

Recurrence of Intracranial Meningioma after Surgery: Analysis of Influencing Factors and Outcome

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Objective: To analyze the recurrent rate, timing, and influential factors of recurrence, including clinical outcome in patients with intracranial meningioma who underwent surgery.

Material and Method: The medical records of surgically treated intracranial meningioma patients with histological confirmation were reviewed. The diagnosis of recurrence was based on clinical condition and imaging study during follow-up. The recurrent rate, timing of recurrence, factors that influence the recurrence and clinical outcome were analyzed. Clinical outcome was measured by the Glasgow outcome scale.

Results: One hundred eighty one patients were recruited. Mean tumor diameter was 4.9 cm (1.2-9 cm). Mean follow-up was 32.3 months. Median recurrent time was 21.6 months and overall recurrent rate was 21.5% with 5-year recurrence-free survival rate of 65%. Factors associated with tumor recurrence were headache at presentation ($p = 0.002$), Simpson grade III ($p = 0.012$), Simpson grade IV ($p < 0.001$), Simpson grade V ($p = 0.004$), WHO grade II ($p = 0.004$) and WHO grade III ($p < 0.001$). Mortality rate in recurrent group was 12.8% compared with 3.5% in non-recurrent group ($p = 0.039$). The favorable outcome was higher in non-recurrent group 91.5% compared with 76.9% in recurrent group ($p = 0.02483$).

Conclusion: The risk factors of recurrence were headache at presentation, extent of resection, and histological grading. The extent of resection identified by Simpson grading effect the recurrent rate as stated previously in the literature. The higher histological grade was associated with higher recurrent rate. The wide range of timing of tumor recurrence needs both clinical evaluation and imaging study in short- and long-term follow-up especially in high-risk group. Recurrent meningioma increased rate of morbidity and mortality.

Keywords: Meningioma, Recurrence, Surgery

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Meningioma was first described as meningothelioma by Harvey Cushing in 1915. It arise from arachnoid cell cluster. Before Cushing's era, the surgical mortality was 50% from bleeding and infections, but was reduced to 10% of 2,886 patients with meticulous technique of coagulation and dura and scalp closures in his report⁽¹⁾.

The incidence of meningioma was six per 100,000 per year and 19.2% of all intracranial tumors^(2,3). The most common age group was fourth to sixth decades and twice as common in female⁽⁴⁾. The known etiologies were genes, cranial irradiation, and hormone receptor⁽⁵⁾.

Meningiomas are regarded as common benign tumors that can be totally resected out. However, their recurrent rate is high and may increase morbidity and mortality^(6,7). Meningioma has been graded into three grades from WHO classification of intracranial neoplasm according to risk of recurrence and invasion of these tumors⁽⁸⁾.

Clinical presentation depends on its site as the compressive symptom, increased intracranial pressure from the tumor itself or combining with perilesional edema, and deformity of the skull or facial bone. Surgery is the primary treatment. The aim of the surgery was for total tumor resection and the invaded surrounding organ. However, some tumors cannot be accessed for total removal due to locations that are adherent to surrounding vital structures. The residual tumor may lead to recurrence but timing was uncertain⁽⁹⁻¹³⁾. Simpson reported surgical grading and recurrent rate at 10 years were 9, 19, 29, and 44% in

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grade I, II, III, and IV respectively. Toshihiko et al proposed Simpson grade 0 was grossly tumor resected including 2 cm dura border and abnormal bone excision without recurrence at 5-year^(10,14). Our report describes a single institution's experience with the surgical management of intracranial meningioma including its recurrent rate, timing of recurrence, factors that influenced the recurrence, and clinical outcome.

Material and Method

The medical records of 196 consecutive patients with the diagnosis of intracranial meningioma who were treated at Songklanagarind Hospital between 2002 and 2008 were analyzed. Collected data were studied with the focus on the patient's age and sex, tumor, presenting symptoms, neurological deficits, neuroimaging appearance, extent of surgical resection (Simpson grade⁽¹⁰⁾), histological study (WHO classification⁽⁸⁾), time of recurrence, and reoperation and outcome (Glasgow Outcome Scale⁽¹⁵⁾). After discharge, patients were given appointments to have regular visit at outpatient clinic. Participants were neurologically examined regularly. Brain MRI was done annually for five years.

Evaluation of treatment

The extent of removal was evaluated by intraoperative observation according to Simpson study⁽¹⁰⁾ (grade I: gross total resection with excision of dural attachment and abnormal bone, grade II: gross total resection with endothermy coagulation of dural attachment, grade III: gross total resection without resection or coagulation of dural attachment, grade IV: partial resection, grade V: simple decompression). Postoperative enhanced CT or MR imaging was done within three months of surgery. Gross-total removal was determined by intraoperative evidence of no remaining tumor together with no evidence of enhancing tumor on postoperative radiographic evaluation.

Clinical follow-up

Patients were examined at the outpatient clinic of Songklanagarind Hospital. The patients with recurrent symptoms also underwent CT or MR imaging. The primary outcomes were recurrent rate, timing to recurrence, and factors that influence the recurrence. The recurrences included both recurrence and regrowth of meningiomas. Recurrence was the newly detected meningioma after gross total resection

at the same location and regrowth was defined as a $\geq 25\%$ increase in size of residual tumor in greatest diameter after subtotal resection. The recurrent date was the date of imaging detection of recurrence or regrowth.

The secondary outcome was neurological outcome and death after surgery, as measured by the Glasgow outcome scale (GOS)⁽¹⁵⁾. The GOS measures global functioning as a combination of neurological function and dependence on others, with five outcome categories scored 1 to 5: death = 1, persistent vegetative state = 2, severe disability: conscious but dependent on others for daily activities = 3, moderate disability: disabled but independent in daily activity = 4, and good recovery = 5. We measured outcome at discharge and at the last time of the follow-up. Favorable outcomes included good recovery and moderate disability, whereas unfavorable outcomes consisted of severe disability, persistent vegetative state, and death.

Statistical analysis

Descriptive analysis was used to examine baseline characteristics and relevant baseline clinical information. Recurrence-free survivals were estimated using the Kaplan-Meier method.

Cox-proportional hazard ratio were used to see the associated variables of tumor recurrence using significant level at $p < 0.05$. Hazard ratios (HRs), 95% confidence interval (95% CI) and p -value were obtained. Cox-Mantel tests were used to compare recurrence-free survival time distributions in different subgroups. All statistical analysis was performed using commercially available software (Program R epical version 2.9.1).

Results

One hundred ninety six patients with intracranial meningiomas were surgically treated with histological confirmation. Fifteen patients were excluded due to missing data and lost follow-up. Therefore, 181 patients with meningiomas (multiple meningiomas in 11 patients) entered the study. Ten of the 181 patients who died without evidence of recurrence (5 days to 14 months after the primary operation) should not be included for follow-up. The patient characteristics are summarized in Table 1. There were 146 females and 35 males (a ratio of 4:1), age ranging from nine to 83-years-old (mean 48.1 years, SD = 13.9). A peak incidence of 96 patients with tumor occurred in the fourth to the sixth decades of life (53%). Headache was the most common complaint

Table 1. Baseline and procedural characteristics of the patients comparison between recurrent group (n = 39) and non-recurrent group (n = 142)

	Total n = 181 (%)	Recurrence n = 39 (%)	Non-recurrence n = 142 (%)	p-value
Age				0.067
≤20 years	5 (2.8)	3 (7.7)	2 (1.4)	
21-40 years	45 (24.9)	13 (33.3)	32 (22.5)	
41-60 years	96 (53.0)	18 (46.2)	78 (54.9)	
>60 years	35 (19.3)	5 (12.8)	30 (21.1)	
Sex				0.499
Male	35 (19.3)	9 (23.1)	26 (18.3)	
Female	146 (80.7)	30 (76.9)	116 (81.7)	
Clinical presentation				
Headache	72 (39.8)	22 (56.4)	50 (35.2)	0.027
Weakness	36 (19.9)	12 (30.8)	24 (16.9)	0.090
Numbness	4 (2.2)	0 (0)	4 (2.8)	0.579
Proptosis	7 (3.9)	1 (2.6)	6 (4.2)	1
Visual problems	50 (27.6)	10 (25.6)	40 (28.2)	0.912
Anosmia	2 (1.1)	0 (0)	2 (1.4)	1
Seizure	23 (12.7)	2 (5.1)	21 (14.8)	0.172
Decreased level of consciousness	20 (11.0)	6 (15.4)	14 (9.9)	0.386
Others (e.g., incidental finding, vertigo)	15 (8.3)	3 (7.7)	12 (8.5)	1
Sites				
Convexity	37 (20.4)	6 (15.4)	31 (21.8)	0.509
Sphenoid wing	36 (19.9)	8 (20.5)	28 (19.7)	0.907
Parasagittal	21 (11.6)	8 (20.5)	13 (9.2)	0.085
Falx	12 (6.6)	2 (5.1)	10 (7.0)	1
Sellar + suprasellar	25 (13.8)	4 (10.3)	21 (14.8)	0.642
Cerebellopontine angle	17 (9.4)	4 (10.3)	13 (9.2)	0.764
Olfactory groove	13 (7.2)	1 (2.6)	12 (8.5)	0.304
Tentorial	10 (5.5)	3 (7.7)	7 (4.9)	0.451
Petroclival	8 (4.4)	3 (7.7)	5 (3.5)	0.372
Cavernous sinus	6 (3.3)	0 (0)	6 (4.2)	0.343
Foramen magnum	4 (2.2)	0 (0)	4 (2.8)	0.579
Cerebellum	3 (1.7)	1 (2.6)	2 (1.4)	0.519
Optic nerve sheath	2 (1.1)	0 (0)	2 (1.4)	1
Intraventricular	1 (0.6)	0 (0)	1 (0.7)	1
Central skull base	1 (0.6)	0 (0)	1 (0.7)	1
Total	196	40	156	
Length (maximum diameter)				0.846
<3 cm	23 (12.7)	6 (15.4)	17 (12.0)	
3-5.9 cm	104 (57.5)	22 (56.4)	82 (57.7)	
≥6 cm	54 (29.8)	11 (28.2)	43 (30.3)	
Simpson grade				<0.001
I	38 (21.0)	3 (7.7)	35 (24.6)	
II	54 (29.8)	4 (10.3)	50 (35.2)	
III	10 (5.5)	5 (12.8)	5 (3.5)	
IV	75 (41.4)	25 (64.1)	50 (35.2)	
V	4 (2.2)	2 (5.1)	2 (1.4)	
WHO grade				0.004
I	168 (92.8)	32 (82.1)	136 (95.8)	
II	11 (6.1)	5 (12.8)	6 (4.2)	
III	2 (1.1)	2 (5.1)	0 (0)	

upon admission, followed by visual problems, and motor weakness respectively. The most frequent anatomical locations was in convexity 37 (20.4%), sphenoid wing 36 (19.9%), and parasagittal and falx 33 (18.2%). The mean maximum diameter was 4.9 cm (range 1.2-9 cm). The mean follow-up was 32.3 months, SD = 26 (range 1.2-111.35 months).

Tumor recurrence

The median recurrent time was 21.6 months (range 2-89 months). The overall rate of recurrence was 21.5%. The 5-year recurrence-free survival rate was 64% (95% CI 54-75.6%) (Fig. 1). The median recurrence-free survival time was 88.6 months. On univariate analysis (Table 1), headache presenting symptom, Simpson grade and WHO grade, were significant predictive factors for recurrence. Patient age, gender, location, and tumor size were not deemed significant. Cox proportional hazard model for adjusted hazards ratio of the independent factor that associated with tumor recurrence for multivariate analysis, the factors that statistically significant were headache presentation (adjusted HR 2.9 (95% CI 1.47-5.75)), Simpson grade III (adjusted HR 8.08 (95% CI 1.57-41.45)), grade IV (adjusted HR 9.84 (95% CI 2.73-35.44)), and grade V (adjusted HR 17.25 (95% CI 2.53-117.61)), WHO grade II (adjusted HR 5.56 (95% CI 1.73-17.91)), and III (adjusted HR 49.86 (95% CI 7.21-344.81)) (Table 2).

The recurrent rate of according to extent of resection was three (7.9%) in Simpson grade I, four (7.4%) in Simpson grade II, five (50%) in Simpson grade III, 25 (33%) in Simpson grade IV, and two (50%) in Simpson grade V. The median recurrent time was 54.7, 6.6, 22.2, 17.1, and 5.1 months respectively

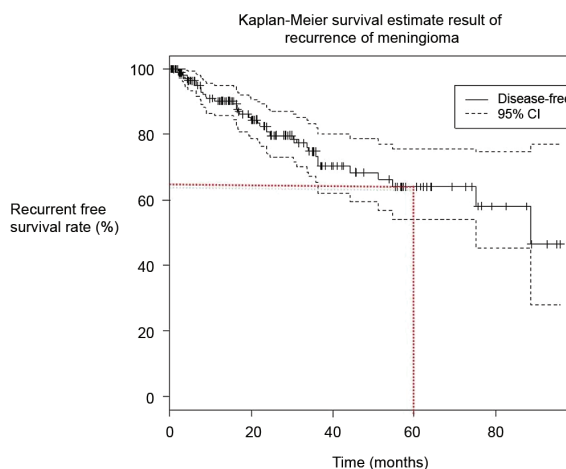


Fig. 1 Kaplan-Meier survival analysis about the 5-year recurrence-free survival rate at 64%.

(p -value = 0.021) (Table 3). The distribution of time at detectable recurrence was showed in Fig. 2.

According to pathological grade, WHO grade I recurrence was 32 (19%) and median recurrent time was 21.9 months, in WHO grade II and III groups recurrence were five (45.5%) and two (100%) and median recurrent time were 8.2 months and 5.5 months respectively (p -value = 0.017) (Table 4). The distribution of recurrent time was showed in Fig. 3.

Surgical complications and clinical outcomes

Post-operative motor deficit, visual deficit and mortality rate were higher in recurrent group (Table 5). The rate of motor deficit of recurrent group was 38.5% compared with 12% of non-recurrent group and visual defect rate was 12.8% compared with

Table 2. The association of prognostic factors for tumor recurrence by Cox proportional hazards model

Associated factors	Crude HR (95% CI)	Adjusted HR (95% CI)	p -value
Presenting symptom			
Headache	2.54 (1.34, 4.8)	2.91 (1.47, 5.75)	0.002
Simpson grade			
I	1.0	1.0	
II	1.24 (0.28, 5.58)	1.36 (0.30, 6.15)	0.693
III	8.52 (2.03, 35.75)	8.08 (1.57, 41.45)	0.012
IV	6.25 (1.87, 20.82)	9.84 (2.73, 35.44)	<0.001
V	19.10 (3.09, 117.86)	17.25 (2.53, 117.61)	0.004
WHO grade			
I	1.0	1.0	
II	3.64 (1.41, 9.41)	5.56 (1.73, 17.91)	0.004
III	28.52 (6.06, 134.11)	49.86 (7.21, 344.81)	<0.001

HR = hazard ratio

Table 3. The recurrence of tumor and median recurrent time according to extent of resection

Simpson grade	n	Recurrence (%)	Median recurrent time (IQR) (months)
Simpson grade I	38	3 (7.9)	54.7 (45.4, 71.7)
Simpson grade II	54	4 (7.4)	6.6 (4.1, 11.6)
Simpson grade III	10	5 (50.0)	22.2 (7.7, 36.2)
Simpson grade IV	75	25 (33.3)	17.1 (8.6, 30.4)
Simpson grade V	4	2 (50.0)	5.1 (3.6, 6.7)

Table 4. The recurrence of tumor and median recurrent time according to histological grade

WHO grade	n	Recurrence (%)	Median recurrent time (IQR) (months)
WHO grade I	168	32 (19.0)	21.9 (10.4, 34.5)
WHO grade II	11	5 (45.5)	8.2 (3.2, 8.9)
WHO grade III	2	2 (100)	5.5 (4.4, 6.6)

1.4% in recurrent group and non-recurrent group respectively and both were different significantly (p -value <0.05). The overall mortality rate was 5.5% (10:8 death from post-operative complication and 2 death from tumor recurrence) and surgical mortality rate was 4.4%⁽⁸⁾. Mortality rate in recurrent group was

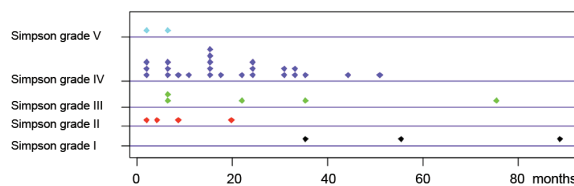


Fig. 2 Distribution of recurrent time by Simpson grade.

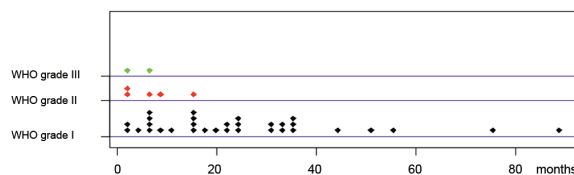


Fig. 3 Distribution of recurrent time by WHO grade.

12.8% compared with 3.5% in non-recurrent group (p -value = 0.039). The favorable outcome was higher in non-recurrent group 91.5% compared with 76.9% in recurrent group (p -value = 0.02483).

Discussion

The findings in the present study confirm the high incidence of intracranial meningiomas of the fourth to the sixth decades of life. Eighty percent of patients with meningiomas are women. Headache was the most common clinical presentation, which might be from dural invasion or relatively large tumor size resulted in increased intracranial pressure. The

Table 5. Surgical complications and clinical outcomes of the patients comparison between recurrent group (n = 39) and non-recurrent group (n = 142)

	Recurrence n = 39 (%)	Non-recurrence n = 142 (%)	p -value
Complications			
Hematoma	3 (7.7)	14 (9.9)	1
Infarction	4 (10.3)	11 (7.7)	0.743
Motor deficit	15 (38.5)	17 (12.0)	<0.001
Visual defect	5 (12.8)	2 (1.4)	0.006
Infection, meningitis	1 (2.6)	7 (4.9)	1
Death	5 (12.8)	5 (3.5)	0.039
Other (myocardial infarction, deep vein thrombosis, extracranial infections)	8 (20.5)	30 (21.1)	0.89
Glasgow outcome scale			
Death	5 (12.8)	5 (3.5)	<0.001
Vegetative state	0 (0)	1 (0.7)	
Severe disability	4 (10.3)	6 (4.2)	
Moderate disability	11 (28.2)	12 (8.5)	
Good recovery	19 (48.7)	118 (83.1)	
Outcomes			
Favorable outcome	30 (76.9)	130 (91.5)	0.02483
Unfavorable outcome	9 (23.1)	12 (8.5)	

large tumor size at presentation could be from medical service inaccessibility, low socioeconomic, or patient education problems. Median recurrent time was 21.6 months (range 2-89 months), recurrent-free survival at 5-year was 64% and median recurrent-free survival time was 88.6 months. These findings may guide timing and duration of clinical and imaging follow-up especially in the patients with headache at presentation, higher Simpson grade and WHO grade II and III.

Headache presenting symptom was found to be a factor of recurrence in the present study. It might occur from the rapid rate of tumor growth or the nature of microscopic invasion of the tumor. The correlation was still uncertain.

Highly suspicious of recurrence and rapid recurrent time in the patients with higher histological grade will guide for duration and frequency of serial clinical and imaging follow-up.

The authors reviewed and concluded the rate of recurrence according to extent of resection, recurrence free survival and mortality rate from previous studies^(10,12,13,16-18). From the classic paper of Simpson⁽¹⁰⁾, the recurrent rate were higher in more remaining residual tumor groups but in the present study and Chan et al⁽¹⁶⁾ found grade III resection had higher rate of recurrence than grade IV resection (grade III = 50% and grade IV = 37%). The possible explanation was not readily available but it might be from relatively few cases in grade III resection groups.

The recurrence of tumor was associated with higher rate of unfavorable neurological outcomes and increased mortality (Table 5) due to progression of neuronal injury after tumor recurrence and reoperation for tumor resection. The overall mortality rate was 5.5%⁽¹⁰⁾ and surgical mortality rate was 4.4%⁽⁸⁾, two died from advanced tumor recurrence.

Limitation

The present study is a single institute retrospective study. There were 15 missing data from 196 patients (7.65%). Extents of tumor resections were from individual surgeon's determination, which could be varied. The authors used post-operative imaging to confirm but in a small amount of cases, post-operative imaging were not performed within three months especially in Simpson grade I resection. The routine post-operative imaging protocol could be suggested but may increase the cost. The recurrent dates were documented by imaging study date in all patients with or without recurrent symptoms. That date may be

delayed for the exact recurrence date in prolonged symptomatic patient with tumor recurrence. Relatively short duration of follow-up may lead to missing the late recurrent group.

Conclusion

The baseline characteristics were not different from other reported studies. The wide range of timing of tumor recurrence (2-89 months) need both clinical evaluation and imaging study in short term and long term follow-up, especially in high risk group. The risk factors of recurrence were headache as presenting symptom, extent of resection and histological grading. The higher histological grade was carried out higher recurrent rate. The extent of resection according to Simpson grading, Simpson grade I and grade II the recurrent rate were low and Simpson grade III had higher recurrent rate than grade IV. Recurrent meningioma increased rate of morbidity such as motor deficit, visual defect and higher mortality rate.

What is already known on this topic?

The recurrent rate was high in the patients with incomplete tumor removal (high Simpson grade) and/or high histological grade of WHO classification. Many studies showed the recurrent rate in simple percent. However, there are only two studies to present with the recurrent free survival at 5-year, 80% and 93%, calculated by Kaplan-Meier survival analysis.

What this study adds?

We added our local data into the literature. This study showed that presentation with headache is one of risk factors of tumor recurrence but tumor size and location do not constitute the risk factor. In addition, we present the recurrent free survival at 5-year of 65% calculated by Kaplan-Meier survival analysis. Our recurrent free survival at 5-year was not as good as the other two studies. Nearly 30% of our cases have tumor diameter more than 6 cm. In addition, nearly half of our cases were in the sphenoid wing and parasagittal location that were the most common location of recurrence because of difficult approach to remove. The recurrent free survival at 5-year may guide timing and duration of postoperative imaging and clinical follow-up. The recurrent meningioma was related to higher rate of unfavorable outcomes and increased mortality rate.

Potential conflicts of interest

None.

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การกลับเป็นซ้ำหลังผ่าตัดของ *intracranial meningioma*: วิเคราะห์ปัจจัยที่มีผลต่อการกลับเป็นซ้ำและผลการรักษา

ภาควิชา ศัลยกรรมประสาท, โรงพยาบาลศิริราช, คณะแพทยศาสตร์ศิริราชพยาบาล, กรุงเทพมหานคร

วัตถุประสงค์: เพื่อวิเคราะห์อัตราการกลับเป็นซ้ำ ระยะเวลา และปัจจัยที่มีผลต่อการกลับเป็นซ้ำรวมถึงผลการรักษาในผู้ป่วย *intracranial meningioma* ที่ได้รับการรักษาด้วยการผ่าตัด

วัสดุและวิธีการ: เก็บรวบรวมข้อมูลจากเวชระเบียนในผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็น *meningioma* ในกะโหลกศีรษะที่ได้รับการรักษาด้วยการผ่าตัดที่มีผลพยาธิวิทยายืนยัน การวินิจฉัยการกลับเป็นซ้ำขึ้นกับอาการ และภาพถ่ายทางรังสีวิทยาระหว่างการตรวจติดตามอาการ ทำการวิเคราะห์อัตราการกลับเป็นซ้ำ ระยะเวลาการกลับเป็นซ้ำ ปัจจัยที่มีผลต่อการกลับเป็นซ้ำ และผลการรักษา ประเมินผลการรักษาด้วย *Glasgow outcome scale*

ผลการศึกษา: มีผู้ป่วยทั้งสิ้น 181 ราย เนื้องอกมีขนาดเฉลี่ย 4.9 เซนติเมตร (1.2-9 ซม.) ระยะเวลาในการติดตามการรักษาเฉลี่ย 32.3 เดือน ระยะเวลาการกลับเป็นซ้ำเฉลี่ย 21.6 เดือน และอัตราการกลับเป็นซ้ำทั้งหมดเท่ากับ ร้อยละ 21.5 รวมทั้งมีระยะปลอดโรค 5 ปี เท่ากับ ร้อยละ 65 ปัจจัยที่มีผลต่อการกลับเป็นซ้ำได้แก่ อาการปวดศีรษะเป็นอาการนำ ($p = 0.002$), ระดับขอบเขตการผ่าตัดตามแบบ *Simpson* เกรดสาม ($p = 0.012$), *Simpson* เกรดสี่ ($p < 0.001$) และ *Simpson* เกรดห้า ($p = 0.004$), ผลพยาธิวิทยาตามการแบ่งเกรดขององค์การอนามัยโลกเกรดสอง ($p = 0.004$) และเกรดสาม ($p < 0.001$) อัตราตายในกลุ่มที่มีการกลับเป็นซ้ำอยู่ที่ร้อยละ 12.8 เปรียบเทียบกับกลุ่มที่ไม่มีการกลับเป็นซ้ำร้อยละ 3.5 ($p = 0.039$) ผู้ป่วยที่ผลการรักษาน่าพอใจในกลุ่มที่ไม่มีการกลับเป็นซ้ำพบร้อยละ 91.5 เปรียบเทียบกับร้อยละ 76.9 จากกลุ่มที่มีการกลับเป็นซ้ำ ($p = 0.02483$)

สรุป: ปัจจัยเสี่ยงการกลับเป็นซ้ำได้แก่ อาการปวดศีรษะเป็นอาการนำ ระดับขอบเขตการผ่าตัดตามแบบ *Simpson grading* และผลชิ้นเนื้อตามการแบ่งเกรดขององค์การอนามัยโลก ระดับขอบเขตการผ่าตัดตามแบบ *Simpson grading* มีผลต่อการกลับเป็นซ้ำ เช่นเดียวกับการศึกษาในอดีต ผลพยาธิวิทยาที่มีเกรดสูงกว่าจะมีอัตราการกลับเป็นซ้ำที่สูงกว่าระยะเวลาการกลับเป็นซ้ำมีช่วงค่อนข้างกว้าง จำเป็นที่ต้องการการตรวจติดตามอาการและการถ่ายภาพทางรังสีวิทยาทั้งในระยะสั้นและระยะยาว โดยเฉพาะในกลุ่มที่มีความเสี่ยงสูงการกลับเป็นซ้ำเพิ่มอัตราการเกิดภาวะแทรกซ้อน และมีอัตราการตายที่สูงกว่า
