Predictors of Severe Complications in Intracranial Meningioma Surgery: A Population-Based Multicenter Study

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■ OBJECTIVE: **To investigate predictors of complications after intracranial meningioma resection using a standardized reporting system for adverse events.**

■ METHODS: **A retrospective review was conducted in a Scandinavian population−based cohort of 979 adult operations for intracranial meningioma performed at 3 neurosurgical centers with population-based referral between January 1, 2007, and June 30, 2013. Possible predictors of severe complications were identified and analyzed in univariable analyses. Variables with a *P* value < 0.10 were included in a multivariable model.**

■ RESULTS: **Severe complications were observed in 68 (7%) operations. Univariable analyses identified patient age >70 years (*P* < 0.001), male sex (*P* = 0.03), Charlson Comorbidity Index >1 (*P* = 0.02), Simpson grade >3 (*P* = 0.03), Karnofsky performance scale score <70 (*P* < 0.001), and duration of surgery >4 hours (*P* < 0.001) as significant predictors of severe complications. Age >70 (odds ratio = 2.5, *P* < 0.01), duration of surgery >4 hours (odds ratio = 3.2, *P* < 0.001), and Karnofsky performance scale score <70 (odds ratio = 2.5, *P* < 0.01) were independent predictors of severe complications in the multivariable regression analysis.**

■ CONCLUSIONS: **Severe complications after meningioma resection are more encountered often in elderly patients (>70 years old), dependent patients (Karnofsky performance scale score <70), and patients who underwent longer lasting surgery (>4 hours). Patient selection, including careful consideration of the individual risk-benefit ratio, is important in improving the safety of intracranial meningioma resection.**

INTRODUCTION

Intracranial meningiomas represent 30% of all primary intracranial tumors (31). As the oldest segment of the population continues to increase along with increased use of magnetic resonance imaging (MRI), the incidence of intracranial meningiomas is expected to increase (17, 29). In patients with a growing or symptomatic meningioma, craniotomy with tumor resection is usually the first-line treatment. Although surgical resection offers a potential cure and preservation or even improvement of neurologic function, it is associated with morbidity and mortality (10, 19). A standardized way of reporting adverse events was introduced for neurosurgical procedures in recent years (16). For meningioma surgery, standardized reports on complications are so far lacking. Most studies on complications and adverse events after meningioma surgery are single-institution series spanning previous decades with limited external validity and questionable relevance to contemporary microneurosurgical approaches. The results from these studies are varied and conflicting, possibly secondary to the patient selection, study length, and methodology (4, 10, 13, 20, 22, 30). Nevertheless, old age and reduced functional status have often been

Key words
- Charlson Comorbidity Index
- Complications
- Ibanez classification
- Karnofsky performance scale
- Meningioma
- Outcome

Abbreviations and Acronyms
CI: Confidence interval
KPS: Karnofsky performance score
MRI: Magnetic resonance imaging
OR: Odds ratio

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mentioned as predisposing factors to poor outcome after intracranial meningioma surgery (23). In this retrospective, population-based, multicenter study, we explored frequencies and predictors of severe complications occurring within 30 days after intracranial meningioma surgery using a standardized reporting form of adverse events.

MATERIALS AND METHODS

The Regional Committee for Medical and Health Research Ethics in Central Norway and the Regional Ethics Committee in Stockholm, Sweden, approved the study protocol.

Patients

All adult patients (≥18 years old) with a histologically confirmed meningioma treated with craniotomy and tumor resection in the period between January 1, 2007, and June 30, 2013, were eligible for inclusion. Patients operated with a transsphenoidal approach and patients undergoing biopsy only were excluded.

Patients from a consecutive population-based cohort at 3 neurosurgical departments were included. Statistics Norway and Statistics Sweden were used to estimate the mean population of the catchment areas of the hospitals in the study period. The study centers were University Hospital of North Norway (n = 466,699; 14% of study total [Statistics Norway]), St. Olavs University Hospital representing Central Norway (n = 673,874; 21% of study total [Statistics Norway]), and Karolinska University Hospital representing the greater Stockholm area and Gotland (n = 2,129,919; 65% of study total [Statistics Sweden]). The Scandinavian public health care system with regional neurosurgical centers and strict regional referral practice limits the possibility of referral bias and ensures a representative population-based study.

Treatment Characteristics

All patients were evaluated with contrast-enhanced MRI before surgery unless contraindicated. Steroids were administered to selected patients with tumor edema verified by preoperative MRI. Prophylactic anticonvulsants were not routinely administered. Tumor resection was performed using standard microneurosurgical techniques with additional frameless neuronavigation, intraoperative ultrasound, and electrophysiologic monitoring if deemed necessary. At Karolinska University Hospital in Sweden, cloxacillin 2 g was administered before surgery; cefalotin 2 g was the antibiotic of choice at both Norwegian neurosurgical centers.

Study Variables

Data were collected from electronic patient charts. Patient characteristics and preoperative status including Charlson Comorbidity Index (6) and Karnofsky performance scale (KPS) score (27) were registered. Tumor characteristics included location (falcine/parasagittal, convexity, sphenoid wing, olfactory/planum/sella, and infratentorial/other); duration of surgery as a marker of surgical difficulty grouped into <2 hours, 2–4 hours, and >4 hours; histopathologic grading (21); and Simpson grade of resection (28). Adverse events within 30 days were classified according to Ibanez et al. as follows: grade I, any non–life-threatening deviation from normal postoperative course treated without invasive procedures; grade II, complications requiring invasive management such as surgical, endoscopic, and endovascular procedures; grade III, life-threatening adverse events requiring treatment in an intensive care unit, subdivided into IIIa, complications involving single-organ failure, and IIIb, complications involving multiorgan failure; and grade IV, deaths as a result of complications (16).

Statistical Analysis

Outcome was classified in 2 clinically relevant subgroups: 1) patients with no or nonsevere complications (Ibanez grade I–II); 2) patients with major complications (Ibanez grade III–IV). We used quantile-quantile plots to test whether data were normally distributed. Categorical variables were assessed with χ^2 test. Univariable analyses included screening of all gathered outcome predictors, with age as a continuous variable, whereas all other predictors were categorical. Outcome predictors with a P value ≤ 0.1 were included in a final multivariable regression model. To test if the model was robust, the variables were also analyzed with full information (i.e., no categorization). $P \leq 0.05$ was considered statistically significant. We used SPSS for Windows version 18.0 (SPSS, Inc., Chicago, Illinois, USA) to analyze data.

RESULTS

We identified 979 operations with craniotomy and resection of intracranial meningioma performed during the study period. There were 123 operations (13%) performed at University Hospital of Northern Norway, 230 operations (23%) performed at St. Olavs University Hospital, and 626 (64%) operations performed at Karolinska University Hospital. The difference between expected proportion of caseload compared with the actual caseload was not significant ($P = 0.93$). Crude incidence rates of craniotomy and meningioma resection were 4.1/100,000/year at University Hospital of North Norway, 5.3/100,000/year at St. Olavs University Hospital, and 4.5/100,000/year Karolinska University Hospital.

Patient Characteristics

Mean patient age was 57.1 years ± 12.5, and 675 (69%) patients were female. In 911 (93%) operations, patients experienced no or nonsevere complications (Ibanez grade I–II); in 68 (7%) operations, patients experienced severe complications or death (Ibanez grade III–IV). There was no difference in severe complications between centers (7%, 4%, and 8%, $P = 0.18$). The overall 30-day mortality was 6 of 979 (0.6 %), and 4 of 6 deaths were due to surgical complications. Baseline and treatment characteristics for the 2 complications groups are presented and compared in Table 1. Patients with severe complications were older, were more often men, had more comorbidities, had lower functional status, more often underwent subtotal resection, and underwent longer duration surgery.

Ordinal variables may be difficult to interpret in multivariable analyses because each step may not be uniform; we used age >70 years and duration of surgery >4 hours as categorical variables because there were marked differences in the proportion between groups (Table 1). As seen in Figure 1, the independent predictors for experiencing severe complications were age >70 years ($P \leq 0.01$, odds ratio [OR] = 2.5, 95% confidence interval [CI] = 1.3–4.6), duration of surgery >4 hours ($P < 0.001$, OR = 3.2,

Table 1. Baseline Characteristics of Meningioma Operations ($n = 979$) Grouped According to Occurrence of No or Nonsevere versus Severe Complications Within the 30-Day Postoperative Period

	No or Nonsevere Complications (Ibanez I–II) (n = 911; 93%)	Severe Complications (Ibanez III–IV) (n = 68; 7%)	P Value
Age (years), mean (SD)	56.7 (12.5)	62.6 (11.4)	<0.001*
Age group			<0.001*
18–40	96 (11%)	1 (2%)	
41–50	194 (21%)	12 (18%)	
51–60	243 (27%)	13 (19%)	
61–70	263 (29%)	22 (32%)	
>70	115 (13%)	20 (29%)	
Female	636 (70%)	39 (57%)	0.03*
CCI >1	111 (12%)	15 (22%)	0.02*
KPS score ≥70 (n = 976)	809 (89%)	48 (71%)	<0.001*
Location (n = 978)			0.153
Falx and parasagittal	238 (26%)	13 (19%)	
Sphenoid wing	157 (17%)	11 (16%)	
Convexity	242 (27%)	14 (21%)	
Olfactory/planum/sella	143 (16%)	14 (21%)	
Other infratentorial	130 (14%)	16 (24%)	
Duration of surgery, hours (n = 976)			< 0.001*
<2	105 (12%)	0 (0%)	
2–4	349 (38 %)	18 (27 %)	
>4	454 (50 %)	50 (74 %)	
Previous meningioma surgery	137 (15%)	14 (21%)	0.22
WHO grade I (n = 971)	779 (86%)	55 (81%)	0.22
Simpson grade 1–3 (n = 975)	636 (70%)	39 (57%)	0.03*
Edema (n = 975)	418 (46%)	38 (56%)	0.12
Proximity to venous sinus (n = 978)	308 (34%)	25 (37%)	0.62
LMWH prophylaxis initiated within 24 hours after surgery (n = 971)	587 (65%)	49 (72%)	0.24

CCI, Charlson Comorbidity Index; KPS, Karnofsky performance scale; WHO, World Health Organization; LMWH, low-molecular-weight heparin.
*Included in multivariable analyses (n = 979 unless otherwise specified).

95% CI = 1.7–5.7), and KPS score <70 (P < 0.01, OR = 2.5, 95% CI = 1.3–4.5).

In the sensitivity analysis using the same selection (age, sex, comorbidity, functional status, resection grade, and duration of surgery), but with all information from the variables, age (P ≤ 0.01, OR = 1.04, 95% CI = 1.01–1.06), duration of surgery per started hour (P < 0.001, OR = 1.19, 95% = CI 1.10–1.28), and each increasing step in KPS score (P < 0.001, OR = 0.97, 95% CI = 0.96–0.98) were independently associated with severe complications. Charlson Comorbidity Index (P = 0.94, OR = 1.01, 95% CI = 0.80–1.27), male sex (P = 0.12, OR = 1.53, 95% CI = 0.90–2.62), and Simpson grade (P = 0.56, OR = 1.06, 95% CI = 0.86–1.31) were not independently associated with severe complications.

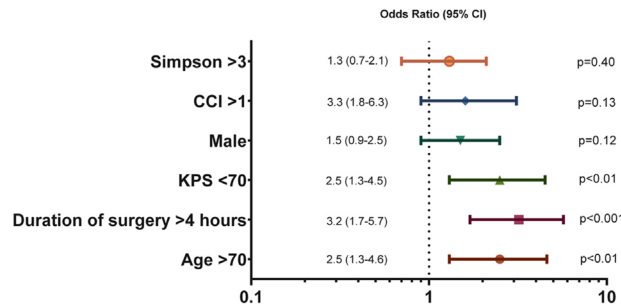

Figure 1. Multivariable regression analysis, including univariable predictors with *P* value ≤ 0.1. CCI, Charlson comorbidity index; KPS, Karnofsky performance scale. . GraphPad Prism version 5.0 (GraphPad Software, Inc., La Jolla, California, USA) was used to construct this figure.

Based on our results, we created a risk score prediction model encompassing the variables 1) age >70 years, 2) duration of surgery >4 hours, and 3) KPS score <70, with each individual variable having equal significance giving a 4-tier scoring system. Depending on the number of variables present, patients were subdivided into categories with 1) low, 2) medium-low, 3) medium-high, and 4) high risk of encountering a severe complication. Increasing score was significantly associated with severe complications (P < 0.001). The analysis revealed a risk of encountering severe complications when none of the variables were present of 2.2% (low risk); with 1 variable present, 7.6% (medium-low risk); with 2 variables present, 14.2% (medium-high risk); and with all 3 variables present, 46.7% (high risk).

In addition, we described the subgroup of patients experiencing the most severe complications (Ibanez grade IIIb and grade IV). Table 2 provides an overview of patient characteristics; tumor localization, lesion size, and topography according to Sawaya et al. (26); and treatment characteristics including perioperative blood loss and whether hemodynamic conditions during surgery were uneventful or if any unexpected events occurred (eventful). Also included is whether significant postoperative hematoma contributed to the complications. Other frequent complications were respiratory insufficiency and cerebral infarctions. Causes of death were large myocardial infarction (patients 1 and 9), massive intraoperative bleeding and edema (patients 5 and 7), herniation secondary to edema (patient 6), and cerebral infarction with multiorgan failure (patients 11 and 12).

Table 2. Characteristics of 25 Patients Who Experienced the Most Severe Complications—Multiorgan Failure and Perioperative Death (Ibanez Grade IIIb and IV)

Number	Age (years)	Sex	CCI	KPS Scale	Hours (t)	Simpson Grade	Location	Hematoma	Diameter (cm)	Sawaya Grade*	Blood Loss (mL)	OR†
1‡	**72**	F	3	**50**	**>4**	**4**	Falx§	No	**3**	1	200	U
2	**71**	F	0	90	**>4**	**4**	Sphenoid	Yes	**5**	3	400	U
3	69	M	0	80	**>4**	**2**	Olfactory‖	Yes	**4**	2	1500	U
4	**74**	M	2	**20**	**>4**	**4**	Other	Yes	**2**	3	1400	E
5‡	51	F	0	70	**>4**	**4**	Falx	Yes	**8**	1	10000	E
6‡	**78**	F	0	**50**	2–4	2	Falx	No	3	1	300	U
7‡	55	F	2	70	**>4**	4	Sphenoid	No	**3**	3	2900	E
8‡	**72**	F	1	90	**>4**	4	Other	No	**3**	2	1100	U
9‡	**77**	M	0	70	**>4**	4	Falx	No	**4**	2	400	U
10	**79**	M	1	**60**	2–4	1	Convexity	No	4	1	700	U
11	**77**	F	0	**60**	**>4**	1	Sphenoid	Yes	**3**	1	200	U
12	**74**	F	2	**60**	2–4	4	Falx	Yes	3	2	400	U
13	61	F	0	70	**>4**	4	Falx	Yes	**6**	2	2200	U
14	61	F	0	70	2–4	4	Other	Yes	4	1	800	U
15	63	M	0	90	**>4**	4	Sphenoid	Yes	**5**	1	2200	U
16	56	F	0	**20**	2–4	3	Other	Yes	5	1	700	U
17	56	F	0	70	2–4	1	Falx	No	5	1	800	U
18	54	M	0	**10**	**>4**	1	Convexity	No	**7**	1	3000	E
19	**71**	F	2	**50**	**>4**	4	Other	No	**4**	2	2150	U
20	65	M	1	100	2–4	2	Sphenoid	No	4	1	1200	U
21	64	F	2	**20**	**>4**	4	Other	No	**5**	2	500	U
22	63	M	0	100	**>4**	1	Olfactory	No	**3**	1	200	E
23	55	M	0	**40**	**>4**	4	Other	No	**4**	2	650	U
24	47	F	0	70	**>4**	4	Other	No	**5**	2	700	U
25	46	F	0	80	**>4**	4	Other	No	**4**	2	1450	U

Risk factors independently associated with severe complications, as shown in **Figure 1**, are in bold type.
CCI, Charlson Comorbidity Index; KPS, Karnofsky performance scale; OR, odds ratio; F, female; M, male; t, hours of surgery, from skin to skin.
*Tumor topography according to Sawaya grading: grade 1, noneloquent brain; grade 2, near-eloquent brain; and grade 3, eloquent brain.
†Hemodynamic conditions during surgery, classified as eventful (E) or uneventful (U).
‡Patient died secondary to complications (Ibanez grade IV); the other patients experienced grade IIIb complications.
§Falx and parasagittal.
‖Olfactory, planum, and sella.

DISCUSSION

In this large, multicenter, population-based study of patients with meningioma undergoing tumor resection, we found that 7% of patients experienced severe complications (i.e., resulting in death or need of treatment in an intensive care unit). In a multivariable regression analysis, we found that age >70 years, KPS score <70, and duration of surgery >4 hours were independent risk factors for severe perioperative complications. These findings should aid in patient selection and allow for a more reliable comparison of results across neurosurgical centers.

Our study gives a reliable population-based estimate of severe complications in need of intensive care unit treatment. The defined geographic catchment areas and a strong tradition of regional referral practice ensure population-based data. Also, the observed surgical rates did not differ significantly from the expected rates based on the population of the catchment area. The crude incidence rates of craniotomy and meningioma resection in our 3 participating centers were similar, further strengthening the population-based nature of this study. Because of homogeneous data in a large multi-institutional dataset, we decided to create a score predicting severe complications (defined as Ibanez grade III—IV). Based on this simple score, there seems to be a large and synergistic effect of the factors age >70 years, KPS score <70, and surgery duration >4 hours. The presence of 1 factor increased the risk of experiencing a severe complication from 2.3% to 7.6%, whereas the presence of all factors increased the risk of experiencing a severe complication to 46.7%. This should serve as an explorative dataset, and the risk score should be validated in an independent dataset. If this score is validated, it would be a simple and useful score to improve patient selection to minimize serious adverse events.

To our knowledge, no other studies have evaluated risk of meningioma surgery using a standardized reporting system. However, increasing age, reduced functional status, and comorbidity were previously reported to increase risk of bad outcome of meningioma resection (5, 8, 13, 14). We additionally report that the duration of surgical procedures seems to be important. In this study, we considered duration of surgery as a marker of surgical difficulty, an important factor that is otherwise difficult to control for. However, we appreciate that a potential important confounder equally difficult to control is surgeon skill (2). Because we are unable to distinguish between factors prolonging surgery, we think that further speculation on these factors is not indicated. The link between duration of surgery and complications may be obvious in cases that are prolonged because of occurrence of intraoperative complications. However, longer lasting surgery may not be related only to intracranial complications. There is also a likely association with nonsurgical complications, such as pneumonia, urinary tract infection, and deep vein thrombosis or pulmonary embolism. Also, surgical site infections could be caused by longer duration of surgery; however, among the patients with the most severe complications in this study (Ibanez grade IIIb and IV), only 1 patient had a regional infection (meningitis). Given the strong association with complications, anticipated duration of surgery should be considered as an important factor in preoperative risk assessment, and if the benefit of surgery is not obvious, one should reconsider surgery or the surgical strategy in elderly patients with surgically challenging meningiomas (12). Conventional radiotherapy or radiosurgery could be considered the primary therapeutic option in selected elderly patients without symptoms related to local or global mass effect, with promising results reported in the literature for tumor control and the risk of complications (9, 15, 18).

As the elderly segment of the population continues to increase along with the availability of MRI, management of elderly patients with intracranial meningioma will be an increasingly common challenge in neurosurgical practice in the years to come. When interpreting the findings of the present study, it is necessary to acknowledge that the indication for meningioma resection differs among age groups. In younger patients, surgical resection offers the chance of cure and is often recommended even for patients with smaller and nonsymptomatic meningiomas, especially if growth is demonstrated on subsequent imaging. In elderly patients, conservative treatment is often recommended even in cases of larger, symptomatic meningiomas. If conservative treatment fails (i.e., severe symptoms develop), surgery is offered. The increased surgical risks reported in elderly patients may at least be partially explained by the higher incidence of large, symptomatic meningiomas in this patient group.

The standardized Ibanez grading system for reporting operative complications in neurosurgery was adapted from other medical fields. It is important that such a system is implemented and validated in neurosurgery so that subjective interpretations of surgical negative outcomes can be minimized (7, 24, 25). If patient referral and selection are fairly similar, a standardized system allows for more reliable comparisons among centers (7, 11), which can improve patient safety and quality of neurosurgical care (1, 3). To our knowledge, our population-based study is the first to implement this standardized classification system of operative complications to identify and verify risk factors for intracranial meningioma resection. Because the results are in accordance with most of the existing relevant literature, we also validate the Ibanez classification for this purpose.

Although its retrospective nature and short follow-up time are limitations of the present study, this study illustrates the importance of meticulous preoperative preparations and careful consideration in whether or not to offer surgery to patients with increased risk of complications. However, a standardized way of reporting adverse events may not reveal the entire spectrum of disability induced by the surgery. For example, cerebral infarction causing significant disability may be classified as a grade I complication, whereas an otherwise uncomplicated cerebrospinal fluid leak treated with extra stitches or lumbar drain is a grade II complication. However, we believe that the drawbacks of this reporting system are outweighed by the advantages of a standardized assessment allowing more reliable comparisons.

CONCLUSIONS

Patient selection, including careful consideration of the individual risk-benefit ratio, is important in improving the safety of intracranial meningioma resection. This study evaluated predictors of severe perioperative complications in a Scandinavian population—based cohort of patients with meningioma. There was increased risk of severe complications in elderly patients, patients with poorer functional status, and patients who underwent longer lasting operations. The Ibanez grading scale seems to be a feasible method for standardized reporting and risk assessment in meningioma surgery.

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