

## ORIGINAL ARTICLE

# Clinicopathological Characteristics of Meningiomas:

## A tricentric Study

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### Abstract

**Background and Aims:** Meningioma is the most common brain tumor in Jordanian adults. This study aimed to analyze the macro- and microscopic features of meningiomas with emphasis on the correlation with tumor recurrence.

**Materials and Methods:** This retrospective study comprised all the meningioma cases diagnosed at three major tertiary care centers in Jordan in 2007-2021. The clinicopathologic data were retrieved from the patients' records.

**Results:** A total of 690 cases were studied, with the peak age being 45 years. The female-to-male ratio was 2.3:1. Based on the available data for most patients among the cohort, tumor size ranged from 0.5 cm to 11.5 cm, and the most common site was the frontal lobe. The great majority of tumors were grade 1 (80.2%). Male sex was significantly associated with a higher tumor grade and a larger tumor size ( $p = 0.003$  and  $0.001$ , respectively). The 5-year follow up data was retrieved for 206 patients. The recurrence rate was about 28%. Recurrence was significantly associated with tumor size ( $p = 0.000$ ). The tumor size was also significantly associated with the histologic grade ( $p = 0.003$ ). Multivariate analysis showed that intracranial tumors were significantly more associated with recurrence than spinal ones ( $p = 0.017$ ), and that mitotic index was significantly associated with recurrence ( $p = 0.002$ ).

**Conclusions:** Our results were concordant with international reports. Spinal tumors showed less recurrence rate than intracranial ones, and the mitotic index and tumor size were significantly associated with a higher recurrence rate.

**Keywords:** Meningioma, Brain tumors, Histopathology, Recurrence, Prognosis

**Abbreviations:** EMA: Epithelial membrane antigen, PR: Progesterone receptor

## INTRODUCTION

Meningioma is an intracranial tumor that mainly affects adults, especially in late or middle adulthood [1]. It affects females more than males [1]. Meningiomas arise from the leptomeningeal arachnoid cells [2]. Most of these tumors are benign (grade I, 90%), with a minor proportion are grade II (atypical) meningiomas, followed by grade III (anaplastic/malignant) ones [3]. In neurosurgical practice, meningioma is the most common primary tumor of the brain in adults, representing about 36% of brain tumors in this age group [4]. About 1% of meningiomas occur in children [5]. The symptoms of meningioma largely depend on the site of the tumor [6]. They can arise at any site along the dura, where the cerebral convexity, falx cerebri and tentorium cerebelli are among the most common sites [7,8]. About 10% of the cases occur in the spine. Choroid plexus and optic nerve sheath can also be affected. Extradural sites have also been reported [9]. These tumors tend to remain asymptomatic for years. However, focal deficits, alteration of the mental status, seizures, and headache are the most common signs and symptoms [2]. The grade of meningioma is the most important factor in prognosis. The WHO system is the classification system used for meningioma grading [10,11]. If the tumor lacks the criteria of grade II or grade III meningiomas, and not histologically categorized as chordoid, clear cell, papillary, or rhabdoid, then it will be considered grade I. Mitotic count more than or equal to 20 per 10 HPFs, anaplasia (carcinoma-like, sarcoma-like, or melanoma-like), or papillary or rhabdoid histological variants are considered grade III. The tumor is considered grade II meningioma if the following applies: A mitotic count of more than or equal to 4 per 10 HPFs plus 3 out of

the following: Prominent nucleoli, necrosis (not due to irradiation or embolization), sheeting/patternless growth, small cell change, and increased cellularity. Brain invasion and clear cell and chordoid histological variants are at least grade II. The main histological variants identified for meningioma other than the previously mentioned are meningothelial (Syncytial), psammomatous, fibroblastic (fibrous), mixed (transitional), microcystic, angiomatous, secretory, metaplastic, and lymphoplasmacyte-rich [11].

The aim of this study is to correlate between the different clinicopathological and demographic features of meningioma with a focus on recurrence-free survival.

## MATERIALS AND METHODS

This retrospective study was approved by the institutional review board No. 9395/2021/10, 28/04/2021. It involved all meningioma cases diagnosed between 2007 and 2021 at the three major tertiary care centers, and the following data were retrieved from the hospital records: age at diagnosis, gender, histological type, tumor grade, site, side, size, brain invasion, bone invasion, microscopic features, and the 5-year follow up. The age of the patients was used as a continuous and an ordinal variable as highlighted in Table 1. Tumor size was also used as a scale and an ordinal variable (<2, 2-5, and >5 cm).

Patient's age and sex were correlated with tumor size, site, side, type, and grade. The brain and bone invasion were also correlated with age, sex, histologic type, site, and side.

The recurrence-free survival for the patients with 5-year follow up was correlated with patients' demographics and the different tumor characteristics.

Some data were not available for certain

criteria. However, percentages were calculated for available data and missing data were excluded from analysis, and hence the results were not biased.

Data was analyzed using the Statistical Package for the Social Science v 20. Descriptive statistics were used, and Pearson's chi-squared test was applied. P value < 0.05 was considered significant. Univariate and multivariate survival analysis was performed, using the Kaplan-Meier method and the Cox regression model, respectively.

## RESULTS

A total of 690 patients were studied. The age range was 1-93 years (mean: 50, median: 50.5, standard deviation: 15.75). The peak age was 45 years. The female-to-male ratio was 2.3 to 1. There was no significant difference in the mean age between male and female patients (50.8 versus 49.6). Table 1 shows patients' demographic data.

**Table 1: Patients' demographics.**

		Sex		
		Male	Female	Total
<b>Age category (years)</b>	<15	6	9	15
	15-19	2	6	8
	20-29	16	35	51
	30-39	25	57	82
	40-49	41	133	174
	50-59	52	104	156
	60-64	21	51	72
	>64	47	85	132
<b>Total</b>		210	480	690

Over 91% of the tumors were intracranial, while 8.6% of the tumors were spinal. Left-sided tumors were more common than right-sided ones (32.5% compared to 28.8% of the cases). The most common intracranial site

was frontal (13.8%) followed by parasagittal (12.9%). Tumor size ranged from 0.5 cm to 11.5 cm (mean: 4.1 cm, standard deviation: 1.99). Table 2 shows the distribution of tumors according to the site.

**Table 2: The distribution of meningiomas according to the site.<sup>a</sup>**

Site	Number (%)
Frontal	32 (13.8)
Parasagittal	30 (12.9)
Posterior fossa	24 (10.3)
Sphenoid	23 (9.9)
Sellar/Parasellar	17 (7.3)
Parietal	15 (6.5)
Olfactory groove	15 (6.5)
Fronto-parietal	7 (3)
Parieto-temporal	7 (3)

Site	Number (%)
Temporal	5 (2.2)
Fronto-temporal	5 (2.2)
Occipital	3 (1.3)
Parieto-occipital	3 (1.3)
Skull base	3 (1.3)
Orbital	3 (1.3)
Optic nerve	2 (0.9)
Cavernous	2 (0.9)
Vertex	1 (0.4)
Hard palate	1 (0.4)
Sylvian	1 (0.4)
Spinal	33 (14.2)
<b>Total</b>	<b>232 (100)</b>

<sup>a</sup>Some data were not available for certain criteria, percentages are calculated for available data and missing data were excluded from analysis, and hence the results were not biased.

The great majority of tumors were grade 1 (80.2%), while grade 2 and grade 3 tumors represented 17.1% and 2.8% of the cases, respectively. The most common histologic type was meningothelial meningioma, representing 77.7% of the cases. The second

most common type was transitional meningioma (5.8%) followed by psammomatous and fibrotic meningiomas (4.7% and 3.9%, respectively). Table 3 shows the distribution of tumors according to the histologic type.

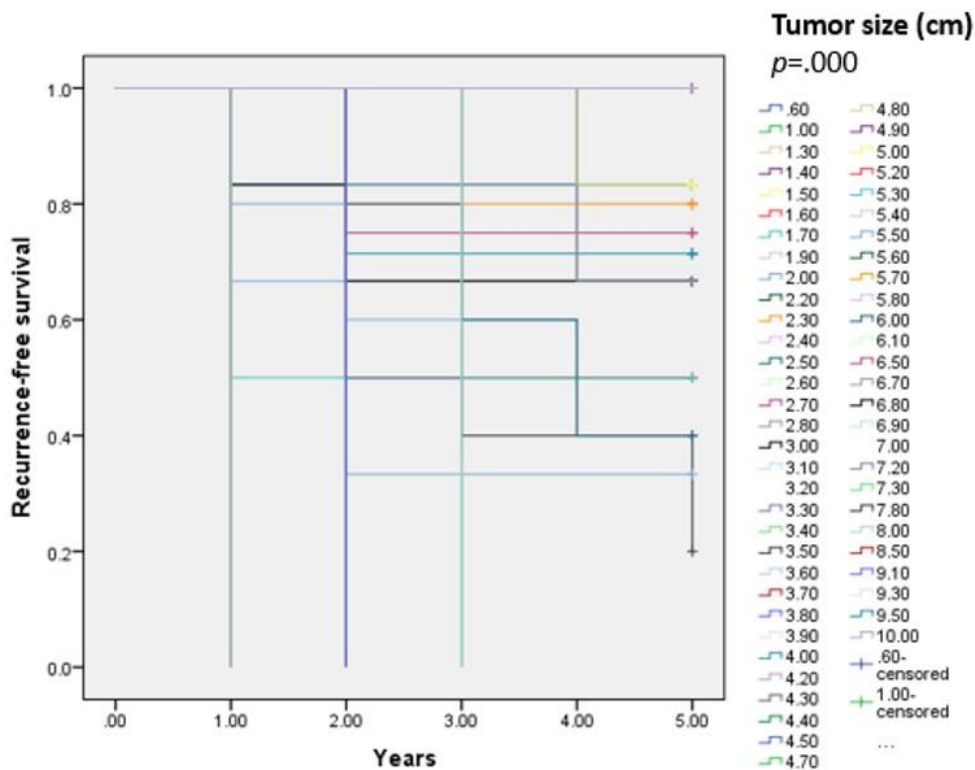
**Table 3: The distribution of meningiomas according to the histologic type.<sup>a</sup>**

Type	Number (%)
Meningothelial	494 (77.7)
Transitional	37 (5.8)
Psammomatous	30 (4.7)
Fibrotic	25 (3.9)
Malignant	17 (2.7)
Chordoid	9 (1.4)
Secretory	6 (0.9)
Angiomatous	5 (0.8)
Metaplastic	4 (0.6)
Rhabdoid	3 (0.5)
Papillary	3 (0.5)
Clear cell	2 (0.3)
Microcystic	1 (0.2)
<b>Total</b>	<b>636 (100)</b>

<sup>a</sup>Some data were not available for certain criteria, percentages are calculated for available data and missing data were excluded from analysis, and hence the results were not biased.

Patient's age and sex were correlated with tumor size, site, side, type, and grade. Interestingly, male sex was significantly associated with a higher tumor grade and a larger tumor size ( $p = 0.003$  and  $0.001$ , respectively). Brain invasion was identified in 9.1% of the cases, while bone invasion was found in 13.2% of the cases. A highly significant association was found between bone and brain invasion ( $p = 0.000$ ). However, no significant association was

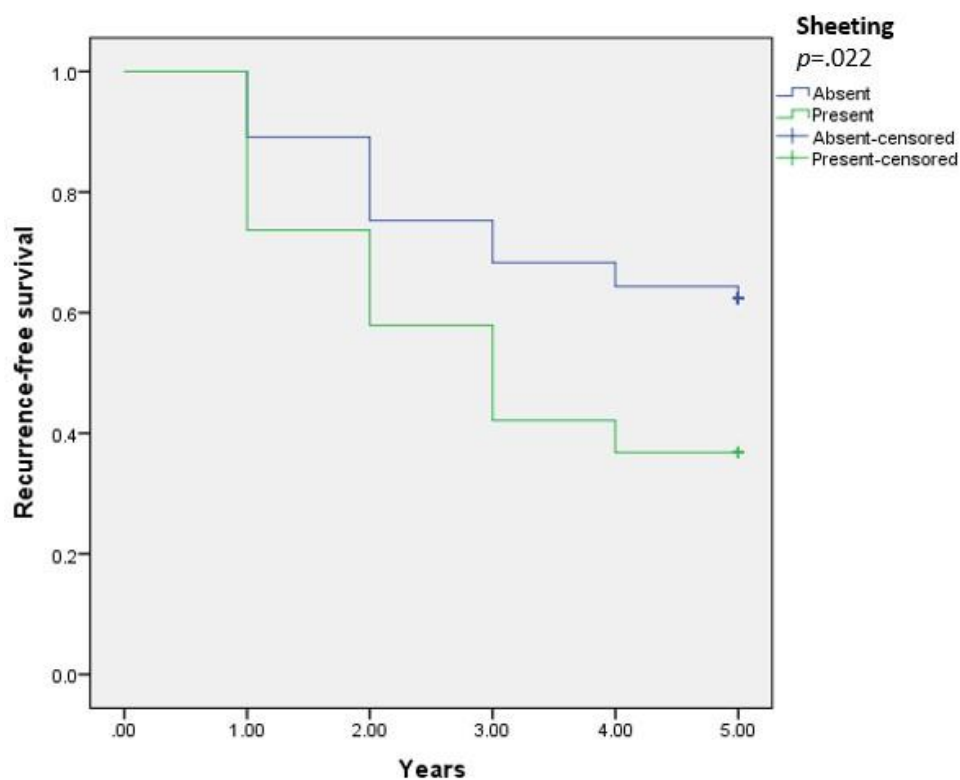
found upon correlating brain and bone invasion with age, sex, histologic type, site, and side. The 5-year follow up data was retrieved for 206 patients. The recurrence rate was about 28%. The recurrence-free survival was not significantly associated with patient's age nor patient's sex ( $p = 0.409$  and  $0.900$ , respectively). Recurrence was associated with increased tumor grade ( $p = 0.135$ ), and it was significantly associated with tumor size (Fig. 1).



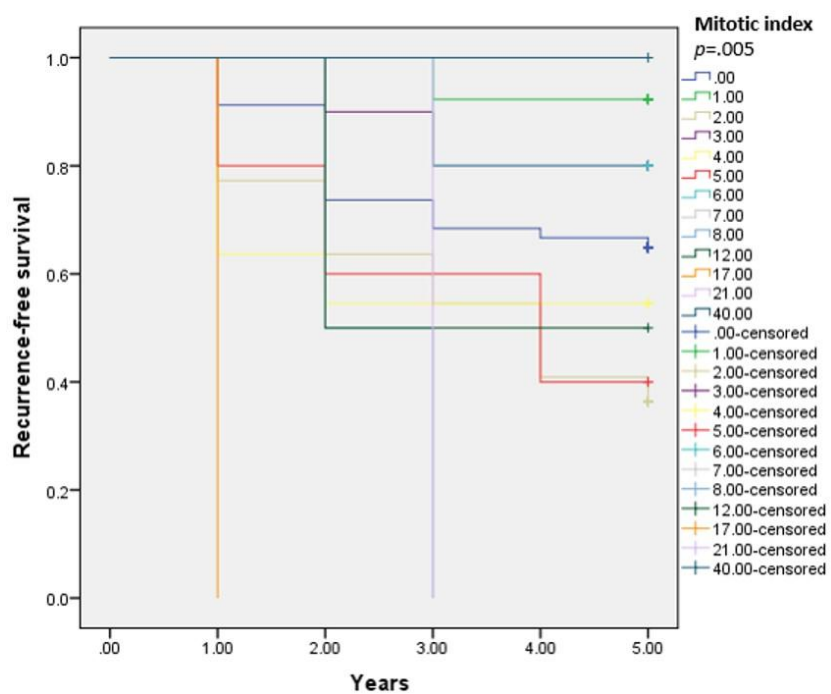
**Fig. 1: Recurrence-free survival according to tumor size.**

The tumor size was also significantly associated with the histologic grade ( $p = 0.003$ ). Bone invasion was not associated with increased recurrence. Among the

histologic features, sheeting and mitotic index were significantly associated with increased recurrence (Fig. 2 and Fig. 3, respectively).



**Fig. 2: Recurrence-free survival according to presence or absence of sheeting (patternlessness).**



**Fig. 3: Recurrence-free survival according to mitotic index.**

However, in multivariate analysis using the Cox regression model, mitotic count was the only microscopic variable that showed significant association with recurrence ( $p = 0.002$ ). Multivariate analysis also showed that intracranial tumors were significantly more associated with recurrence than spinal ones ( $p = 0.017$ ). Regarding the immunohistochemical findings in meningiomas, Epithelial Membrane Antigen (EMA) positivity was found in 95.1% of tumors, which was the same as Progesterone Receptor (PR). S100 was positive in 23.1% of the tumors.

## DISCUSSION

Anatomic site and patient demographics

Meningioma is the most common intracranial tumor in Jordanian adults [12]. It arises from the meningotheelial cells, mostly attached to the dura [10]. Our study revealed that the most common site was cerebral convexity, which is concordant with international reports [7,8], and it showed that the most common age group affected was 40-49, which is relatively younger than the peak age range reported from several reports worldwide. Baldi et al. showed a peak age range of 75-89. They studied both operated and non-operated tumors [13]. In a nationwide French study, it was shown that the peak age range was 60-64. Like our study, they analyzed the cases that are operated/with tissue diagnosis [14]. This relatively younger age might be explained by the fact that elderly patients are less likely to undergo invasive procedures. The present study showed that females are affected 2.3 times more than males. In an epidemiologic study on brain tumors in Jordan, meningioma was the most common histologic subtype of primary brain tumors, and the same study reported an adulthood and female

predominance [12]. These results are comparable to international reports; Kaguri and Black et al. reported a female-to-male ratio of 2.2:1 and 2.5:1, respectively [15,16]. In a large series by Cushing et al., the ratio was 1.5:1 [17]. These results were different from the results of Awori et al.'s study which showed male predominance [18].

Histopathologic features and their effect on the recurrence rate

The recurrence rate in the present study was 28%, which is concordant with international reports. A recurrence rate of 34% was reported by Korshunov et al. [19]. Maier et al. reported a rate of 11% [20]. Perry et al. stratified meningioma cases into classic, atypical, and brain-invasive with recurrence rates of 12%, 41%, and 56%, respectively [21].

The present study showed that the mitotic index was significantly associated with recurrence. It is well known that the mitotic index is a major criterion for grading of meningioma according to the WHO classification, and this significance was reported in many studies worldwide. In Olar et al.'s study, cases were segregated into those with a mitotic index of 0-4 and those with  $>4$  mitotic index, and a significant association with recurrence-free survival was found ( $<0.01$ ) [22].

In a recent study by Kwon et al., a significant association was reported between increased mitotic index and malignant transformation of atypical meningiomas [23]. The study emphasized the point that despite the well-defined WHO criteria regarding mitotic index and grading of meningioma, the differences in mitotic index can also be correlated with heterogeneity of behavior within the same grade of tumor. This was also supported by the results of the studies by Vranic et al. and Lee et al., which showed a



significant association between recurrence and mitotic index as a continuous variable [24,25]. Interestingly, this was also found in the present study ( $p = 0.005$ ). Although our results showed a significant association between sheeting and recurrence, it is more prone to inter-observer variability, and mitotic index remains the most important histopathological feature as highlighted by the multivariate analysis. The present study showed that bone invasion was not associated with increased recurrence. Similar results were found by Miller's study, in which no significant association was found between bone invasion and recurrence [26]. In another study by Ong et al., there was no significant association between bone and brain invasion [27]. Interestingly, the present study showed a highly significant association between bone and brain invasion ( $p = 0.000$ ). Tumor size was significantly associated with recurrence and grade ( $p = 0.000$  and  $0.003$ , respectively). Similar to our results, Ildan et al. found a significant association between tumor size and recurrence on the univariate analysis [28]. Similar results were found by Nakasu et al. [29]. In McCarthy et al.'s exploration of meningioma cases from nearly 1000 hospitals in the American College of Surgeons tumor registry program, tumor size was among the prognostic factors for benign tumors but not for malignant ones [30]. Our results showed that spinal meningiomas are significantly less associated with recurrence than intracranial ones. This was also found by Mirimanoff et al. and King et al. [31,32]. A low recurrence rate of spinal meningiomas was also found by Solero et al. and Levy et al. [33,34]. However, the tumor grade and

length of follow up should be taken into consideration [35,36]. The present study showed that 95.1% of the tumors are positive for EMA. EMA is known to be positive in 50-100% of meningiomas [37]. A similar high percentage of positivity was also found with PR staining, which is known to be positive in 88% of meningiomas [38]. S100 positivity was observed in 23.1% of the cases. In Behling et al.'s recent study of 1669 cases, S100 was strongly positive in 13.1% [39].

This study analyzes in detail the clinicopathological features of meningiomas in Jordan with a focus on the recurrence-free survival rates in relation to the other parameters studied. It gathers the work of three major referral centers in Jordan over many years of experience.

## CONCLUSION

The results of the present study are concordant with international reports. However, the tumors occurred at a relatively younger age. Male sex was significantly associated with a higher tumor grade and a larger tumor size. Spinal tumors showed less recurrence rate than intracranial ones, and the mitotic index and tumor size were significantly associated with a higher recurrence rate.

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**Statement of Ethics:** The study protocol was approved by the institute's committee on human research.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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## الخصائص السريرية والمرضية للأورام السحائية: دراسة ثلاثية المراكز

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### الملخص

**الخلفية والأهداف:** يُعد الورم السحائي أكثر أورام الدماغ شيوعاً لدى البالغين الأردنيين. هدفت هذه الدراسة إلى تحليل السمات العيانية والمجهريّة للأورام السحائية مع التركيز على ارتباطها بتكرار رجوع الورم.

**منهجية الدراسة:** شملت هذه الدراسة الاستيعادية جميع حالات الورم السحائي التي شُخصت في ثلاثة مراكز رعاية صحية رئيسية في الأردن خلال الفترة 2007-2021. استُرجعت البيانات السريرية والمرضية من سجلات المرضى.

**النتائج:** دُرست 690 حالة، وكان عمر الذروة للإصابة 45 عاماً. بلغت نسبة الإناث إلى الذكور 2.3 إلى 1 بناءً على البيانات المتاحة لمعظم المرضى في المجموعة، تراوح حجم الورم بين 0.5 سم و11.5 سم، وكان الموقع الأكثر شيوعاً هو الفص الجبهي. كانت الغالبية العظمى من الأورام من الدرجة الأولى (80.2%). أظهرت نتائج المرضى الذكور ارتباطاً وثيقاً بدرجة الورم الأعلى وحجمه الأكبر. تم استرداد بيانات المتابعة لمدة 5 سنوات لـ 206 مريضاً. بلغ معدل تكرار رجوع الورم حوالي 28%. ارتبط التكرار ارتباطاً وثيقاً بحجم الورم، كما ارتبط حجم الورم ارتباطاً وثيقاً بالدرجة النسيجية. أظهر التحليل متعدد المتغيرات أن الأورام داخل الجمجمة كانت أكثر ارتباطاً بالتكرار من الأورام الشوكية، وأن مؤشر الانقسام لخلايا الورم كان مرتبطاً ارتباطاً وثيقاً بتكرار رجوع الورم.

**الاستنتاجات:** كانت نتائجنا متوافقة مع التقارير الدولية. أظهرت أورام العمود الفقري معدل تكرار أقل من الأورام داخل الجمجمة، وارتبط مؤشر الانقسام الخلوي وحجم الورم ارتباطاً وثيقاً بمعدل تكرار أعلى.

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