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Demographics and outcomes of meningioma patients treated at a tertiary care center in the Middle East

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ABSTRACT

Objective: Meningioma is the most common intracranial primary brain tumor. Risk factors such as age and exposure to radiation as well as prognostic factors such as grade, location, and extent of surgical resection have been reported in the literature worldwide; however, to our knowledge, data from the Middle East is still warranted. In this study, we aim to identify the characteristics, risk factors and outcomes of meningioma patients treated at a multidisciplinary regional referral center in the Middle East.

Patients and methods: This is a retrospective chart review with a prospective follow up of outcomes. It included patients diagnosed with meningioma between January 2005 and December 2015 at the American University of Beirut Medical Center. Patient's demographics, risk factors and outcomes were first retrospectively collected. Then, we conducted phone calls to all included alive patients to update their disease status and outcomes.

Results: One-hundred and ninety-five patients were included. 69 % had grade I tumors and around 31 % with grades II and III meningiomas. The means of the overall survival and progression free survival (PFS) were 198 and 126 months, respectively. The residence area (city vs. countryside), occupation, alcohol use, oral contraceptive use, family history of meningioma, previous head trauma, radiation exposure for head/brain imaging, cell phone use, and finally, the tumor Ki-67 protein level did not correlate with the survival outcomes. The meningioma grade and extent of resection were significant predictors of the PFS on the univariate analysis, whereas, in the multivariate analysis only previous radiotherapy was significant in prolonging PFS.

Conclusion: In our study cohort, that included around 30 % grades II and III tumors, previous radiotherapy use was the only significant prognostic factor for longer PFS in patients diagnosed with meningioma. Future prospective studies should be conducted to evaluate genetic and molecular factors that could possibly be linked to meningioma grade and prognosis in our population of Middle Eastern patients.

1. Introduction

Meningiomas are the most frequently diagnosed intracranial primary brain tumors, accounting for approximately 30 % of all primary central nervous system (CNS) tumors [1,2]. According to the World Health Organization (WHO), meningioma is divided into grade I or benign meningioma, grade II or atypical meningioma, and grade III or malignant meningioma [3]. More than 90 % of meningiomas reported are benign [4]. Atypical meningiomas represent approximately 7–9% of the total cases, while anaplastic and malignant meningiomas represent 1–3% [5].

Exposure to ionizing radiation is a critical modifiable risk factor for developing meningioma. Female gender (which correlates with sex hormones) and increasing age are considered non-modifiable risk factors that are correlated with the development of meningioma [1,6,7]. In other cases, genetics play a key role, such as type 2 neurofibromatosis

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(NF2) [4]. History of head trauma, heavy cell phone use, and allergies are still considered as speculated risk factors for developing meningioma [8,9].

Grade I meningiomas have the best prognosis regardless of radiation or surgery [10]. However, grade II meningiomas are still in the grey zone when it comes to treatment and outcomes. On the other hand, grade III meningiomas show a high rate of recurrence when treated with surgery without adjuvant radiation therapy [11,12].

In the Middle East meningiomas are relatively understudied. Therefore, we aimed to identify the characteristics, risk factors and outcomes of meningioma in the region.

2. Material and methods

This is a retrospective study with a prospective follow up of outcomes, conducted at the American University of Beirut Medical Center, a tertiary care center for cancer diagnosis and management. The study was approved by the Institutional Review Board (IRB) with an approval number of IM.HA.04. The medical records of 208 patients diagnosed with meningioma between January 1, 2005 and December 18, 2015 were identified and 13 were excluded due to missing or inconsistent records. All the cases were reviewed histologically by a neuropathologist. Included alive patients were followed up prospectively through standardized consented phone calls to evaluate each patient's current disease and general status. The phone calls were conducted once at the end of the retrospective data collection and prior to analysis.

The patients' baseline characteristics, demographics, possible meningioma risk factors, treatment types, and tumor characteristics were collected from the patients' medical records as accessed through the hospital, clinical charts, and/or electronic medical records. Each patient's age, gender, body mass index (BMI), nationality, area of residence, occupation, history of oral contraceptive pill (OCP)/hormonal replacement therapy (HRT) use, smoking history, alcohol use/abuse history, previous head trauma, previous known malignancy, previous diagnostic radiation exposure, family history of meningioma, and history of familial neurofibromatosis were collected. Data on treatment modality, including surgery versus a combination of surgery and radiotherapy were collected. Moreover, the surgery type (complete versus suboptimal resection) and pathology details of the tumors were collected.

The numerical variables were summarized by their medians, means, and ranges, and the categorical variables were described by their counts and relative frequencies. The overall survival (OS) was defined as the time from the initial diagnosis until death (due to any cause) or the end of the follow-up (censored observations). The progression free survival (PFS) was calculated from the time of the initial diagnosis to the date of a documented relapse or the end of the follow-up. Both the OS and PFS were estimated using the Kaplan-Meier method, and the various groups were compared using the log-rank test. A Cox regression analysis was performed to examine the OS and PFS, and the final model was adjusted for the age, grade, type of disease, and smoking. Using the backward elimination method, the hazard ratios (HRs) and 95 % confidence intervals (Cis) were calculated for the variables that remained significant in the model. All the p values were 2-sided, and a p value < 0.05 was considered to be significant in all the analyses. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23.0.

3. Results

The records of 195 patients were analyzed. Table 1 shows the patients' demographics and tumor characteristics. Median age at diagnosis was 56 years old (range: 9–86). The majority of patients were females, with diagnoses of low-grade meningiomas that were treated by surgical resections alone. Grade II and III meningiomas comprised around 31 % of the cohort. The patients were followed up for a median time of 4.5 years, from six months to 11.75 years.

Table 1
Patient and Tumor Characteristics.

Characteristic	N	%
Total	**195**	**100**
Age		
< 60	113	57.4
> 60	84	42.6
BMI		
< 30	92	46.7
> 30	59	29.9
Missing	46	23.4
Gender		
Male	57	29.2
Female	138	70.8
Area of Residence		
City	128	65.6
Country side	40	20.5
Missing	27	13.8
Occupation		
Field job	19	9.7
Desk Job	14	7.2
Student	24	12.3
Housewife	45	23.1
Other	6	3.1
Missing	87	44.6
Smoking		
Yes	60	30.8
No	135	69.2
History of Head Trauma		
Yes	13	6.7
No	182	93.3
History of Neurofibromatosis		
Yes	3	1.5
No	192	98.5
OCP/HRT Use		
Yes	10	5.1
No	185	94.9
History of Brain ionizing radiation exposure		
Yes	16	8.2
No	179	91.8
Family History of Meningioma		
Yes	6	3.1
No	189	96.9
Treatment		
Type of Surgery		
Complete resection	121	62.1
Partial	74	37.9
Meningioma Grade		
1	135	69.2
2	39	20.0
3	21	10.8
Ki-67		
< 5%	63	32.3
5 – 20%	62	31.8
> 20 %	11	5.6
Missing	59	30.3
Treatment received		
Surgery only	169	86.7
Surgery + Radiotherapy	26	12.8

Abbreviations.
OCP: Combination Oral Contraceptive.
HRT: Hormone Replacement Therapy.

At the time of the last follow up (November 2016), 20 patients (10.3 %) had disease progression compared to 175 patients (89.7 %) who were disease free. Moreover, 11 patients (5.6 %) were deceased, while 184 (94.4 %) patients were alive. The OS and PFS means for the entire cohort were 198 and 126 months, respectively. No difference in the OS was noted between the genders. Smoking slightly affected the PFS in the univariate analysis ($p = 0.05$). The smokers and nonsmokers were stratified by gender. Among the females and males, no statistically significant difference was seen between the smokers and nonsmokers ($p = 0.072$ for females) and ($p = 0.112$ for males).

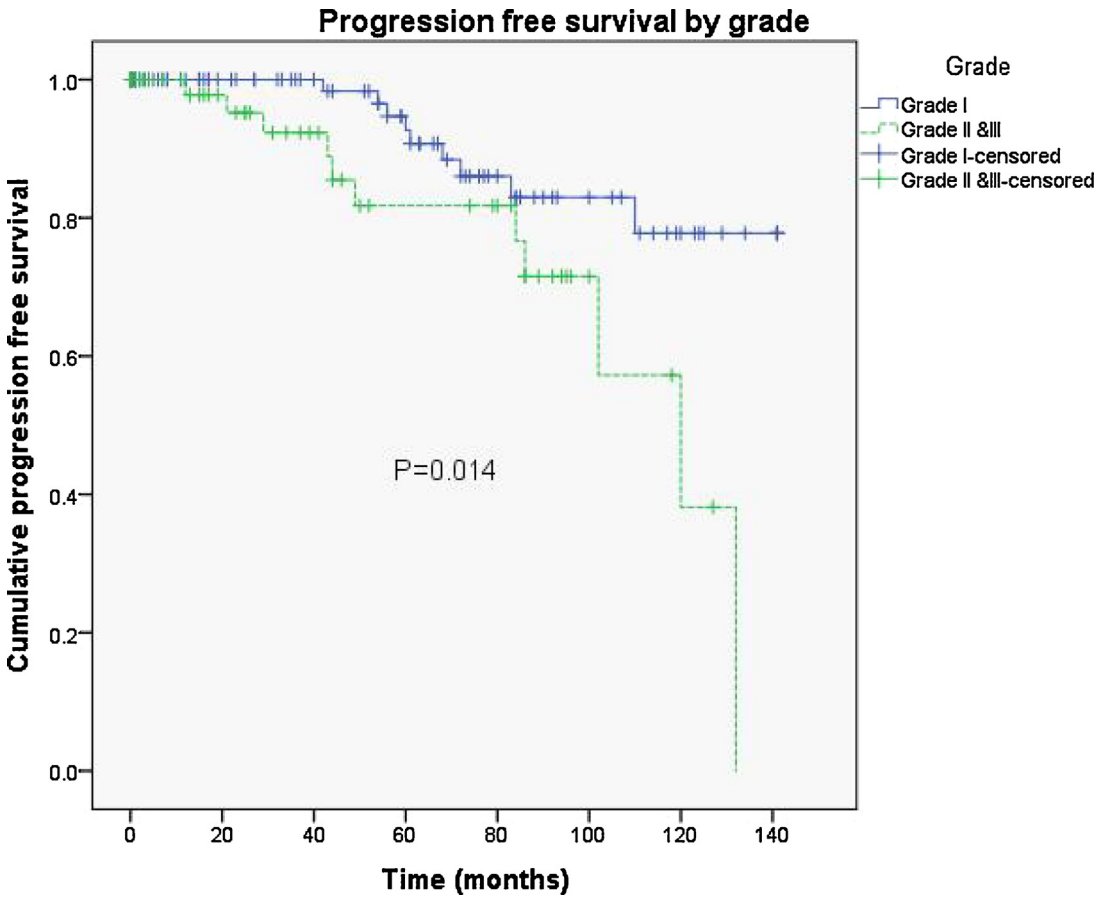

Fig. 1. A: PFS by grade (1) VS (2 + 3). P-value 0.014. B: OS by grade (1) VS (2 + 3). p-value 0.14.

Among the patients who received radiotherapy, those with recurrent disease had significantly worse outcomes than those with newly diagnosed meningiomas.

When compared to the patients with low grade tumors, those with intermediate and high grade tumors had statistically significantly worse outcomes in terms of PFS (p = 0.014), but not OS (Fig. 1A/B). However, when grade 1 tumors were compared to either grade 2 or grade 3 tumors, PFS and OS were not significantly different. Moreover, a complete tumor resection was associated with an improved PFS (p = 0.018), but not an improved OS, when compared to a partial resection (Fig. 2A/B).

Finally, as part of our neuropathology meningioma reporting, Ki-67 value was available on 142 patients. Analysis did not correlate with outcomes (p = 0.51).

3.1. Univariate and multivariate analyses

The patients' ages, genders, BMIs, nationalities, areas of residence, occupations, alcohol use histories, OCP/HRT use, histories of other malignancies, family histories of meningioma, previous head traumas, histories of neurofibromatosis (NF), brain diagnostic radiation exposures, grade, type of surgery, whether the patient received radiotherapy, cell phone use, and Ki-67 protein values were all examined in the univariate analysis, and they were found not to correlate with the survival outcomes (P > 0.05) (Table 2). However, the extent of tumor resection and tumor grade showed significant correlations; Partial resection and higher-grade meningiomas were worse predictors of PFS only on univariate analysis.

None of the variables tested in the univariate analysis showed correlation with survival outcomes (P > 0.05). For the multivariate analysis, we adopted the Cox regression analysis to identify the variables affecting the time-to progression by adding diagnostic radiation exposure, grade, head trauma history, type of surgery, radiotherapy, and history of previous tumor using the backward conditional elimination. Radiotherapy remained in the model as a significant factor influencing PFS; patients who underwent radiotherapy, had significantly higher odds of prolonged PFS, compared to patients who didn't receive radiotherapy (HR: 0.31, 95 % CI: 1.10 − 9.58, P = 0.033) (Table 3). Those who didn't receive radiotherapy had a risk of progression 3.25 times higher than those who underwent radiotherapy.

4. Discussion

Most of the characteristics of our cohort of meningioma patients were consistent with those reported in the literature; for example, our median age of 56 years old was comparable to the median age of 59 years old cited in the literature [13]. The female preponderance (70 %) was only slightly higher than the female:male ratio of approximately 2:1 seen in most series [6,14]. However, in our series, the percentage of grade II and III meningiomas (31 %) was higher than that reported by the United States Brain Tumor registry (USBTR), where atypical and malignant meningiomas made up a small fraction of the total (~5%) [15]. In a study by Linda Bi et al., next generation sequencing on around 140 patients with high-grade meningioma found that they carry a higher number of mutations and copy number alterations compared to lower grade [16]. Our finding of higher-grade meningiomas in our cohort might be related to the genetics in the region or the possibly underreported history of exposure to ionizing radiation, such as the old practice of using radiation therapy for the treatment of tinea capitis, for example. One study from the region included patients from Saudi Arabia also showed a relatively higher percentage of grades II and III meningiomas (around 20 % total) compared to the USBTR. It's worth

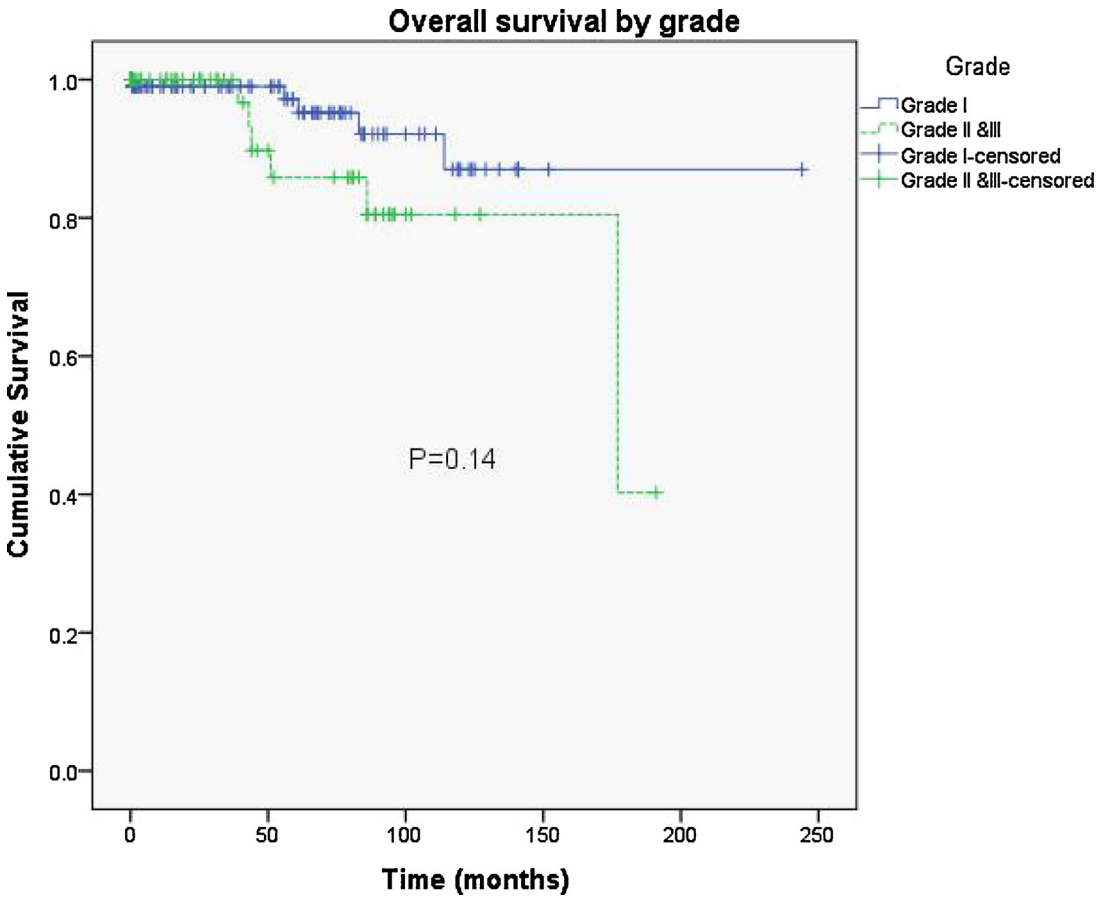

Fig. 1. (*continued*)

noting however that the majority of their patients had skull base meningiomas and their genetic sequencing revealed a range of mutations outside the known cancer driver *NF2*, such as *TERTp* c.–124: G > A and FGFR3 mutations, that may be linked to meningioma prognosis [17]. Further studies are still needed to identify the prognostic significance of their identified mutations and to focus on whether specific mutations could be linked to higher-grade meningiomas. However, this observation should be taken with caution, knowing that it might be the result of a bias that skewed the results towards more aggressive grades of meningioma; our study was conducted at a tertiary care referral center, where higher grade meningiomas diagnosed in the region are usually referred to.

With a median follow-up time of 4.5 years, survival reached 94.4 % in our series of patients, despite the fact that we had a relatively high percentage of Grades II and III meningiomas. With the current improvements in the diagnostic and therapeutic modalities, grade I meningioma patients have a near normal life expectancy, with 5 and 10-year survival rates of 94 % and 86 % respectively, which is comparable to our study. This indicates that grade II and III meningiomas have similar survival outcomes to grade I meningiomas [18]. Moreover, the PFS showed a trend of better outcomes in female patients. Varlotto et al., in their study distinguishing between grade I and the higher meningioma grades without biopsies, showed that the group most likely to have grade I meningiomas consisted of postmenopausal women [13]. This is one possible explanation that might have skewed the PFS toward better outcomes in females.

As noted previously, on univariate analysis, complete tumor resection was significantly associated with improved PFS in our sample, but not with an improved OS, when compared to a partial resection. Previous studies have shown that the extent of resection is the most important predictor of the long-term outcome. In a retrospective study on 900 patients by Gousias et al., Simpson Grade II rather than Grade I resection almost doubled the risk of recurrence at 10 years (18.8 % vs 8.5 %) [19]. Moreover, other studies have revealed the great benefits of a gross total resection with regard to the survival outcomes [20]. There are several studies that show an association between adjuvant radiotherapy and better survival outcomes in patients with suboptimal resections [21]. Adjuvant radiation therapy is mostly administered to patients with grades II and III tumors who generally have worse outcomes. Thus, on Univariate analysis, we failed to show a correlation between adjuvant radiotherapy and outcomes. However, on multivariate analysis (MVA), adjusting for other variables, there was an association between the use of adjuvant radiotherapy and improvement in PFS, but not OS. The lack of OS benefit might probably be related to the low number of events in the MVA model.

Tumor resection extent and meningioma grade were not significant predictors of outcomes in the multivariate analysis model adjusting for the other covariates included in this study. Higher meningioma grade was associated with worse PFS only on our Univariate analysis. From the literature, the recurrence rate for grade I tumors has been reported to be around 6 %, in contrast to the much higher rate exhibited by grade III meningiomas, which can reach 50–94 % [22]. However, the probable reason for the lack of significant association on MVA with outcomes is that those patients with higher grade are the ones who are most likely to be treated more aggressively and with the addition of adjuvant radiotherapy. Also, the same applies for the extent of resection; even though the extent of resection has been reported to correlate with survival outcomes, the use of adjuvant radiotherapy might tip the results. A suboptimal resection followed by adjuvant external beam radiation therapy has been shown to result in a long-term survival rate comparable to that of a gross tumor resection (OS: 86 % vs. 88 %, respectively), when compared to a survival rate of 51 % with an

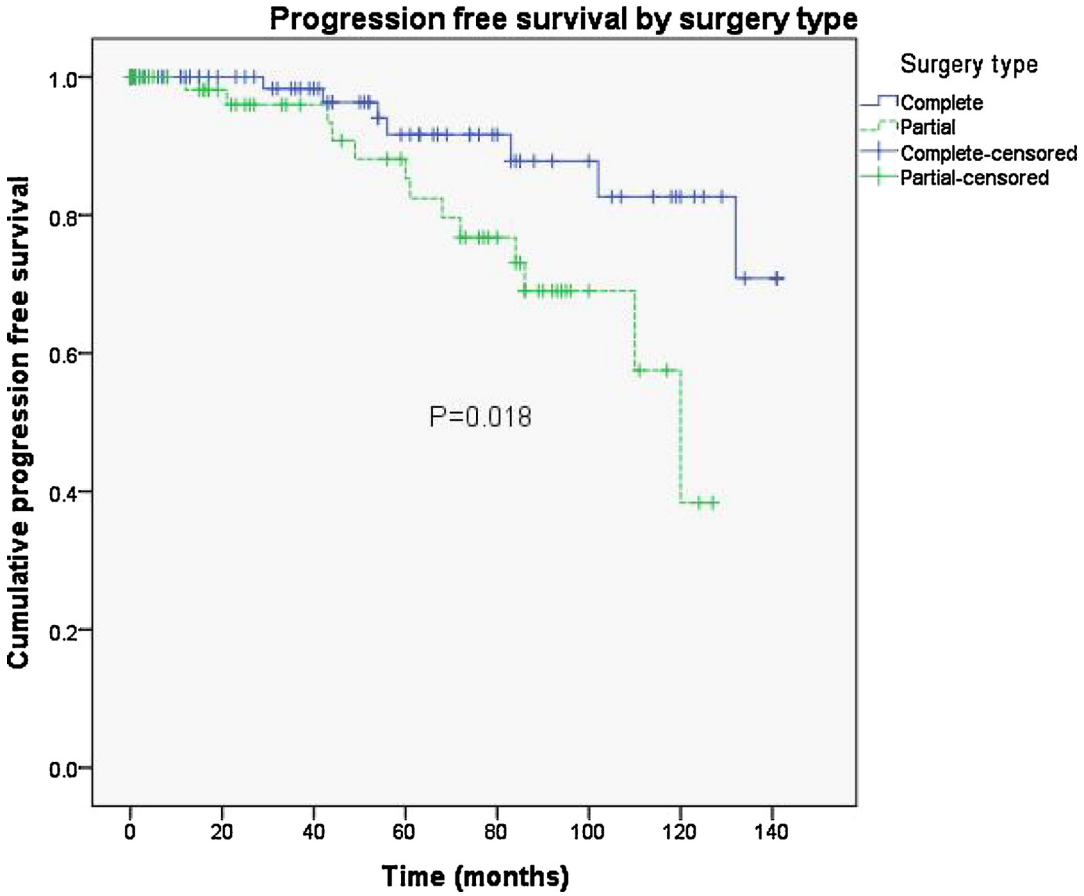

Fig. 2. A: PFS by Surgery type. Complete VS partial. P-value 0.018. B: OS by surgery type. Complete VS partial. p-value:0.244.

incomplete resection alone [8]. Overall, the use of stereotactic radiation therapy is currently evolving. In one study of 200 patients that compared surgery with stereotactic radiation as the primary treatment for small meningiomas, the 7-year PFS was comparable to that of patients with gross tumor resections and superior to that of those undergoing incomplete resections [9].

With regard to systemic therapy, such as chemotherapy or targeted therapy, there are currently no recommended options in the primary setting, and none were used in our study cohort.

Among the prognostic factors, the Ki-67 protein, which is frequently reported by our institution's neuropathologist, did not correlate with the outcomes of our patient cohort. This indicates that this marker should probably be omitted from the pathological report for meningiomas used at our institution and several surrounding institutions in the region. Therefore, sticking with the WHO accepted classification markers, such as the mitotic count per high power field, certain pathological subtypes, brain invasion, and features of increased cellularity, would provide better outcome predictors than Ki-67 [4]. Moreover, more recent studies are investigating molecular classifications where in one retrospective study by Sahm et al., DNA methylation-based meningioma classification had a higher power than classical WHO grades for predicting tumor recurrence and outcomes [23].

The main limitations in our study consist of the relatively small sample size, bias of being conducted at a tertiary care referral center, no available genetic information on our cohort, and absence of information on tumor location. However, the main strength of our study was that it evaluated meningiomas in an understudied population of Middle Eastern patients with a follow up of around 4.5 years. This could open way to more future studies in this specific population that focuses more on genetic factors. Moreover, our outcome results were updated via phone calls to patients.

Studies are still ongoing for defining prognostic factors in meningiomas, other than the well-known grade and surgery extent. For example, the rate of p53 overexpression was positively correlated with tumor recurrence and malignant progression in a study by Karamitopoulo et al. [24]. In addition, p53 was shown to be associated with an increase in the proliferation marker MIB-1 [24]. It has also been shown that the levels of vascular endothelial growth factor (VEGF) and the VEGF receptor (VEGFR) (as well as the microvessel density) increase with the meningioma grade, and they may prove to be of prognostic significance [25].

This study emphasizes the need for future prospective studies that explore prognostic factors including genetic factors associated with meningiomas in our region in order to discover whether there is a truly higher incidence of grade II and III disease that can be attributed to genetics or whether this was simply a selection bias of a study conducted at a tertiary care center. Moreover, future studies identifying additional reliable prognostic factors for recurrence or further molecular classifications similar to the DNA methylation based classification in meningioma patients are especially important when making decisions about adjuvant radiation therapy in cases in which there is no strong recommendation for or against treatment. This is the case in atypical grade II meningiomas in which the National Comprehensive Cancer Network recommendation states that physicians can "consider" radiation therapy in completely resected grade II meningiomas [26].

5. Conclusion

In our study cohort, that included around 30 % grades II and III tumors, higher grade and partial surgical resection were significant predictors of worse PFS only on Univariate analysis. However, previous radiotherapy use was the only significant prognostic factor for longer

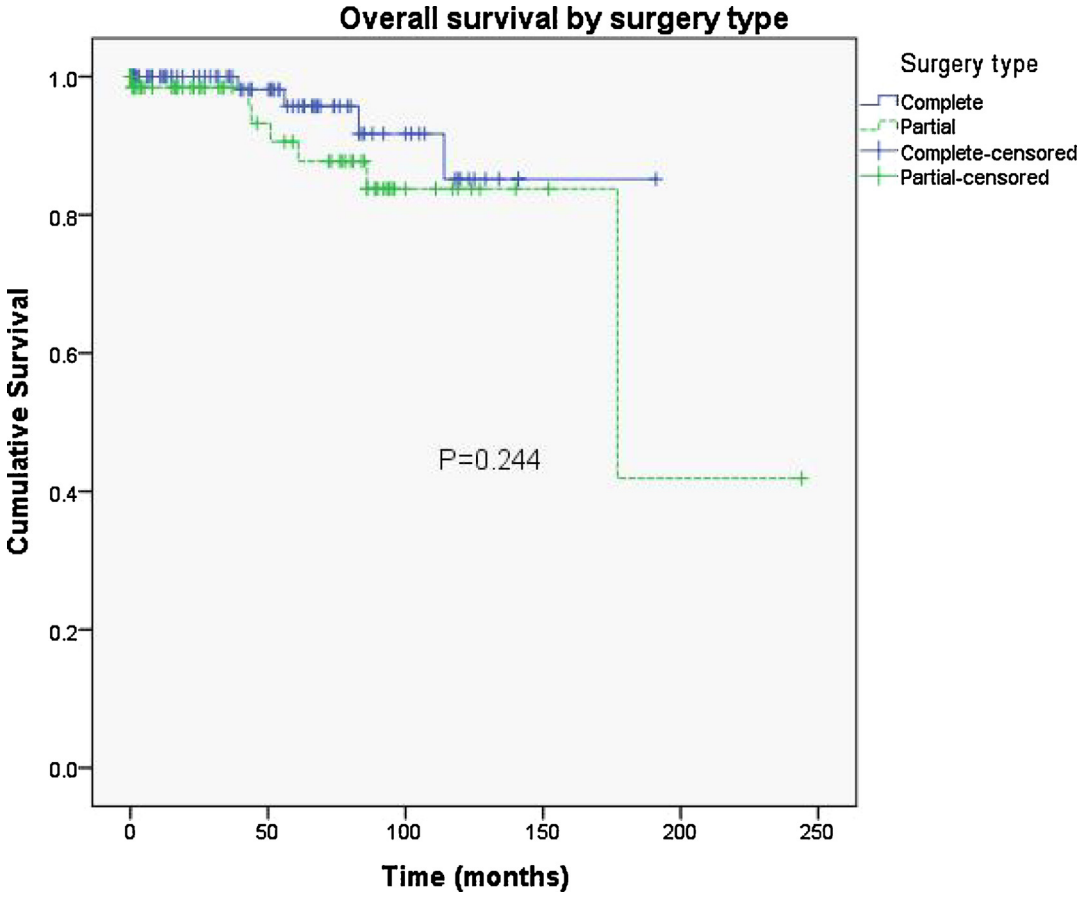

Fig. 2. (*continued*)

Table 2
Univariate analysis of factors affecting Progression Free Survival.

Factor	Mean Survival (95 % CI)	p-value
Gender	All 119.5 (111 – 127)	0.089
	Males 108 (90 – 126)	
	Females 123 (115 – 132)	
Surgery type (complete vs. partial)	All 119.5 (111 – 127)	**0.018**
	Complete 128 (119 – 137)	
	Partial 103 (92 – 113)	
Grade 1 vs. 2&3	All 119.5 (111 – 127)	**0.014**
	Grade 1 126 (118 – 135)	
	Grade 2&3 103 (88 – 118)	
Grade 1 vs. 2 vs. 3	All 119.5 (111 – 127)	**0.049**
	Grade 1 126 (118 – 135)	
	Grade 2 99 (82 – 115)	
	Grade 3 106 (78 – 134)	
Smoking	All 119 (111 – 127)	0.054
	Smokers 133 (123 – 143)	
	Non-smokers 113 (103 – 124)	

Table 3
Multivariate analysis of factors affecting Progression Free Survival.

Factor	p-value	Hazard ratio	95 %CI
Diagnostic RT Exposure	0.063	3.89	0.93 – 16.33
Surgery type (complete vs. partial)	0.597	1.40	0.40 – 4.93
Radiotherapy	**0.033**	**0.31**	**1.10 – 9.58**
Head Trauma History	0.208	3.85	0.03 – 2.11
History of Previous Tumor	0.468	1.85	0.10 – 2.84
Grade I	0.288		
Grade II	0.165	2.31	0.71 – 7.54
Grade III	0.199	2.29	0.65 – 8.09

PFS in patients diagnosed with meningioma, after adjusting for other factors such as grade and extent of surgical resection. With the limitation of a relatively small sample size of our cohort and absence of genetic markers, future prospective studies should be conducted to evaluate genetic and molecular factors that could possibly be linked to meningioma grade and prognosis in our population of Middle Eastern patients.

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Ethical approval

All the procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IRB) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all the individual participants included in this study.

Disclosures

The authors have no conflicts of interest, and this work was not supported or funded by any drug company.

CRediT authorship contribution statement

Hazem I. Assi: Conceptualization, Supervision, Writing - review & editing. **Lara Hilal:** Writing - original draft, Writing - review & editing. **Ibrahim Abu-Gheida:** Investigation, Data curation, Validation. **Juliett Berro:** Investigation, Visualization. **Fares Sukhon:** Methodology, Investigation. **Ghassan Skaf:** Writing - original draft. **Fady Geara:** Writing - original draft. **Fouad Boulos:** Writing - original draft. **Maya Charafeddine:** Formal analysis. **Abeer Tabbarah:** Writing - original draft. **Jessica Khoury:** Project administration, Writing - review & editing. **Marwan Najjar:** Conceptualization, Supervision, Writing - original draft.

Declaration of Competing Interest

All the authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or the materials discussed in this manuscript.

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