroomrami@gmail.com](mailto:dr.alqroomrami@gmail.com)

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# The Sovereignty of Primary Cranial Tumors—Meningiomas: Vetting the Cardinal Epidemiological Features

Alqroom Rami<sup>1</sup>, Eteivi Suzan<sup>2</sup>, Aldrous Rafeed<sup>1</sup>, Al Manaseer Nooruddeen<sup>3</sup>, Arabiyat Lamees<sup>4</sup>, Alshurbaji Duaa<sup>5</sup>, Abu Nowar Hussam<sup>1</sup>, Al Shurbaji Amer<sup>1</sup>

## ABSTRACT

**Introduction:** Cranial meningiomas considered one of most frequently encountered primary intracranial tumors in our daily neurosurgical practice, represent about 36% of brain neoplasms. **Aim:** In this cohort analysis, we investigated epidemiological features of brain meningiomas diagnosed at a single institution. Special highlighting has been dedicated to demographic features, foretelling radiological signs, and concomitant factors predictive of tumor atypia. **Material and Methods:** This retrospective analysis was conducted by revising all medical registries of patients aged  $\geq 18$  years, with a diagnosis of brain meningioma treated at King Hussein Medical Center, patients were retrieved from the electronic hospital database during a 12-year period (2004 to 2015). Preoperative radiology reports were examined to confirm tumor site and size based on largest measured dimension. Level of resection was based on surgical operative reports and post-operative radiological imaging. **Results:** A total of 665-patients operated for intracranial meningiomas were analyzed out of total 2047-patients operated for intracranial neoplasm during the same period. Demographic analysis showed; female to male ratio 2.4:1. Mean age 49.6-years. Average follow-up of 8.7 years. Tumor locations were classified as parasagittal (39.55%), convexity (27.52%), tentorial/ falx (6.17%), intraventricular (2.04%). Mean tumor size was 3.86 cm and tumor size was  $>4.5$ cm in (28.07%) of cases. In this study we achieved gross total resection in (73.1%) of cases, subtotal resection in (22.6%). The majority of patients evolved favorably with respect to their neurological examination post-operatively, though a neurological deficit persisted in 64-cases and 16-cases developed a new neurological deficit. Ninety five cases developed recurrence during the observation period. Surgical mortality was reported in 11-cases in the immediate post-operative period and in 42-cases further cases during the observation period related to other causes. **Conclusion:** Neurosurgery faces a large number of intracranial meningioma patients in daily practice. Because of its “benign” nature; the variability in management strategy, Neurosurgery is more and more challenged with the concern of intracranial meningioma treatment in the daily practice. Because of its “benign” nature; the variability in management strategy, research regarding the meningioma etiology and epidemiology has lagged behind that for more malignant intracranial neoplasms. These risk factors piloted a revitalization in the study of meningiomas.

**Keywords:** Meningioma, Grade II meningioma, Radiosurgery, Atypical Meningioma.

## 1. INTRODUCTION

Meningiomas are mesenchymal tumors that originate from the arachnoid cells of the leptomeninges casing the central nervous system (1-10). Meningiomas are the most frequently encountered primary intracranial tumors in most neurosurgical practice, represent about 36% of brain neoplasms in adults (11-20). However, these tumors may also occur in children, meningiomas in pediatric population account for  $<1\%$  of all meningiomas (21-27). Adult incidence peaks between the ages of 60 to 70 years and the female to male ratio is about 3:2 (28). The most fre-

quent locations are parasagittal, lateral convexity, the sphenoid wings, anterior fossa close to the olfactory nerve, the sellar region, and the posterior fossa and foramen magnum, respectively (28, 29-32). Large and enlarging meningiomas can cause significant mass effect, but these tumors do not typically invade the surrounding brain structures due to the pial-glial basement membrane bound. They usually present with seizures or with clinical symptoms that slowly evolve over time, though the severity of the symptoms and prognosis is heavily dependent on

the tumor’s histologic heterogeneity, its location and size (3, 10).

Histologically most meningiomas are benign. Meningiomas are classified based on the World Health Organization (WHO) classification system into three histological grades (1, 2, 3) and 15 subtypes (30, 31). High grade meningiomas are rare, accounting for less than 5% of all meningiomas (16). Histologic grade has a noteworthy influence on prognosis, risk of recurrence, and the need for adjuvant therapy (7).

**2. AIM**

In this analysis, we examined the epidemiological features of brain meningiomas diagnosed and treated at a single institution. Special emphasis is given to demographic features, the cardinal predictive radiographic features, surgical management, concomitant histopathological prognosticators (e.g. tumor atypia) and the clinical impact of these factors, including risk factors related to the tumor treatment itself.

**3. MATERIAL AND METHODS**

This retrospective study was conducted by reviewing all medical records of patients aged ≥18 years, with a pathological diagnosis of brain meningioma treated at King Hussein Medical Center (Amman, Jordan) over a 12-year period (2004 to 2015). Patients’ clinical entries and radiographic data were retrieved from the electronic hospital database for analysis. Patients: younger than 18-years of age; those lost during follow-up and patients with extracranial meningiomas were excluded. Demographic features assessed were; sex, age, tumor location, histopathological grading, size of tumor, extent of resection, any post-operative history of radiation therapy, and documented recurrences.

Preoperative radiology analytical observations (CT post contrast and/or MRI T1 axial cuts post gadolinium) were used to confirm tumor location and size based on measuring tumor size in more than one plane and to evaluate peritumoral signal changes, largest single dimension, pre-surgical CT imaging used to assess for bony invasion. Extent of resection was based on surgical operative notes and post-operative imaging.

*Surgical details*

After induction and general anesthesia, the patient is positioned supine with the head positioned according to the pre-planned approach. Brain relaxation and control of intracranial pressure maintained using dehydrating agents and moderate hyperventilation prior to and during surgery. One burr hole performed as initial step, then we perform circle craniotomy around the lesion. If no tumor in the bone flap, we keep it for replacement, if involved we send it for biopsy and we perform cranioplasty. The dura beneath the flap if not involved opened in flap fashion and then re-sutured. The abnormal dura around the tumor usually resected and if need a dural patch is placed. Our strategy is always to aim for gross total resection (Simpson 1-2).

**4. RESULTS**

Our cohort consisted of 665 adult patients operated for pathologically confirmed intracranial meningioma. Demographic analysis revealed female to male ratio of 2.4:1. Mean age of the cohort was 49.6-years, ranging from 22-87 years, while mean age for male patients was 58.67, for female patients mean age was 43.12 (Table 1). Mean follow up after clinical diagnosis was 104-months (ranging between 34-168 months). Tumor locations were: parasagittal (39.55%), convexity (27.52%), tentorial/falx (6.17%), posterior fossa meningiomas (8.27%) and intraventricular (2.04%)

Linear growth assessment done by measuring the largest linear axis of the tumor in any direction on at least two MRI images cuts (axial, coronal, and sagittal). Patients were categorized into three group by using the average greatest single dimension. Tumor size was >4.5cm in 28. 07% of patients (Table 2).

Clinically, majority of patients (64.21%) presented with headache and seizure activity (36.39%) which were the dominant complaints, other presentations; neurological deficit, hearing loss, visual disturbances (Table 1).

All patients were clinically monitored with an average post-surgical follow-up of 8.7 years. Contrasted MRI was performed for follow up every 6-months in those with histologically verified grade II meningioma, or if any change in clinical presentation developed. All these patients underwent surgical resection at one stage of follow-up either due to the tumor size (larger than 4.5 cm) or due to the clinical symptoms. In this study we achieved gross total resection in 73.1% of cases, subtotal resection in 22.6%, and 4.3% had unknown extent of surgical resection. All evolved favorably with respect to their post-surgical neurological examination, except 64-cases that had a persistent deficit, 16/665-cases developed a new neurological deficit. Ninety five cases developed a recurrence during the post-operative observation period, 67-cases underwent re-do sessions, while 20- cases underwent adjuvant radiotherapy and 8-cases were subjects to stereotactic radio surgery SRS. Surgical mortality reported in 11-cases in immediate post-operative period (within 30-days) and 42- patients passed away during the

Parameter	Number
Gender	
Male	201
female	464
Age	
>55	247
<55	418
Clinical Presentation	
Seizures	242
Headache	427
Mental status alteration	113
Focal signs	135
Nausea/vomiting/dizziness	328

**Table 1. Demographic features and leading signs and symptoms of atypical meningioma diagnosed in our department**

Locations		
parasagittal regions	263	39.55%
cerebral convexity	183	27.52 %
cerebral falx/ tentorium	41	6.17 %
sphenoid ridge	39	5.86 %
middle cranial fossa	43	6.47 %
olfactory groove	54	8.12 %
cerebellar convexity	15	2.25 %
suprasellar	14	2.11 %
intraventricular	13	2.04 %
multiple	27	4.60 %
Peri-tumoral edema		
no	213	32.03 %
mild(<2cm)	268	40.3 %
medium (2-4cm)	137	20.60 %
severe (>4cm)	47	7.10 %
Texture		
homogeneous	376	56.54 %
calcified	179	27.07 %
necrotic	52	7.82 %
cystic	35	5.27 %
hemorrhagic	23	3.50 %
mixed	67	10.10 %
Size (cm) (mean 4.72 cm)		
≤2.5	184	27.70 %
2.5-4.5	295	44.40 %
≥4.5	186	28.07 %

Table 2. Topographic and radiological features of meningioma diagnosed in our center

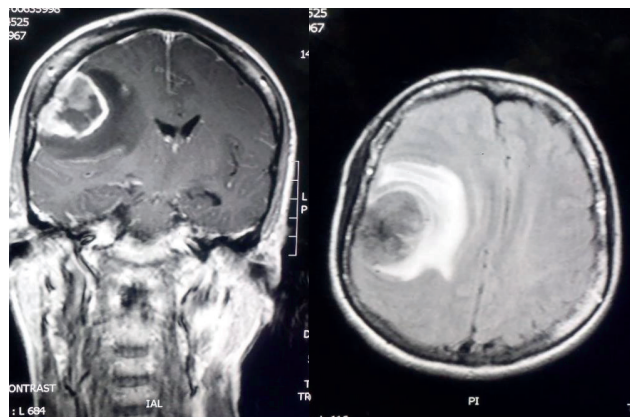


Figure.1. Coronal and axial contrasted MRI images showing the extensive peri-tumoral edema surrounding the atypical meningioma.

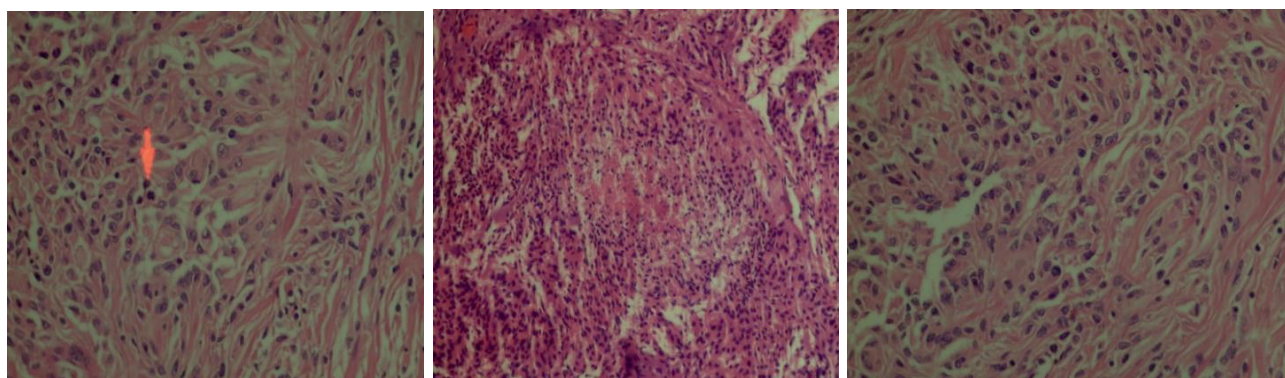


Figure.2. Histopathological slides showing: a- Meningioma with high mitotic activity (only one HPF shown), b- Meningioma with focus of necrosis, c- Meningioma with sheet like growth, small cells with high N/C ration and prominent nucleoli.

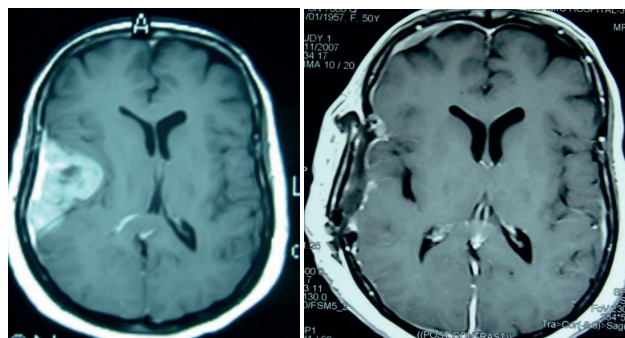


Figure.3. Post-contrast, axial cuts, pre- and post-operative MRI, showing total resection.

follow-up period due to other causes (e.g. pulmonary embolism).

Histopathological assessment showed: 410-patients with WHO grade 1, 199-patients with WHO grade 2, and 56-patients with WHO grade 3 meningiomas.

### 5. DISCUSSION

Meningioma is considered the most common primary central nervous system tumor. Typically these tumors are histologically benign (14). The estimated annual incidence of intracranial meningiomas is 1.2–3.1/100,000 population and the prevalence of pathologically-confirmed meningioma in the United States is approximately 97.5/100,000 with over 170,000 individuals currently being diagnosed with this tumor (8, 33-35). The documented ratio of female: male patients is approximately 2:1 and may be inverted for rare pre-pubertal meningiomas (18, 23, 34). This study revealed 464/665 cases observed among female-patients. In the female group, mean age was 42.5 years, which is considerably lower than the mean age of the entire cohort.

Clinically, symptoms from meningiomas are determined by the location of the mass and by the time course over which the tumor develops. Meningiomas are considered slow growing neoplasm and remain often asymptomatic for long times. They can grow anywhere along the dura matter, most frequently contained within the skull and at sites of dural reflection (falx cerebri, tentorium cerebelli) (32). Other sporadic sites include the optic nerve sheath and choroid plexus; roughly 10 percent arise in the spine. Seldom, meningiomas can also arise at extradural sites (21). The signs and symptoms found prominently in our study were focal signs, followed by



mental status alteration, seizures, and headache. Notably, a considerable part was serendipitously diagnosed (Table 1).

Radiological imaging is crucial in both pre-operative evaluation of tumor size and post-operative tumor resection extent and recurrence. In order to assess and measure the tumor size; growth ideally, volumetric analysis is the best method; second best is 3D measures (33). In our center we use the linear growth assessment done by measuring the maximum linear diameter of the tumor in any direction on at least two MRI images cuts (axial, coronal, and sagittal). The typical characteristics on CT and MRI images include a dural tail, peri-tumoral edema, hyperostosis/bony infiltration, and calcifications which are all important and features which bear relevance for prognosis (32) (Figure 1). Noteworthy associations have been found between histological atypia/higher histological grade and observed tumor size (>40mm), shape, localization (base of skull), presence of brain invasion, and the existence of peri-tumoral edema (6, 15, 22, 25, 26). The radiographic growth rate of intracranial meningiomas has been reported as 2.4–5.3 mm per year, depending on mitotic activity as well as initial size (26, 27, 36). Other studies have reported that hyper intensity on T2-weighted imaging, a non-skull base location and the absence of calcification on radiographic imaging are positive indicators of accelerated tumor growth in intracranial meningiomas (12, 13).

Cardinal concomitant factors indicating higher histological grade in this cohort analysis were: massive peri-tumoral edema; high proliferation index (Ki-67); large tumor size and distinct texture (Table 2).

The World Health Organization (WHO) classification system categorizes meningiomas into three histological grades (1-2-3) and 15 subtypes (19, 30). The histopathological classification of meningiomas is powerful herald for its natural history, with higher grades associated with faster growth and greater rates of morbidity and mortality. However, clinical outcome in a subset of patients lies beyond the assigned pathologic grade for the respective tumor (5, 19, 30). Patients with atypical meningiomas seem to have a worse prognosis than patients with benign (WHO Grade I) meningiomas. Unfortunately, there still is limited understanding of the pathological risk factors that affect long-term tumor control following combined treatment with surgery and radiation therapy. Brain and/or bone involvement, and a high mitotic index significantly predicted an increased risk of treatment failure despite combination therapy (17). The presence of clinical symptoms and any observed tumor growth are main determining factors which permeate the clinical decision-making strategy (5, 29). Standard of care typically invokes surgical resection for the majority of these cases.

In general, complete surgical resection without compromise of neurological function confers the best prognosis for the patient, achieves the best quality of life for the patient and reduces the risk of recurrence. The extent of resection is commonly graded according to Simpson (24). However, there remains significant controversy re-

garding the role of adjuvant radiotherapy for even completely resected grade II tumors, the optimal timing and approach for such radiation therapy in various clinical settings. Various trials to address this problem are currently undertaken. Of note, the various in management strategies for intermediate grade meningiomas are further complicated by shifts in diagnostic criteria over time (2, 4, 11, 24, 33, 34).

Recent reports supports that adjuvant radiotherapy even after Simpson Grade I, II, or III resection was found to improves local control for atypical meningiomas (6, 22). Although, some authors advocate observation alone after gross resection of atypical meningioma, this was not associated with increased risk of tumor recurrence or mortality (21). In our series we achieved a gross total resection in 61% of cases, subtotal resections in 33.4%, and 5.6% of cases had undergone an unknown extent of resection (Figure 3).

Our strategy until 2013, was to offer adjuvant radiotherapy in higher grade lesions based on empiric experience. Nowadays, in cases in which we achieve microscopic complete resection and without recurrence on regular 6-month follow-up radiological images, we observe. Relapsing patients receive adjuvant radiotherapy. Our analysis revealed 19/665 cases developed a recurrence, 13-cases had previous STR and 4 cases had GTR

## 6. CONCLUSION

Contemporary Neurosurgery remains challenged with the quest for best intracranial meningioma management in daily practice. Although the vast majority of meningiomas are benign, higher histological grade reported with increasing frequency. Because of their mostly “benign” nature; and significant variation in management, research in meningioma epidemiology and etiology has lagged behind that of malignant intracranial neoplasms. However, newly identified risk factors ushered a renaissance in the study of meningiomas. The archetypical demographics of these tumors; younger age group, gross total resection is crucial for recurrence, adjuvant radiotherapy is still controversial.

- **Author’s contribution:** Each author gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. Each author had a part in article preparing for drafting or revising it critically for important intellectual content, and each author gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest.
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