Clinical Outcome and Recurrence After Meningioma Surgery: An Experience from a Developing Country, Nepal

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■ BACKGROUND: **Meningioma is the most common primary brain tumor, constituting more than half of all benign central nervous system tumors. This study aims to analyze the clinical outcome and recurrence after surgery of intracranial meningioma in Nepal.**

■ METHODS: **This is a retrospective study of newly diagnosed intracranial meningioma patients operated at Nepal Mediciti Hospital between 2007 and 2019. Demographics; clinical, radiologic, and perioperative details; histopathology; and clinical outcome variables were reviewed. Association of independent variables with primary outcome variables: modified Rankin Scale (favorable [≤ 3] vs. unfavorable [>3]) and recurrence was analyzed. Logistic regression model was designed to calculate adjusted odds ratio with 95% confidence interval (CI).**

■ RESULTS: **Of 233 patients, mean age was 47 years, female individuals were affected twice as much as male individuals. Location was supratentorial in 83.3%, 83.7% had tumor greater than 5 cm in size. Gross total resection (SM 0-III) was achieved in 85.4%. A total of 98.7% had grade I meningioma. Favorable outcome was found in 94.8%. Recurrence rate was 6.9%. Tumor size less than 3 cm (adjusted odds ratio [AOR] 0.024 95% CI 0.001–0.416, $P = 0.010$), gross total resection (AOR 19.737, 95% CI 4.69–83.063, $P < 0.001$), and comorbidity (AOR 0.202, 95% CI 0.052–0.785, $P = 0.021$) were significantly associated with favorable outcome whereas age (AOR 3.491, 95% CI 1.029–11.850, $P = 0.045$) and WHO grade (AOR 0.024, 95% CI 0.002–0.344, $P = 0.006$) were independently associated with recurrence. The complication and surgical mortality rates were 30% and 1.72%, respectively.**

■ CONCLUSIONS: **Tumor size, extent of resection, age, tumor grade, and medical comorbidities were significantly associated with postoperative outcome. We recommend a prospective study with standardized follow up protocol to assess the long-term outcome.**

INTRODUCTION

Meningioma is the most common primary brain tumor, constituting more than one third of all primary central nervous tumors and 53.4% of all benign central nervous system tumors.[1] More than 90% are benign and solitary. Multiple meningiomas are mostly associated with genetic syndromes or radiation.[2] Meningioma arises from the arachnoid cap cells and are most commonly located along the convexities, parasagitally and along the sphenoid wings.[2,3] Occasionally, they may arise within the skull, ventricles, or even within the brain parenchyma. Approximately 12% of meningiomas are spinal, with the most common being intradural and cauda equina region tumors in adults.[1,4] The lifetime risk of developing meningioma is approximately 1% and is more common among female individuals with higher annual incidence than male individuals (10.5 vs. 4.8 cases per 100,000).[1,2]

Histopathologically, meningiomas are classified into 3 grades by World Health Organization (WHO).[2] Grade I tumor constitutes 80%–90% of all meningiomas with recurrence rates of 7% to 25%. Rrecurrence rates of grade II and grade III meningiomas

Key words
- Intracranial
- Meningioma
- Outcome
- Recurrence

Abbreviationand Acronyms
CI: Confidence interval
CP: Cerebellopontine
GTR: Gross total resection
MRI: Magnetic resonance imaging
mRS: Modified Rankin Scale
OR: Odds ratio
WHO: World Health Organization

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are 29%–52% and 50%–94%, respectively.[2] Grade I meningioma is benign and total surgical excision offers the best chance of cure. The overall prognosis and recurrence have been found to be associated with extent of surgical resection and histopathologic grade. This study aims to describe the challenges and circumstances of performing surgery in low-resource setting and also aims to analyze the clinical outcome and recurrence after surgical management of intracranial meningioma in Nepal.

METHODS

Study Population

A retrospective study was designed. All patients with newly diagnosed intracranial meningioma who had undergone surgical excision at the Department of Neurosciences of Nepal Mediciti Hospital, Lalitpur, Nepal, between April 2007 and October 2019 were included in the study. Intracranial meningiomas were managed expectantly, recurrent cases and spinal meningiomas were excluded.

Data Collection and Management

Ethical clearance was received from the ethics review board of Nepal Health Research Council. Demographics, clinical and radiologic details, perioperative information, histopathology reports, and clinical outcome variables (postoperative modified Rankin Scale, complication, mortality and tumor recurrence) were retrospectively collected from the medical record files.

Primary Study Outcome

Modified Rankin Scale (mRS) at follow-up visit. For the purpose of statistical analysis, mRS scale was dichotomized as favorable (independent after surgery, mRS 0–3) and unfavorable (dependent, mRS >3).[5]

Study Variables

Our study variables included demographic variables (age, sex, race), clinical variables (clinical feature at presentation, medical comorbidity, postoperative new onset neurological event, reoperations and their indication, surgical mortality [defined as death within 30 days of surgery], duration of hospital stay, recurrence, and postoperative adverse events), radiologic variables (location and size of the tumor in preoperative imaging studies, evidence of tumor recurrence in follow-up magnetic resonance imaging [MRI]), surgical variables (extent of resection [Simpson grade], histopathologic grade, and subtype as per WHO classification system), and outcome variables (postoperative mRS and recurrence rate).

Statistical Analysis

Dichotomous and categorical variables were reported using frequencies and percentages, and mean was reported in continuous variables. Stratification with respect to age, sex, race, medical comorbidity, location and size of the tumor, Simpson grade and histopathologic grade, and subtype was performed. For statistical purposes, age was dichotomized to less than or more than the mean; size of the tumor was divided into 3 categories <3 cm, 3–5 cm, and >5 cm; extent of surgical resection was dichotomized as gross total resection (SM 0-III) or subtotal resection (SM IV-V); and the clinical outcome was dichotomized to favorable (mRS ≤3) versus unfavorable (mRS >3). SM grade 0 was used for convexity meningioma in which tumor-free dural margin of 2 cm is resected along with the tumor. Association of independent variables with the primary outcome variable (mRS) was analysed using the χ^2 test. Statistical significance was determined at $P < 0.05$. Bivariate logistic regression was performed to identify unadjusted odds ratio (OR) with 95% confidence interval (CI). Then, multivariate logistic regression model was designed for those variables with $P < 0.1$ at bivariate level to calculate adjusted OR with 95% CI. Analysis was performed in SPSS 17 (IBM, Chicago, IL).

Perioperative Management

Patients were evaluated clinically by either consultant neurosurgeon or neurosurgical registrar (a qualified neurosurgeon who works under the consultant neurosurgeon in the department) prior to surgery. Dexamethasone 4 mg intravenous stat dose then every 6 hours was started a day before surgery. After general anaesthesia patients were positioned according to the site of the tumor. Localization was made using craniometric surface landmarks. Intraoperative monitoring and stereotactic neuronavigation were not used due to lack of these facilities. Patients were operated by the senior author (GRS) himself or under his direct supervision. Postoperative care was provided in the high dependency ward or intensive care unit for 48 hours. Postoperative computed tomography scan of the brain was done in all cases on the first postoperative day. Subgaleal drain was removed after 48 hours and then patients were shifted to ward. All patients received prophylactic antibiotics, which was continued for 7 days postoperatively. Sutures were removed and patient discharged if no complications were recorded. For patients who presented with seizure and were already on antiseizure medication, antiepileptic drugs were continued for 2 years after surgery and then gradually tapered after normal electroencephalogram report. Prophylactic antiepileptic (injection phenytoin or levetiracetam or sodium valproate) was routinely used in our practice which was usually continued for 6 months after surgery then gradually tapered off if electroencephalogram returned normal.

Follow-Up

First follow-up was scheduled after 1 week if possible, if not then in 1 month, and then at 3, 6, and 12 months after surgery and annually afterwards. Functional status was documented using mRS at the time of follow-up visit. Histopathologic results were collected from the Pathology Department. All grade III meningiomas were given radiotherapy after surgical excision and were followed up clinically. Second surgery was performed for recurrence with significant mass effect after proper counseling regarding outcome and prognosis. Grade II meningiomas were closely monitored for recurrence, and reoperated if there was recurrence. Radiotherapy was given only for recurrence after the second surgery in grade II meningioma.

RESULTS

Patient Characteristics

A total of 246 patients were operated for intracranial meningiomas during the study period. Of these, 233 patients were included in

Table 1. Clinical Presentation of Operated Intracranial Meningioma Patients (n = 233)

Clinical Presentation	Number of Patients (%)
Headache	186 (79.8)
Seizure	103 (44.2)
Cranial nerve palsy	79 (33.9)
Paresis	35 (15)
Gait disturbances	27 (11.6)
Cognitive disturbance	23 (9.87)
Medical comorbidity	77 (33)

the study. More than two thirds (68.7%) were female. The mean age at presentation was 47 years (SD ±13.23, range: 13–85). More than half of the patients identified as Khas people (58.45%). The most common presenting symptom was headache in 79.8%, followed by seizure (Table 1). Second nerve palsy was the most common cranial nerve deficit seen in 21.46%. One third (33%) had medical comorbidities such as hypertension, diabetes, or chronic obstructive pulmonary disease.

Preoperative Imaging and Tumor Characteristics

MRI was the most common imaging modality, performed in 98.3%. Only 4 patients were operated solely based on computed tomography imaging. Tumors with maximum diameter of >5 cm were seen in 83.7%. The majority of the tumors were located in the supratentorial region (83.3%). Cerebral convexity (26.8%) was the most common location among supratentorial tumors while cerebellopontine (CP) angle (43.6%) was the most common location in the infratentorial region (Figure 1).

Surgical Excision and Histopathology

Gross total resection (SM grade 0 to III) was achieved in 85.4%, and 14.6% had subtotal resection (Figures 2 and 3). Two hundred thirty patients (98.7%) had grade I meningioma and 3 had grade II meningioma. Meningothelial and transitional meningiomas were the most common histologic subtypes, each accounting for 30.5% (Table 2).

Surgical Morbidity and Mortality

Mean duration of hospital stay was 18.7 days (SD ±6.9 days, range: 4–60 days). Fifteen patients were reoperated during the hospital stay. Indications for reoperation were evacuation of symptomatic cavity hematoma in 7 patients, removal of bone flap for sudden increase in intracranial pressure secondary to brain swelling (n = 3), external ventricular drain (EVD) placement for hydrocephalus (n = 3) and VP shunting (n = 2). Surgical mortality rate was 1.7% (n = 4). Of those who died, 3 had supratentorial lesions and 1 had petroclival meningioma. The causes of death were intractable seizure in 2 cases; chest infection and malignant brain edema were attributed to the death of the other 2 patients. Overall postoperative complications were found in 30%. New focal deficit after surgery was noted in 15.9%. Postoperative paresis developed in 21 patients, cranial nerve palsy in 16 patients, and 12 patients had cerebrospinal fluid leak from the incision site. Significant brain edema, symptomatic cavity hematoma, and hydrocephalus were seen in 9, 7, and 5 patients, respectively.

Postoperative Outcome and Recurrence

Ninety-nine percent of patients turned up for their first follow-up within 30 days. The follow-up rate gradually declined after 12 months: at 6 months (93.1%), 12 months (83.3%), 24 months (71.2%), 36 months (39.3%) 5 years (33%), 7 years (18.2%), and 9 years (10.8%). Favorable outcome (mRS 0–3) was seen in 94.8%. Supratentorial location (P = 0.02), tumor size <5 cm (P = 0.046), gross total resection (GTR) (P < 0.001), and absence of medical

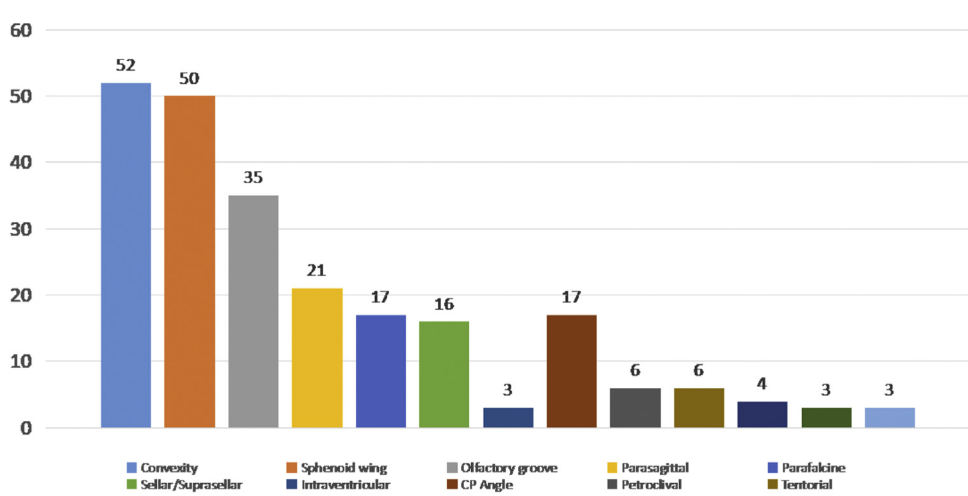

Figure 1. Location of meningiomas in our sample.

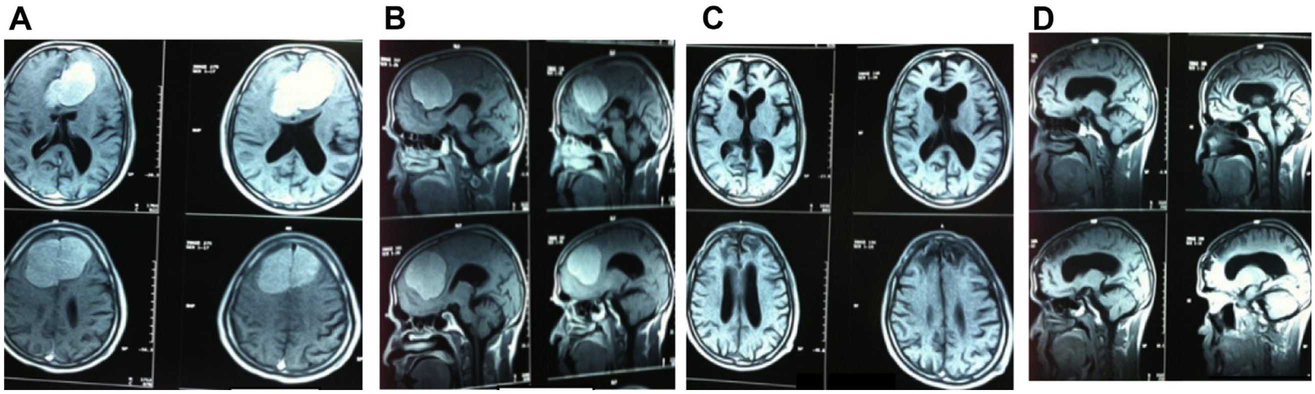

Figure 2. (**A, B**) Preoperative cranial MRI of brain (axial and coronal) with gadolinium contrast showing giant parafalcine meningioma extending in both frontal lobes. (**C, D**) Postoperative cranial MRI (3 months after total excision) with gadolinium contrast showing no residual tumor.

comorbidity ($P = 0.01$) were significantly associated with favorable outcome. Multivariate logistic regression analysis found tumor size <3 cm ($P = 0.01$), resection grade ($P < 0.001$), and comorbidity ($P = 0.02$) as significant factors associated with favorable outcome (Table 3). Tumor recurrence was seen in 6.9%. Recurrence was greater among patients who had higher tumor grade (WHO grade II, $P < 0.001$), tumor size >5 cm ($P = 0.04$), younger age (younger than 47 years; $P = 0.04$).

With regard to site of tumor, recurrences were found all among supratentorial meningiomas ($P = 0.048$). Simpson grade of resection (dichotomized as GTR for SM I–III and subtotal resection [SM IV–V]) did not show any statistical association with recurrence (7% in GTR vs. 5.6% in subtotal resection, $P = 0.8$). After multivariate adjustment, only age (OR 3.49; 95% CI 1.029–11.850; $P = 0.04$) and WHO grade (OR 0.024; 95% CI 0.002–0.344; $P = 0.006$) were found to be statistically significant for recurrence (Table 3).

DISCUSSION

According to the report of the Central Brain Tumor Registry of the United States (CBTRUS), incidence of meningioma increases with age, median age at diagnosis was 65 years, non-malignant meningiomas account for 98.7%, and are more common in women and the Black population.[1,2] In our series both the mean and median age at presentation was 47 years, women were affected twice as often as men, and WHO grade I meningioma were found in 98.7%—with meningothelial and transitional meningioma being the most common subtypes. This finding was consistent with reports from India (48 years)[6] and Ethiopia (39.7 ±12.6 years)[7] and other previous studies.[1,8] In contrast, atypical and malignant meningiomas constitute a small fraction of the total and are more commonly found in the male population.[1,9,10] We found only 1.3% of our patients having grade II meningiomas and all of them were female. This discordance was probably due to smaller sample size in our study.

The most common anatomical site of origin was cerebral convexity, seen in 22.3%, followed by sphenoid wing (21%). This finding was consistent with Laeke et al.,[7] who reported convexity meningioma in 34.2% followed by sphenoid wing in 24.1%. Mezue et al.[11] and Bhat et al.[12] reported cerebral convexity as a site of origin of meningioma in 21.2% and 16.04%, respectively. CPA meningiomas constitute 7% of all and 43.58% of

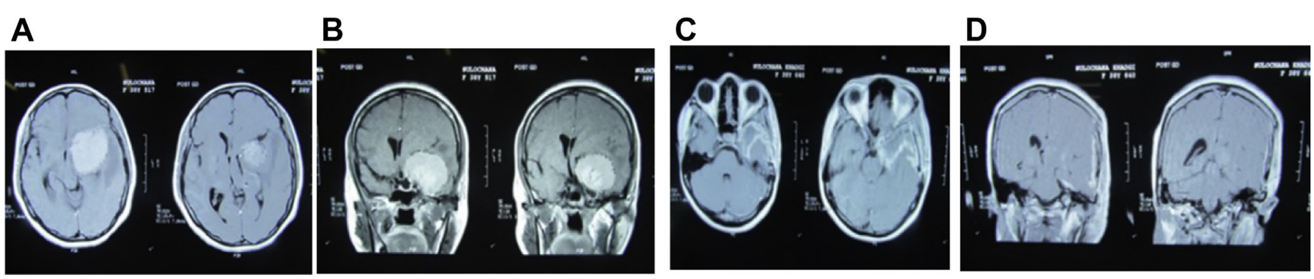

Figure 3. (**A, B**) Preoperative MRI of brain with IV contrast (axial and coronal, depicting large left clinoidal brilliantly enhancing meningioma with left carotid artery encasement by tumor. (**C, D**) Postoperative MRI of brain (3 months postoperatively) with gadolinium contrast showing some temporal enhancement but there was no evidence of residual tumor.

Table 2. Histologic Subtype of Intracranial Meningiomas ($n = 233$)

WHO Grade	Subtype	Number of Patients (%)
Grade I		230
	Meningothelial	71 (30.55)
	Transitional	71 (30.55)
	Psammomatous	38 (16.3)
	Fibroblastic	33 (14.2)
	Microcystic	7 (3)
	Angiomatous	6 (2.6)
	Secretary	2 (0.9)
	Papillary	1 (0.4)
	Lymphoplasmacyte	1 (0.4)
Grade II		3
	Atypical	2 (0.9)
	Chordoid	1 (0.4)

infratentorial meningiomas in our series. Ali Elkady et al.,[13] in their review of infratentorial meningiomas, reported CP angle as the most common site of origin in 40%. Headache (79.8%) was the most common presentation, followed by seizure and cranial nerves palsy, which is similar to the findings reported in the existing literature.[7,14,15] GTR was achieved in 85.4%, which is comparable to that of Correl et al.[16] and Laeke et al.,[7] who reported GTR rates in their studies as 86.6% and 93%, respectively.

Comparable to that reported in Laeke et al.[7] (21 days) but higher than that reported by Mezue et al.[11] (7.5 days), the average length of hospital stay in our series was 18.66 days. The longer hospital stay in our study is due to fact that majority of the patients lived out of the capital city and they preferred to stay longer due to fear of immediate complication and inconvenience of urgent return to hospital from their home. Surgical mortality rate of 1.7% in our series was consistent with that of reported in the literatures.[16,17]

Overall postoperative complication was seen in 30%. Fifteen patients (6.43%) required a second surgery. The reported reoperation rate after intracranial meningioma surgery was found to be 5.2% to 13.2%.[7,16,17] Postoperative hematoma collection was the most common cause of re-surgery in our series ($n = 7$, 46.6%). Laeke et al. also reported postoperative hematoma collection as the most common cause of re-surgery, seen in 25%.[7] New onset neurological deficit after surgery was seen in 15.85% of our patients, which was comparable to that reported by a Swedish population-based study (14.8%).[16]

Although most meningiomas are classified as benign, studies have shown that survival is still shorter than in matched controls.[18,19] Prognostic factors reported are age, tumor size and location, extent of resection (SM grade), mitotic index, molecular and histologic features, and initial therapy.[1,20-22] In our study, location, tumor size, resection grade, and medical comorbidity were associated with postoperative functional outcome. For statistical purpose we have categorized tumor size into 3 categories (<3 cm, 3–5 cm and >5 cm); only <3 cm compared to >5 cm has significant association with favorable outcome, with no difference in outcome between 3–5 cm and >5 cm. On adjusted multivariate analysis, only resection grade and medical morbidity were found to be significantly associated with better functional outcome (mRS 0–3). The adjusted odds of having better functional outcome after GTR was 19.737 (95% CI 4.69–83.063; $P < 0.001$). In contrast to the findings of Cahill et al.,[23] in which younger age and female sex were associated with decreased hazard ratios for death, none of these variables were associated with outcome in our study. Previous studies have shown a strong association of tumor size with postoperative functional outcome.[11,14,15,24] However, this association was not observed in our study after multivariate adjustment ($P = 0.61$).

According to WHO grading, grade I meningioma has recurrence rate of 7%–25%, and 29%–52% for grade II.[2] In our study, tumor recurrence was found in 6.9% of patients in up to 11 years of follow up. Recurrence rate for grade I meningioma was 6.1%, while it was 66.7% for grade II. Mubeen et al., from Kasmir, reported a recurrence rate of 4.87% among intracranial meningiomas, with higher rate of recurrence among SM II and III grade of resection.[6] In our series, in univariate analysis, higher tumor grade (WHO grade II, $P < 0.001$), tumor size >5 cm ($P = 0.04$), and age less than 47 years ($P = 0.04$) were found to be associated with recurrence, whereas age (adjusted OR 3.491; 95% CI 1.029–11.850; $P = 0.04$) and WHO grade (adjusted OR 0.024; 95% CI 0.002–0.344; $P = 0.006$) were only statistically significant after multivariate adjustment. Nanda et al. reported recurrence in 21% after excision of grade I meningiomas, which was significantly associated with extent of resection ($P = 0.001$).[25] They found female sex and Karnofsky Performance Scale score of more than 70 as independent predictors of recurrence-free survival after resection. The recurrence rate of 6.1% in our patients with grade I meningioma could be underestimated because of steady loss to follow-up over a period of time, as the overall status of these patients could not be analyzed in this study.

Although widely used, the clinical significance of the Simpson grading alone as a predictor of recurrence has been questioned in recent studies.[25-27] Spille et al. compared the predictive value of residual tumor volume with extent of resection (SM grade) and found postoperative tumor volume (hazard ratio 1.05, $P < 0.001$) but not the Simpson grading ($P = 0.39$) as a predictor for recurrence.[28] Similarly low apparent diffusion coefficient on MRI and DNA methylation patterns have been found to equally or more accurately predict tumor recurrence than the current WHO grading system.[29-31] Nanda et al. reviewed their experience in resecting WHO grade I meningiomas over 20 years and argued that SM grade still maintains its relevance and prognostic value.[25]

Perioperative Management: Problems and Challenges

Delay in seeking medical care is one of the major issues in our context. Patients usually present late because of lower education level, superstitious belief, lack of accessibility and availability of neurosurgical services in nearby facilities, and financial constraints. The majority of population in this world still consider seizure as a consequence of previous misdeed.[32] Most people

Table 3. Univariate and Multivariate Regression Analysis of Clinical and Demographic Factors Associated With Functional Outcome and Recurrence

	Odds Ratio for mRS			Odds Ratio for Recurrence		
Variable	**Unadjusted (95% CI)**	**Adjusted (95% CI)**	***P* Value**	**Unadjusted (95% CI)**	**Adjusted (95% CI)**	***P* Value**
Age group						
Below mean (47 years)	3.027 (0.798–11.480)	2.508 (0.454–13.84)	0.291	2.435 (0.819–7.244)	3.491 (1.029–11.850)	0.045*
Above mean	1	1		1	1	
Location						
Supratentorial	0.255 (0.76–0.849)	2.438 (0.555–10.704)	0.238			
Infratentorial	1	1				
Comorbidity						
Yes	0.227 (0.066–0.779)	0.202 (0.052–0.785)	0.021*			
No	1	1				
Tumor size						
<3 cm	0.086 (0.007–1.045)	0.024 (0.001–0.416)	0.01*			
3–5 cm	0.456 (0.115–1.812)	0.668 (0.139–3.217)	0.615			
>5 cm	1					
Resection						
GTR	15.000 (4.221–53.310)	19.737 (4.69–83.063)	<0.001*			
STR	1					
Histology						
WHO Grade I				0.032 (0.003–0.380)	0.024 (0.002–0.344)	0.006*
WHO Grade II				1	1	

CI, confidence interval; GTR, gross total resection; mRS, modified Rankin Scale; STR, subtotal resection.
*Statistically significant.

resort to spiritual healers and shamans (those who are believed to be blessed by divine power), which has led to not only delay in diagnosis and treatment but also few have succumbed to the pathology in the name of the Almighty. This could be reflected in our data, in which the majority of the tumors were larger (>5 cm) and seizure was one of the most common clinical presentations.

Similarly, surgical planning and execution had to be improvised according to limited resources. Neuronavigation and stereotactic and preoperative embolization services were not available. Surgical planning and approach were based on neuroanatomical landmarks and clinical background. For larger meningiomas, staged surgery was not convenient because of the additional cost associated with second surgery. Likewise, postoperative contrast-enhanced MRI could not be performed in all cases due to financial constraints.

On the other hand, management of postoperative complications is one of the very challenging situations in Nepal, where the close relatives of the patient do not readily comply for a second intervention. Despite proper preoperative counseling and meticulous surgical techniques, the misunderstanding with accusation to surgeons is widely prevalent, which might be due to various reasons such as lower level of education, higher expectation irrespective of pathology and inability to bear the cost with insufficient and inadequate national health insurance.[33]

Limitations

There are several limitations of this study. Being a retrospective study, this is subject to unbalanced confounders that may influence outcome. Multivariate adjustment was used to help address this inherent concern of retrospective study. The standardized follow-up protocol at different time periods could not be maintained because of geographical and financial constraints to travel to hospital for follow-up. Also, it was not possible to obtain information about subsequent treatments after reoccurrence that may be important factor for long-term survival.

CONCLUSIONS

In our series of operated intracranial meningioma patients, GTR was achieved in 85.4%. Favorable outcome was seen in 94.8%. Recurrence rate was 6.9%. Tumor size, resection grade, and medical comorbidity were significantly associated with favorable outcome after multivariate adjustment. Age and WHO grade were independently associated with recurrence. We recommend a long-term prospective study with standardized follow-up protocol to analyze the overall and progression-free survival of patients with intracranial meningioma managed with surgical excision.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Sharma Gopal Raman: Conceptualization, Data curation, Writing - original draft, Resources, Supervision, Validation, Writing - review & editing. **Paudel Prakash:** Conceptualization, Data curation, Formal analysis, Software, Writing - original draft, Resources, Supervision, Validation, Writing - review & editing. **Joshi Sumit:** Project administration, Investigation, Methodology, Writing - review & editing. **Shah Damber Bikram:** Project administration, Investigation, Methodology, Writing - review & editing. **Karki Prasanna:** Project administration, Investigation, Methodology, Writing - review & editing.

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