CORRELATION BETWEEN MENINGIOMA HISTOLOGICAL SUBTYPES AND ANATOMICAL LOCATION IN OPERATED PATIENTS FROM TERTIARY CENTRES IN JOHANNESBURG

By

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A research report submitted to the faculty of Health Sciences

University of the Witwatersrand, Johannesburg

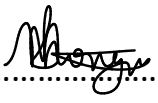
In partial fulfilment of the requirements for the degree of

Master of Medicine in the specialty of Neurological Surgery

Johannesburg, 2022

DECLARATION

I Dr Mpumelelo Shongwe, declare that this research is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted in part or in full for any other degree or examination at this or any other University, nor has it been submitted elsewhere for publication.

- 

……23RD SEPTEMBER 2022 ……

DEDICATION

This research report is dedicated to:

The Lord, God almighty above all else, myself, my family especially my mother.

ABSTRACT

BACKGROUND

Meningiomas are reported to be the most common intracranial neoplasm in Neurosurgical practice. Two important factors that determine progression-free survival are the Histological sub-types (grade) and anatomical location. Anatomical location affects resectability and therefore recurrence. The study aims to find a relationship between these two factors and draw recommendations that would help manage this common neoplasm.

METHODS

This was a 3 year retrospective study of 125 histologically confirmed Meningiomas seen at tertiary hospitals in Johannesburg. We recorded all the histologically confirmed Meningiomas from the NHLS and mapped them against their anatomical location using the PACS system. We then used the Chi squared to analyses the main categorical variables to find their relationship.

RESULTS

Our model predicted 73% of the grades correctly, therefore suggesting that there is a relationship between histological subtypes and location, when location is grouped.

CONCLUSION

Granular location did not prove as predictive. Given the size of the data, we cannot conclude definitively that location alone can predict histological sub-type. What we can say is that in this study, location has shown a more significant relationship to histological sub-type than age and gender.

ACKNOWLEDGEMENT

A special thanks to my supervisor, Professor John Ouma, for his insight, guidance, and patience throughout this project. I also want to thank the heads of departments in the three tertiary hospitals in Johannesburg namely, Prof Ouma at Chris Hani Baragwanath Academic Hospital, Dr Mayoyo at Charlotte Maxeke Johannesburg Academic Hospital and Dr Profyris at Helen Joseph Hospital for enabling and driving academic processes that allowed us the opportunity to study and enjoy this great science.

I would also like to thank the Wits University Department of Neurosurgery consultants and registrars for their encouragement throughout a physically and psychologically taxing period of my life. I am eternally grateful to Dr Mills and The Clinic Group and the Sincephetelo Motor Vehicle Accident Fund in Eswatini for the financial support that allowed me to pursue my postgraduate studies, away from home as a young man from rural Eswatini.

To my family especially my mother who never lost hope and whose prayers reverberated across geographical borders, may the dear Lord bless you.

Thank you Molefe and Mokganyetji for your time and craft in data management for this project.

A special thank you to Dr Maseko in Eswatini, a Neurosurgeon and a trailblazer who inspired me and became the spark that lit up this flame, I am grateful.

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NOMECLATURE

CHBAH - Chris Hani Baragwanath Academic Hospital

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

CPA - Cerebello-pontine angle

MRI - Magnetic resonance imaging

NHLS - National Health Laboratory Services

PACS - Picture Archiving and Communication System

1 INTRODUCTION

The term ‘Meningioma’ was coined by Harvey Cushing in 1922, after extensive work had been done by multiple authors before him (1). Meningiomas arise from arachnoid cap cells of the meninges of the Central Nervous System (CNS), but rarely they arise in locations where there is no dural attachment like intraparenchymal and intraventricular (2). Arachnoid cap cells are in contact with the venous endothelium of the structure called arachnoid villi, whereby CSF (cerebrospinal fluid) gets absorbed. These are most congregated in areas of Superior Sagittal Sinus, followed by cavernous sinus, tuberculum sellae, lamina cribosa, foramen magnum and torcular herophili (2).

The intracranial distribution has been approximated as: convexity (34%), parasagittal (22%), sphenoid ridge (17%), infratentorial (9%), intraventricular (5%), tuberculum sellae (3%) and others (4%) (1).

Meningiomas are the commonest primary intracranial extra-axial neoplasm (14.3-19%) but an incidence as high as 33.8% has been reported in Johannesburg (3-5). The mean age at presentation was 45.7 ±10.1 years and a female to male ratio of 3.8:1 (4).

The WHO (World Health Organization) classified Meningioma histological subtypes into grades 1-3 and the different grades exhibit more aggressive behaviour the higher the grade (6, 7). (Table 1)

Table 1.1 WHO Meningioma classification

Meningioma Grade	Histological description
Grade 1	
Meningothelial	Densely packed cells arranged in concentric sheets (whorls) with no discernible cytoplasmic border
Fibrous	Multilaminated sheets of interlacing, elongated spindle cells
Transitional	Combination of meningothelial and fibrous
Psammomatous	Mineralised whorls containing calcium apatite and collagen. Psammos means sand in Greek
Secretory	Meningothelial or transitional with occasional intracellular eosinophilic globules.
Lymphoplasmacyte-rich	Lymphoplasmacytic infiltrates often making the meningothelial component inconspicuous.
Microcystic	Cells have elongated processes with loose myxoid background.
Angiomatous	Demonstrate abundant blood vessels within the tumour (>50% of tumour) within a tumour with classic meningothelial differentiation.
Metaplastic	Characterised by tumour cells sharing characteristics of cells from tissues in different parts of the body.
Grade 2	
Chordoid	Columns of cells surrounded by mucoid matrix, resembling chordoma.
Atypical	Increased cellularity, small cells with increased nuclear to cytoplasm ratio, ≥4 mitoses per 10HPF*, local invasion
Clear-cell	Monomorphic round nuclei, arranged back to back like

	oligodendroglioma, but with bands of collagen
Grade 3	
Rhabdoid	Abundant eosinophilic cytoplasm, cytoplasmic hyline inclusions and eccentric nuclei.
Anaplastic	≥20 mitoses per 10HPF*, prominent cellular pleomorphism and necrosis, local brain invasion
Papillary	Increased nuclear-cytoplasmic ratio, prominent mitoses, metastasis via CSF, occasionally outside CNS

*HPF= high power field

Morbidity and mortality also rises with grade due to aggressive behaviour and recurrence of the neoplasm (1, 6, 7).

A classification of how neurosurgeons assess the surgical removal of meningiomas was introduced by Simpson in 1957 (8, 9).

- Grade I - macroscopically complete tumour removal with excision of the tumour's dural attachment and any abnormal bone (9% recurrence rate)
- Grade II - macroscopically complete tumour removal with coagulation of its dural attachment (19% recurrence rate)
- Grade III - macroscopically complete removal of the intradural tumour without resection or coagulation of its dural attachment or extradural extensions (29% recurrence rate)
- Grade IV - subtotal removal of the tumour (40% recurrence rate)
- Grade V - simple decompression of the tumour

Another system different from the macroscopic Simpson resection system was introduced by Kobayashi, and it is based on microscopic resection (10).

Table 1.2 Kobayashi classification of microscopic resection

Grade	Extent of microscopic resection
Grade I	Complete microscopic removal of tumour and dural attachments with any abnormal bone
Grade II	Complete microscopic removal of tumour with diathermy coagulation of its dural attachments
Grade IIIA	Complete microscopic removal of intradural and extradural tumour without resection or coagulation of its dural attachments
Grade IIIB	Complete microscopic removal of intradural tumour without resection or coagulation of its dural attachment or of any extradural extensions
Grade IVA	Intentional subtotal removal to preserve cranial nerves or blood vessels with complete microscopic removal of dural attachment
Grade IVB	Partial removal, leaving tumour of less than 10% in volume
Grade V	Partial removal, leaving tumour of more than 10% in volume, or decompression with or without biopsy

The anatomical location can pose a surgical challenge in terms of resectability, often achieving a higher Simpson grade, which is associated with a higher recurrence rate (8). This could be due to proximity to major venous sinuses including the Cavernous sinus which might require a cuff of tumour to be left behind or total tumour removal with sinus reconstruction, which carries a high morbidity (11). Skull base and posterior fossa location also has a high short term and long term surgical morbidity due to involvement of neurovascular structures like arteries and cranial nerves, therefore surgeons are likely to opt for a higher Simpson grade (8, 12, 13). Recurrence depends primarily on the extent of surgical removal and on the histological characterization of the tumour as grade 2 or grade 3 which have aggressive behaviour and local brain invasion (14). It has been reported that 6 of 7 patients with

recurrence died of the tumour at a mean of 25 months after re-growth (5). Re-operations are notorious for having a higher complication and mortality rate (10). While radiation is another treatment option for meningiomas, it is not the best modality, often reserved for inaccessible and aggressive tumours (1, 3, 5, 10). Radiation is important for local tumour control but has been associated with neurotoxicity to nearby critical structures like cranial nerves, optic apparatus and functionally eloquent brain, resulting in neurocognitive decline. It is also associated with therapy related brain oedema, primary tumour dedifferentiation to higher grade and the development of secondary tumours (5). This dedifferentiation seems to have a different genomic instability pathway compared to de novo Atypical meningiomas, and a loss of Neurofibromatosis (NF2) gene has been documented (15). Unfavourable locations also come with associated deficits and a poor Karnofsky Performance score (10, 12).

A Karnofsky performance score is used to grade the functional status of a patient with cancer, with a score less than 70 often identifying patients with a worse prognosis (1). So finding a link between histological subtypes and anatomical location could help in better planning and management of Meningiomas. The relationship between grade and location needs to be elucidated.

2 LITERATURE REVIEW

The anatomical location often poses a challenge to the Neurosurgeon in terms of approach and extent of resection, Simpson grade and its attendant recurrence rate (10, 13). The histological subtype alerts us to the behaviour of the Meningioma, hence the importance if analysing the correlation of histology

and location. Up to 80% of these lesions have a driver mutation identified via next generation sequencing techniques and correlate with tumour location and embryological origin (16). The clinical implication for these epigenetic factors is in their predictive value of histologic subtypes and tumour progression (16).

Up to 16% of uncommon histological subtypes had common location of origin; sphenoid wing, posterior parafalcine, jugular foramen, peritorcular, intraventricular, Cerebello-pontine angle (CPA), tentorial and petroclival (17). Common sites with increased mortality were found to be; CPA, intraventricular, sphenoid ridge, tuberculum sellae, posterior parafalcine and posterior fossa (17). Skull base, intraventricular and posterior fossa, were common locations for high grade meningiomas with increased mortality (17). Rhabdoid meningiomas were found mostly in the posterior parafalx, tentorial, CPA and peritorcular. Anaplastic was commonly found in the sphenoid, CPA region. Papillary was predominantly found in; intraventricular and tuberculum sellae location (17).

Age is another factor to consider in the management of patients with Meningioma. Paediatric meningiomas differ from those in adults by their male predominance, atypical locations and higher rates of malignant subtypes (18, 19). Patients younger than 35 years with HIV-1 seropositivity were associated with increased risk of developing higher grade Meningiomas (20). Intracranial tumour location, grade of resection and histopathological subtypes were similar between the elderly (>65years) and the younger group, but spinal tumours were more common in older patients than in younger patients (12% vs. 4%, p=0.001) (21).

Meningothelial meningioma is the predominant subtype in midline skull base and spine, one study concluded (22). They found 84% in midline skull base,

58% lateral skull base, 48% non-skull base and 80% of spinal (22). Meningothelial and fibrous meningiomas were the most common subtypes and convexity was the most common location in a different study (23).

Spinal meningiomas present slightly conflicting findings or rather inconclusive findings with some reporting a dominance of Psammomatous subtype (66%) and meningothelial at (11%)(24). Similar figures with; Psammomatous (66%), Fibroblastic (22%) and Meningothelial (11%) were found in another comparative study (25). Psammomatous meningiomas were associated with less favourable neurological outcome postoperatively than resection of other spinal meningioma subtypes, partly due to incomplete resection (25, 26). Another challenge with spinal meningiomas is their location, with ventral location particularly difficult to excise completely especially if the dentate ligament is not released and the patient position is not optimal (26). All these manoeuvres are done in order to create a safe surgical corridor without causing injury to the spinal cord (26). Different studies had conflicting figures of 80% of their spinal meningiomas reported as Meningothelial (22, 24).

Grade I meningiomas are by far the commonest with 82-85%, grade II (11.42%) and grade III (5.71%) (27). Fibrous meningioma (37%) was the predominant subtype in posterior fossa convexity and Psammomatous (24%) at foramen magnum (27). Similar figures regarding the grades; Grade I (80%), grade II (5.9%) and grade III (4.8%) were also found in a different series (17).

The most important factor to influence recurrence is the extent of surgical removal (9, 10, 21). No significant difference in the recurrence rate among the histological subtypes was found, but high grade meningiomas tended to recur earlier (29). Tumour location and its biological behaviour were closely related to the removal rate, prognosis and recurrence, while tumour size was of less

importance (30). In contrast, tumour size, proximity to major sinus, oedema, cortical penetration, Simpson's grade and histopathological classification were significant predictors for recurrence, while age, gender and location were not significant predictors in a different review (31). Close proximity to important neurovascular structures like cranial nerves and venous sinuses makes extent of resection limited in an effort to preserve neurological function (11).

3 PROBLEM STATEMENT

Understanding the anatomical relation to certain Meningioma histological subtypes will address crucial issues in Meningioma management. Meningioma subtypes which are high grade in certain locations could be approached differently once grade mapping for location is defined. For prognostic value, location and histological subtypes are but two of many factors to consider, since certain locations affect maximal extent of resection thereby leading to poor prognosis, and high grade subtypes have been established to be aggressive and recur earlier and frequently. Establishing this relationship will help with better surgical planning and prioritisation of this common neoplasm in our resource limited setting.

4 JUSTIFICATION FOR THE STUDY

For the most common intracranial tumour, there is unfortunately very little literature on the relationship between histological subtype and location, hence the current trend of treating every Meningioma similarly. It also shows there is still a lot to be learnt about this common neoplasm.

5 METHODS

5.1 Research Question

Is there a correlation between Meningioma histological subtypes and anatomical location?

Null hypothesis:

Higher grade Meningiomas do not preferentially occur in less surgically accessible anatomical locations.

5.2 Aim

The aim is to investigate the relationship between the Meningioma histological subtypes and their anatomical location.

5.3 Study Objectives

- Obtain the histology of the different Meningioma histological subtypes
- Identify the location of the confirmed Meningiomas as per the radiological images
- Study the relationship between the histological subtypes and the anatomical location

5.4 **Study design**; a descriptive, retrospective study over a 3-year period from January 2018 to December 2020.

5.5 **Study site;** 3 hospitals namely; Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and Helen Joseph Hospital, under the University of the Witwatersrand.

5.6 **Study population;** all cases of all age groups of histologically confirmed Meningiomas in the 3 hospitals over the specified 3-year period.

5.7 Inclusion criteria:

- All the members of the study population with complete records
- All the brain and spine Meningiomas where complete histology reporting was done
- All the members of the study population where radiological imaging were available

5.8 Exclusion criteria

- Members of the study population with multiple registration numbers
- Members of the study population with incomplete data
- Members of the study population with inconclusive histology

5.9 Limitations

- Records retrieval challenges as this is a retrospective study
- Large tumours causing anatomical overlap

6 INSTRUMENT

A patient data collection template with information like; age, gender, hospital, tumour grade and location was used by the author to populate the data collection sheet. The template information was completed using the hospital

registration number to access the NHLS histology results for tumour type, age, and gender. The same registration number was mapped against the anatomical location on the PACS thereby completing the histology subtypes and location table.

7 DATA ANALYSIS

7.1 **Data sources:** the National Health Laboratory Services (NHLS) will provide the histological results and the radiological PACS (Picture archiving and communication system) from the radiology department will provide the images to assess the anatomical location.

7.2 **Data collection:** data will be collected by the author using a data collection template and data collection sheet.

7.3 Data management:

The data will have age as a continuous variable and discrete variables e.g. tumour grade, gender and location. These categorical variables will form the data sheet and observations, inferences and correlative analysis will be made. Data in Appendix 2 will be used for frequency analysis. The Chi squared test will be used for correlative analysis of the categorical data to prove the null hypothesis. The anticipated number of patients for this study is 100.

7.4 **Statistical analysis;** data will be collected using the data collection template and information will be imported onto a Microsoft Excel spread-sheet, as the data collection sheet and analysed using the R© programme. The Chi-squared test will be used for the two categorical variables of histology grade and location. Its value is to evaluate what the likelihood of the observed frequencies of grade and location will be, assuming the null hypothesis is true.

Using linear regression on 0.025 significance level, we will seek to reject the null hypothesis which H0: there is no relationship between Meningioma

histological subtypes and their anatomical location. The types of variables being analysed are discrete variables, and categorical, thus a multinomial logistic regression method will be employed.

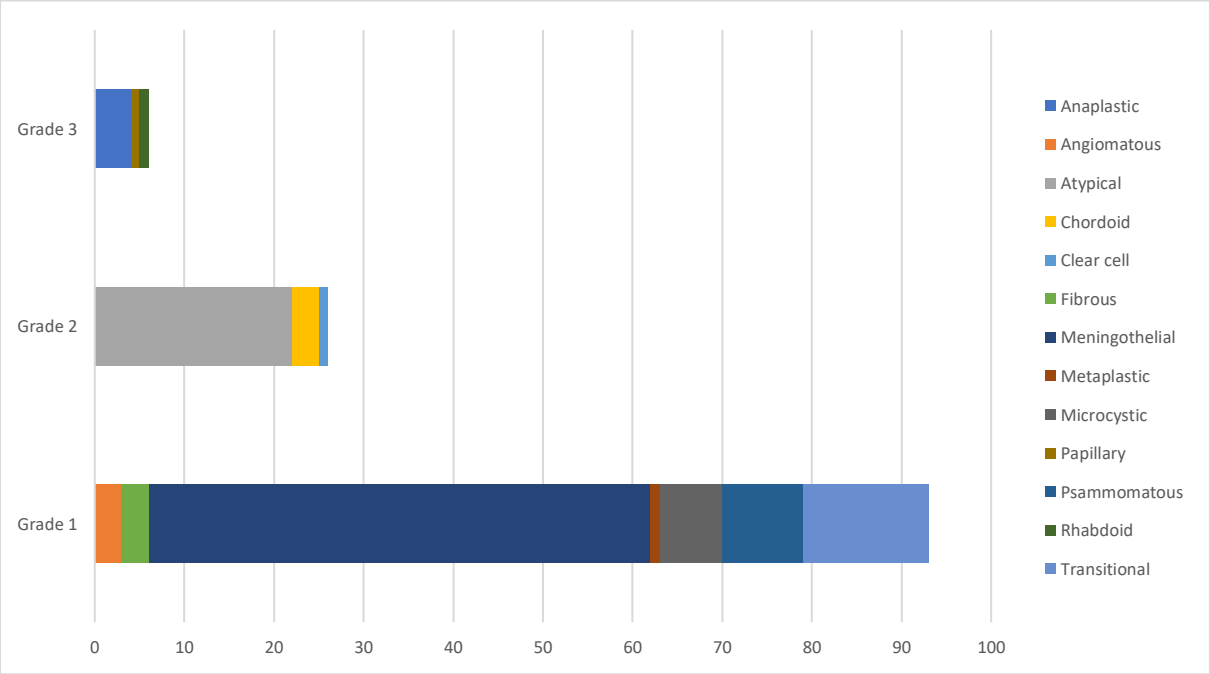
8 STUDY RESULTS

8.1 Data

Data consisting of 125 observations was obtained and will be analysed in the next section to better understand it.

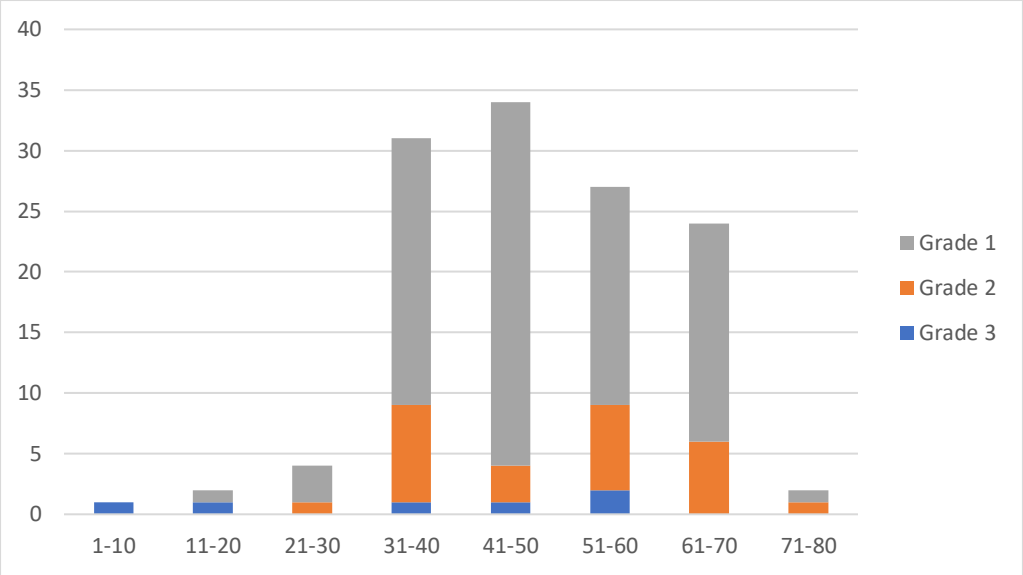
8.2 Summary of data by Histological subtypes

Majority of data (90+ observations) sit in grade 1 as shown in the graph below.



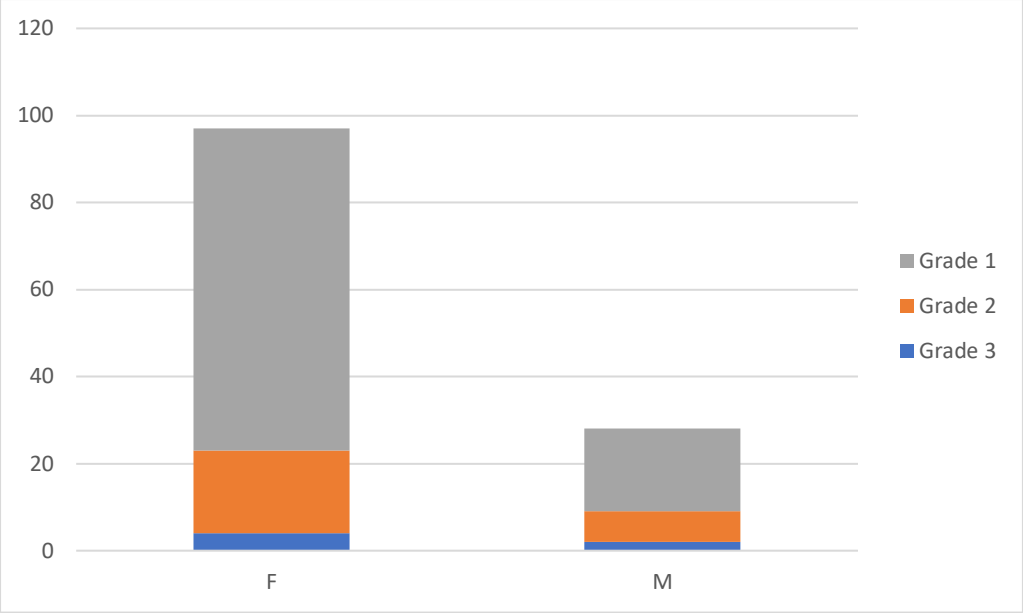
8.3 Histological grade by age

Ages between 31 and 70 have been observed with a high frequency as shown below. The graph also shows the distribution of histological grades across the different ages.



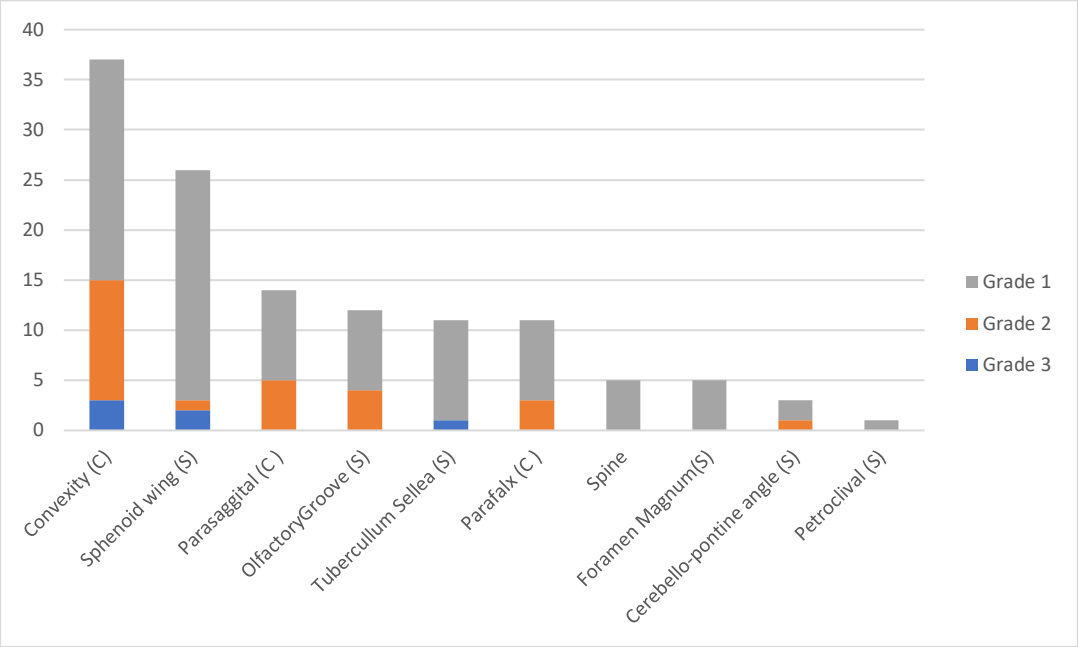
8.4 Histological grade by Gender

More females than males were observed in the data.


120
100
80
60
40
20
0
F
M
Grade 1
Grade 2
Grade 3

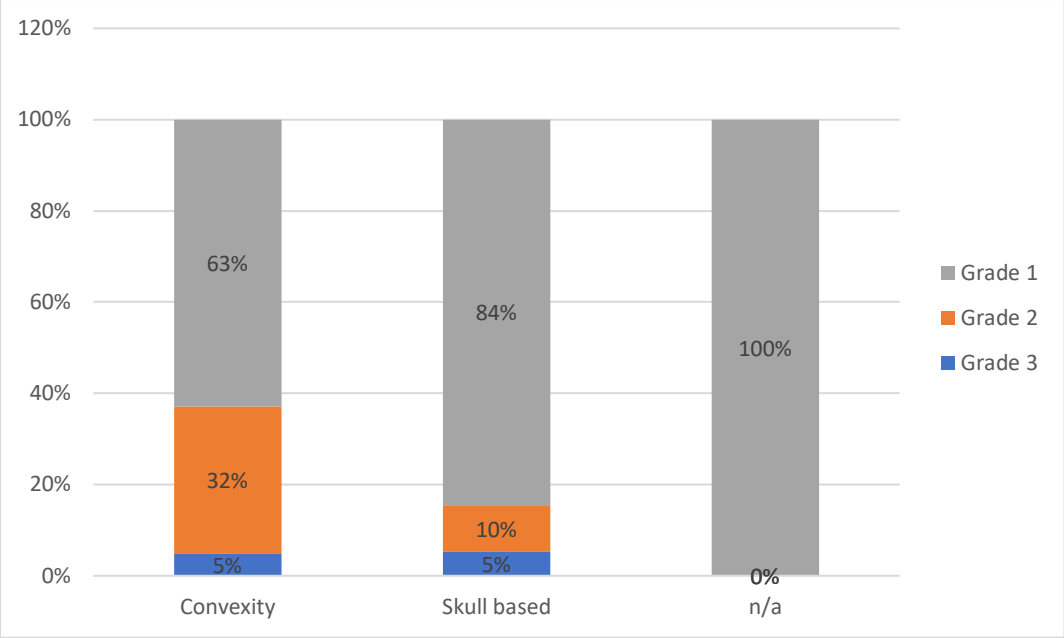
8.5 Histological grade by Location

Convexity and sphenoid wing were observed with the highest and second highest frequency respectively in the data set, while petroclival was observed with the least frequency.



Location was further grouped into Skull based and Convexity, as shown in the results below.

5 observations were located in the spine and could not be classified between the two categories.



8.6 Methodology

An ordinal logistic regression was used to model the relationship between histological sub-types and the available variables, i.e. age, sex or location. This is the best model to use for an ordinal response variable, histological sub-types in this case, because there is a clear ordering of category levels where a higher grade indicates a more aggressive sub-type. Modelling was done using R programing language.

We ran a regression of 'grades' on Age, gender and location and obtained the respective ANOVA tables, which gives us the p value, and confusion matrices for our hypothesis testing.

The confusion matrix tells us how well or not our model predicts the 'grade' given the explanatory variables.

We then tested the respective models to see if they can predict the dependent variable, grade, in our data.

We seek to reject the null hypothesis HϴO: that there is no relationship between Meningioma histological subtypes and their anatomical location. Therefore, higher grade Meningiomas do not preferentially occur in less surgically accessible anatomical locations.

We ran the below separate regressions, firstly with age and gender, to explore all possible explanatory variable, however our main interest is the relationship between histological sub-type and location.

- Regressed grade on age
- Regressed grade on gender
- Regressed grade on gender-age
- Regressed grade on granular location
- Regressed grade on grouped location

8.7 STATISTCAL RESULTS

8.7.1 Age as a predictor of subtype

The p-value gives a 47% (1 – 0.526751675) confidence of a correct grade being predicted by age of a patient. This does not give enough confidence to pass age as a predictive factor.

```
Call:
polr(formula = Grade ~ Age, data = Data_excl_Spine, Hess = TRUE)

Coefficients:
       Value Std. Error t value
Age -0.01081    0.01707  -0.633

Intercepts:
    Value   Std. Error t value
1|2  0.4927  0.8390     0.5873
2|3  2.4305  0.9049     2.6860

Residual Deviance: 169.6649

          Value Std. Error    t value     p value
Age -0.01080564 0.01707126 -0.6329724 0.526751675
1|2  0.49273466 0.83896571  0.5873120 0.556994162
2|3  2.43045649 0.90487443  2.6859600 0.007232175
```

8.7.2 Gender as a predictor of subtype

The p-value gives a 64% confidence of a correct grade being predicted by gender of a patient. This does not give enough confidence to pass gender as a predictive factor.

8.7.3 Age and Gender as predictors of subtype

Confidence of predicting correct grade using age and gender together fall to 44%.

```
Call:
polr(formula = Grade ~ Sex, data = Data_excl_Spine, Hess = TRUE)

Coefficients:
     Value Std. Error t value
SexM 0.433     0.4691   0.923

Intercepts:
    Value  Std. Error t value
1|2 1.1157 0.2398     4.6517
2|3 3.0567 0.4397     6.9521

Residual Deviance: 169.2362
AIC: 175.2362

         Value Std. Error   t value      p value
SexM 0.4329607  0.4690898 0.9229804 3.560174e-01
1|2  1.1156699  0.2398418 4.6516904 3.292252e-06
2|3  3.0567104  0.4396813 6.9521047 3.598762e-12
```

8.7.4 Grouped location (skull-based vs convexity) as a predictor of subtype

The p-value gives a 98% confidence that location can predict the correct histological sub-type. Location in the instance has been reduced to two categories, skull based and convexity.

```
Call:
polr(formula = Grade ~ Location.Code, data = Data_excl_Spine,
    Hess = TRUE)

Coefficients:
                Value Std. Error t value
Location.CodeS -1.094     0.4455  -2.457

Intercepts:
    Value   Std. Error t value
1|2  0.5676  0.2600     2.1834
2|3  2.5574  0.4392     5.8234

Residual Deviance: 163.5482
AIC: 169.5482
                    Value Std. Error   t value
Location.CodeS -1.0943612  0.4454782 -2.456599
1|2             0.5676079  0.2599651  2.183400
2|3             2.5573752  0.4391519  5.823441
                    Value Std. Error   t value      p value
Location.CodeS -1.0943612  0.4454782 -2.456599 1.402593e-02
1|2             0.5676079  0.2599651  2.183400 2.900636e-02
2|3             2.5573752  0.4391519  5.823441 5.764808e-09
```

8.7.5 Granular location as a predictor of subtype - Confusion matrix

This is a performance measurement for classification problem where about can be two or more classes. In this case, we wanted the model to correct classify the observed histological sub-types into 3 classes.

In the below matrix, 88 cases were correctly classified as being grade 1 while the rest were incorrectly classified. This means that the model can correctly classify correct classes 73% of the time.

		Actual Values		
		Grade 1	Grade 2	Grade 3
Precited values	Grade 1	88	26	6
	Grade 2	0	0	0
	Grade 3	0	0	0

8.7.6 Granular location as a predictor of subtype

The granular locations do not improve the model's predictive ability. In fact, the AIC score has increased, which indicates that the model has been penalised for having too many parameters.

Also, a large number of parameters is not recommended given the limited size of the sample data.

```
Call:
polr(formula = Grade ~ Location_Description, data = Data_excl_Spine,
    Hess = TRUE)

Coefficients:
                                              Value Std. Error    t value
Location_DescriptionConvexity (C)          3.946e-01  1.239e+00  3.184e-01
Location_DescriptionForamen Magnum(S)     -1.687e+01  1.311e-06 -1.287e+07
Location_DescriptionOlfactoryGroove (S)    7.915e-06  1.336e+00  5.925e-06
Location_DescriptionParafalx (C )         -2.628e-01  1.369e+00 -1.920e-01
Location_DescriptionParasaggital (C )      9.384e-02  1.312e+00  7.154e-02
Location_DescriptionPetroclival (S)       -1.687e+01  2.623e-07 -6.434e+07
Location_DescriptionSphenoid wing (S)     -1.187e+00  1.344e+00 -8.827e-01
Location_DescriptionTubercullum Sellea (S) -1.433e+00  1.593e+00 -8.998e-01

Intercepts:
    Value         Std. Error    t value
1|2  7.802000e-01  1.195300e+00  6.527000e-01
2|3  2.803300e+00  1.250500e+00  2.241800e+00

Residual Deviance: 157.6171
AIC: 177.6171
```

Since the p-value can never be 0, the p-values that appear as zero only indicate the rejection of the null hypothesis.

```
                                             Value   Std. Error       t value    p value
Location_DescriptionConvexity (C)          3.945650e-01 1.239061e+00  3.184387e-01 0.75015222
Location_DescriptionForamen Magnum(S)     -1.687292e+01 1.311268e-06 -1.286764e+07 0.00000000
Location_DescriptionOlfactoryGroove (S)    7.914811e-06 1.335917e+00  5.924629e-06 0.99999527
Location_DescriptionParafalx (C )         -2.627700e-01 1.368510e+00 -1.920117e-01 0.84773302
Location_DescriptionParasaggital (C )      9.384328e-02 1.311846e+00  7.153526e-02 0.94297176
Location_DescriptionPetroclival (S)       -1.687292e+01 2.622529e-07 -6.433836e+07 0.00000000
Location_DescriptionSphenoid wing (S)     -1.186660e+00 1.344394e+00 -8.826725e-01 0.37741322
Location_DescriptionTubercullum Sellea (S) -1.432989e+00 1.592549e+00 -8.998084e-01 0.36822223
1|2                                        7.801708e-01 1.195276e+00  6.527121e-01 0.51394191
2|3                                        2.803305e+00 1.250487e+00  2.241770e+00 0.02497625
```

8.8 Analyses

The regression of meningioma grade on age or on gender or on gender and age, as a combined variable, were all statistically insignificant thus we had not enough evidence to reject the null hypothesis. These models were not good predictors of grade.

The regression of meningioma grade on each individual meningioma location and meningioma histology, location and histology combined, did not produce a satisfactorily predictive model and the P-values were insignificant, but for foramen magnums and petroclivial, thus we couldn't reject the null hypothesis. Though foramen magnum seems to be a good predictor of grade 1.

We only had one instance of petroclivial so much can't be said about its predictive credibility.

Reducing the variable location to only convexity and skull base. Regressing meningioma grade on this modified meningioma location, we obtained a statistically significant model with enough evidence to reject the null hypothesis. Using this model, given the location, skull based or convexity, we could predict the grades correctly in 75% of the cases on our data. This model seems to have predictive capabilities. It could be that we are missing additional data or an additional variable to consider.

8.9 Conclusion

Below is a summary of the ANOVA results from all five models that were tested. Pr (> Chisq) indicates the p-value and as discussed above, shows a significant relationship for location group (skull based and convexity) compared to the rest of the variables in this study.

This strong relationship could be indicative of missing parameter(s).

Given the size of the data, we cannot conclude definitively that location alone can predict histological sub-type. What we can say is that in this study, location has shown a more significant relationship to histological sub-type than age and gender.

```
Analysis of Deviance Table (Type III tests)

Response: Grade
    LR Chisq Df Pr(>Chisq)
Age  0.39972  1     0.5272
Analysis of Deviance Table (Type III tests)

Response: Grade
    LR Chisq Df Pr(>Chisq)
Sex  0.82841  1     0.3627
Analysis of Deviance Table (Type III tests)

Response: Grade
    LR Chisq Df Pr(>Chisq)
Age  0.34047  1     0.5596
Sex  0.76916  1     0.3805
Analysis of Deviance Table (Type III tests)

Response: Grade
              LR Chisq Df Pr(>Chisq)
Location.Code   6.5164  1    0.01069 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Analysis of Deviance Table (Type III tests)

Response: Grade
                    LR Chisq Df Pr(>Chisq)
Location_Description   12.447  8     0.1323
```

9 DISCUSSIONS

Since tumour grade relates to oncologic aggression and invasion of adjacent structures, it is critically important that it is studied against other variables that make neurological tumour management difficult. While variables like; age and gender were briefly studied from the data set, their significance is in putting context and creating a background upon which the main variable under study; anatomical location, can be emphasized.

Anatomical location of neurological tumours affects resectability and therefore recurrence (12-34). Certain locations like skull base, are inherently dangerous zones due to the proximity of neurovascular structures like cranial nerves

which result in significant morbidity and mortality when aggressive tumour resection is the goal (34, 35).

While age and gender did not have any significant value in predicting tumour grade, their importance cannot be understated since they showed similar trends as seen in other Meningioma studies in broader literature (4).

The histological sub-type analysis also confirmed that grade 1 tumours are the most prevalent, up to 72%, and that grade 3 tumours while not as prevalent, were observed in the less than 20 year age group and some in the peak age groups (35-55) (17, 27). This was also reported in some studies, that paediatric Meningiomas tend to be high grade (18, 19).

The Meningioma frequency by location in this study has also been consistent with most reported case series, with convexity having the highest frequency of 28% and sphenoid ridge and parasagittal locations occupying the top three (3, 36, 37).

The assessment of tumour grade and its relationship to location at a granular level did not yield any statistically significant outcome, owing to a small sample size for that kind of analysis. When location was grouped into convexity which is easily accessible, and skull base which is not easily accessible and so often results in severe morbidity, the tumour grade to location analysis yielded a statistically significant outcome. Grouped tumour location does have predictive value in determining meningioma grade.

10 CONCLUSION

One of our objectives was to study the relationship between Meningioma histological subtypes and anatomical location. By finding evidence against the null hypothesis, we can say there seems to be a relationship between Meningioma subtypes and anatomical location.

More should be done to investigate this relationship where it fails.

Our model predicted 73% of the grades correctly therefore suggesting there is a relationship between Meningioma histological subtypes and anatomical location.

11 RECOMMENDATION

A better structured and well organised patient record storage system or even a digital one can go a long way in securing patient records, allowing easy retrieval for research purposes, more especially in tertiary hospitals. Many cases had to be dropped from this study because of incomplete information, resulting in the 125 cases collected, an underwhelming number for high volume hospitals like CHBAH and CMJAH.

Our statistical analysis yielded significant results when assessing grade against grouped location, but the sample size was not large enough conclusively analyse other parameters. A similar study with a longer study period and a more organised patient record storage system is recommended in Johannesburg still, since it is the most populated city in South Africa.

The ability of our study to show that location has a strong relationship to grade than other parameters will be of great importance in Meningioma management. More should be done to investigate this relationship to help formulate robust protocols that will help the decision-making process in Neurosurgical practice.

APPENDIX

Appendix 1

Data collection template

Date of admission:

Hospital:

Age of patient:

Gender:

Histology result:

Tumour location on imaging:

Appendix 2

Data collection sheet

Hospital	Age	Sex	Location	Histology

Appendix 3

Histology subtypes and location

	Convexity (C)	Parafalx (C)	Parasagittal (C)	Olfactory groove (SB)	Tuberculum sella (SB)	Petroclival (SB)	CPA (SB)	Foramen magnum (SB)	Intraventricular	Spinal
Grade 1										
Meningothelial										
Fibrous										
Transitional										
Psammomatous										
Secretory										
Lymphoplasmacyte-rich										
Microcytic										
Angiomatous										
Metaplastic										
Grade 2										
Chordoid										
Atypical										
Clear cell										
Grade 3										
Rhabdoid										
Anaplastic										
Papillary										

CPA; cerebello-pontine angle

C; convexity

SB; skull base

REFERENCE

1. Rockhill J, Mrugala M, Chamberlain MC. Intracranial meningiomas: an overview of diagnosis and treatment. Neurosurgical Focus FOC. 2007;23(4):E1. DOI: 10.3171/foc-07/10/e1.
2. Zeng Z, Zhang T, Zhou Y, Chen X. Atypical Growth Pattern of an Intraparenchymal Meningioma. Case Rep Radiol. 2016;2016:7985402. DOI: 10.1155/2016/7985402.
3. Greenberg MS. Hanbook of Neurosurgery. 8th ed. New York: Thieme; 2016. 1643 p.
4. Ibebuike K, Ouma J. Demographic profile of patients diagnosed with intracranial meningiomas in two academic hospitals in Johannesburg, South Africa: a 12-month prospective study. Afr Health Sci. 2014;14(4):939-45. DOI: 10.4314/ahs.v14i4.24.
5. Rogers L, Barani I, Chamberlain M, Kaley TJ, McDermott M, Raizer J, et al. Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. Journal of neurosurgery. 2015;122(1):4-23. DOI: 10.3171/2014.7.JNS131644.
6. Villa C, Miquel C, Mosses D, Bernier M, Di Stefano AL. The 2016 World Health Organization classification of tumours of the central nervous system. Presse Med. 2018;47(11-12 Pt 2):e187-e200. DOI: 10.1016/j.lpm.2018.04.015.
7. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-20. DOI: 10.1007/s00401-016-1545-1.
8. Saraf S, McCarthy BJ, Villano JL. Update on meningiomas. Oncologist. 2011;16(11):1604-13. DOI: 10.1634/theoncologist.2011-0193.
9. Nanda A, Bir SC, Maiti TK, Konar SK, Missios S, Guthikonda B. Relevance of Simpson grading system and recurrence-free survival after surgery for World Health Organization Grade I meningioma. J Neurosurg. 2017;126(1):201-11. DOI: 10.3171/2016.1.Jns151842.
10. Nanda A, Thakur JD, Sonig A, Missios S. Microsurgical resectability, outcomes, and tumor control in meningiomas occupying the cavernous sinus. Journal of Neurosurgery JNS. 2016;125(2):378. DOI: 10.3171/2015.3.Jns142494.
11. Han M-S, Kim Y-J, Moon K-S, Lee K-H, Yang J-I, Kang WD, et al. Lessons from surgical outcome for intracranial meningioma involving major venous sinus. Medicine (Baltimore). 2016;95(35):e4705-e. DOI: 10.1097/MD.0000000000004705.
12. Corell A, Thurin E, Skoglund T, Farahmand D, Henriksson R, Rydenhag B, et al. Neurosurgical treatment and outcome patterns of meningioma in Sweden: a nationwide registry-based study. Acta Neurochir (Wien). 2019;161(2):333-41. DOI: 10.1007/s00701-019-03799-3.
13. Kreßner M, Arlt F, Riepl W, Meixensberger J. Prognostic factors of microsurgical treatment of intracranial meningiomas - A multivariate analysis. PLoS One. 2018;13(10):e0202520-e. DOI: 10.1371/journal.pone.0202520.
14. Violaris K, Katsarides V, Karakyriou M, Sakellariou P. Surgical Outcome of Treating Grades II and III Meningiomas: A Report of 32 Cases. Neurosci J. 2013;2013:706481. DOI: 10.1155/2013/706481.
15. Harmancı AS, Youngblood MW, Clark VE, Coşkun S, Henegariu O, Duran D, et al. Integrated genomic analyses of de novo pathways underlying atypical meningiomas. Nat Commun. 2017;8:14433. DOI: 10.1038/ncomms14433.
16. Youngblood MW, Günel M. Molecular genetics of meningiomas. Handb Clin Neurol. 2020;169:101-19. DOI: 10.1016/b978-0-12-804280-9.00006-8.
17. Bhat AR, Wani MA, Kirmani AR, Ramzan AU. Histological-subtypes and anatomical location correlated in meningeal brain tumors (meningiomas). J Neurosci Rural Pract. 2014;5(3):244-9. DOI: 10.4103/0976-3147.133568.
18. Arivazhagan A, Devi BI, Kolluri SV, Abraham RG, Sampath S, Chandramouli BA. Pediatric intracranial meningiomas--do they differ from their counterparts in adults? Pediatric neurosurgery. 2008;44(1):43-8. DOI: 10.1159/000110661.

19. Jaiswal S, Vij M, Mehrotra A, Jaiswal AK, Srivastava AK, Behari S. A clinicopathological and neuroradiological study of paediatric meningioma from a single centre. J Clin Neurosci. 2011;18(8):1084-9. DOI: 10.1016/j.jocn.2010.11.036.
20. Motebejane MS, Kaminsky I, Choi IS. Intracranial Meningioma in Patients Age <35 Years: Evolution of the Disease in the Era of Human Immunodeficiency Virus Infection. World Neurosurg. 2018;109:e292-e7. DOI: 10.1016/j.wneu.2017.09.161.
21. Brokinkel B, Holling M, Spille DC, Hess K, Sauerland C, Bleimuller C, et al. Surgery for meningioma in the elderly and long-term survival: comparison with an age- and sex-matched general population and with younger patients. J Neurosurg. 2017;126(4):1201-11. DOI: 10.3171/2016.2.JNS152611.
22. Lee JH, Sade B, Choi E, Golubic M, Prayson R. Meningothelioma as the predominant histological subtype of midline skull base and spinal meningioma. J Neurosurg. 2006;105(1):60-4. DOI: 10.3171/jns.2006.105.1.60.
23. Wang DJ, Xie Q, Gong Y, Mao Y, Wang Y, Cheng HX, et al. Histopathological classification and location of consecutively operated meningiomas at a single institution in China from 2001 to 2010. Chinese medical journal. 2013;126(3):488-93.
24. Zham H, Moradi A, Rakhshan A, Zali A, Rahbari A, Raee M, et al. Does Histologic Subtype Influence the Post-Operative Outcome in Spinal Meningioma? Iran J Cancer Prev. 2016;9(2):e3838. DOI: 10.17795/ijcp-3838.
25. Schaller B. Spinal meningioma: relationship between histological subtypes and surgical outcome? J Neurooncol. 2005;75(2):157-61. DOI: 10.1007/s11060-005-1469-4.
26. Takami T, Naito K, Yamagata T, Yoshimura M, Arima H, Ohata K. Posterolateral approach for spinal intradural meningioma with ventral attachment. J Craniovertebr Junction Spine. 2015;6(4):173-8. DOI: 10.4103/0974-8237.167862.
27. El Husseini M, Ianovici N, Dumitrescu GF, Mihaila D, Plamadeala P, Haba D, et al. [Posterior fossa meningiomas--topographic and anatomopathologic aspects]. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2010;114(3):777-83.
28. Kunishio K, Ohmoto T, Furuta T, Matsumoto K, Nishimoto A. Factors influencing the recurrence rate of intracranial meningiomas after surgery. Neurologia medico-chirurgica. 1994;34(2):81-5. DOI: 10.2176/nmc.34.81.
29. Chang CG, Cho DY, Lee JC, Yang DY. [Intracranial meningiomas--5 year analysis]. Zhonghua yi xue za zhi = Chinese medical journal; Free China ed. 1989;43(5):321-30.
30. Ildan F, Erman T, Gocer AI, Tuna M, Bagdatoglu H, Cetinalp E, et al. Predicting the probability of meningioma recurrence in the preoperative and early postoperative period: a multivariate analysis in the midterm follow-up. Skull base : official journal of North American Skull Base Society [et al]. 2007;17(3):157-71. DOI: 10.1055/s-2007-970554.
31. Kreßner M, Arlt F, Riepl W, Meixensberger J. Prognostic factors of microsurgical treatment of intracranial meningiomas - A multivariate analysis. PLoS One. 2018;13(10):e0202520. DOI: 10.1371/journal.pone.0202520.
32. Saraf S, McCarthy BJ, Villano JL. Update on meningiomas. Oncologist. 2011;16(11):1604-13. DOI: 10.1634/theoncologist.2011-0193.
33. Han MS, Kim YJ, Moon KS, Lee KH, Yang JI, Kang WD, et al. Lessons from surgical outcome for intracranial meningioma involving major venous sinus. Medicine (Baltimore). 2016;95(35):e4705. DOI: 10.1097/md.0000000000004705.
34. Youmans JR. Youmans Neurological Surgery. Philadelphia, PA: Saunders. Elsevier; 2011.