Risk Factors for High-Grade Meningioma in Brain and Spine: Systematic Review and Meta-analysis

Hong Kyung Shin, Jin Hoon Park, Young Hyun Cho, Young-Hoon Kim, Seok Ho Hong, Jeong Hoon Kim, Sung Woo Roh, Sang Ryong Jeon

■ BACKGROUND: **Histologic grade has important implications for the management in meningioma. It is important to understand the risk of high-grade meningioma (grades II and III). In this article, we systematically reviewed the histologic grade of meningioma depending on the location and sex and its relationship with recurrence.**

■ METHODS: **The PubMed and Embase databases were systematically searched until February 4, 2020. We included studies that were not restricted to specific anatomic locations, histologic grade, or the sizes of the tumors. The proportion of high-grade meningiomas depending on the location and sex and the odds ratio (OR) of recurrence were pooled using a random-effects model.**

■ RESULTS: **Outcome data were analyzed for 20,336 tumors from 34 studies. We found different proportions of high-grade meningiomas in the brain (12.8%) (95% confidence interval [CI], 10.5%—15.1%) versus the spine (2.4%) (95% CI, 1.0%—3.7%) ($P < 0.01$). Skull base meningiomas (8.7%) (95% CI, 5.8%—11.6%) had a lower proportion of high-grade meningiomas than non—skull base meningiomas (16.5%) (95% CI, 11.9%—21.1%) ($P < 0.01$). In addition, high-grade meningiomas were more likely to occur in male patients (18.0%) (95% CI, 10.1%—25.9%) than female patients (7.0%) (95% CI, 3.5%—10.6%) ($P = 0.01$). Higher rates of recurrence (OR = 13.83) were confirmed for high-grade meningiomas than grade I meningiomas (95% CI, 4.10—46.65) ($P < 0.01$).**

■ CONCLUSIONS: **This meta-analysis found that intracranial, nonskull base, and male sex are risk factors for high-grade meningioma, and high-grade meningioma had a much higher recurrence rate as compared with grade I meningioma.**

INTRODUCTION

Meningiomas are the most common primary tumor of the central nervous system, and intracranial meningiomas account for about one third of primary intracranial tumors.[1,2] Spinal meningiomas are relatively rare, accounting for 1.2%—12% of central nervous system meningiomas and 25%—45% of all spinal tumors.[3,4] Most intracranial meningiomas are supratentorial, and only 8%—10% are located in the posterior fossa.[5] In the spine, most meningiomas are located at the thoracic level.[6] The incidence of meningioma increases with age, dominantly occurring in women in the sixth and seventh decades of life. The common presenting symptoms of intracranial meningioma are headaches and seizures, and skull base meningioma is more likely to accompany the focal neurologic deficits such as hearing loss and limb weakness.[7-9] The symptoms of spinal meningioma are usually limb paresthesia, weakness, and gait disturbance.[4]

About 90% of meningiomas are histologically benign (grade I), whereas 5%—7% are atypical (grade II) and 1%—3% are anaplastic (grade III).[10] High-grade meningiomas (grades II and III) are known to have malignant potential.[11,12] Tumor recurrence rates depend on the histologic grade and are 3%—20% for grade I, 30%—40% for grade II, and 70%—90% for grade III.[13,14] Many studies have evaluated the risk factors for recurrence and a higher grade.[15-17] Some studies have reported that a non—skull base location and male sex might be risk factors for high-grade

Key words
- High-grade meningioma
- Meta-analysis
- Recurrence
- Risk factor

Abbreviations and Acronyms
CI: Confidence interval
OR: Odds ratio
WHO: World Health Organization

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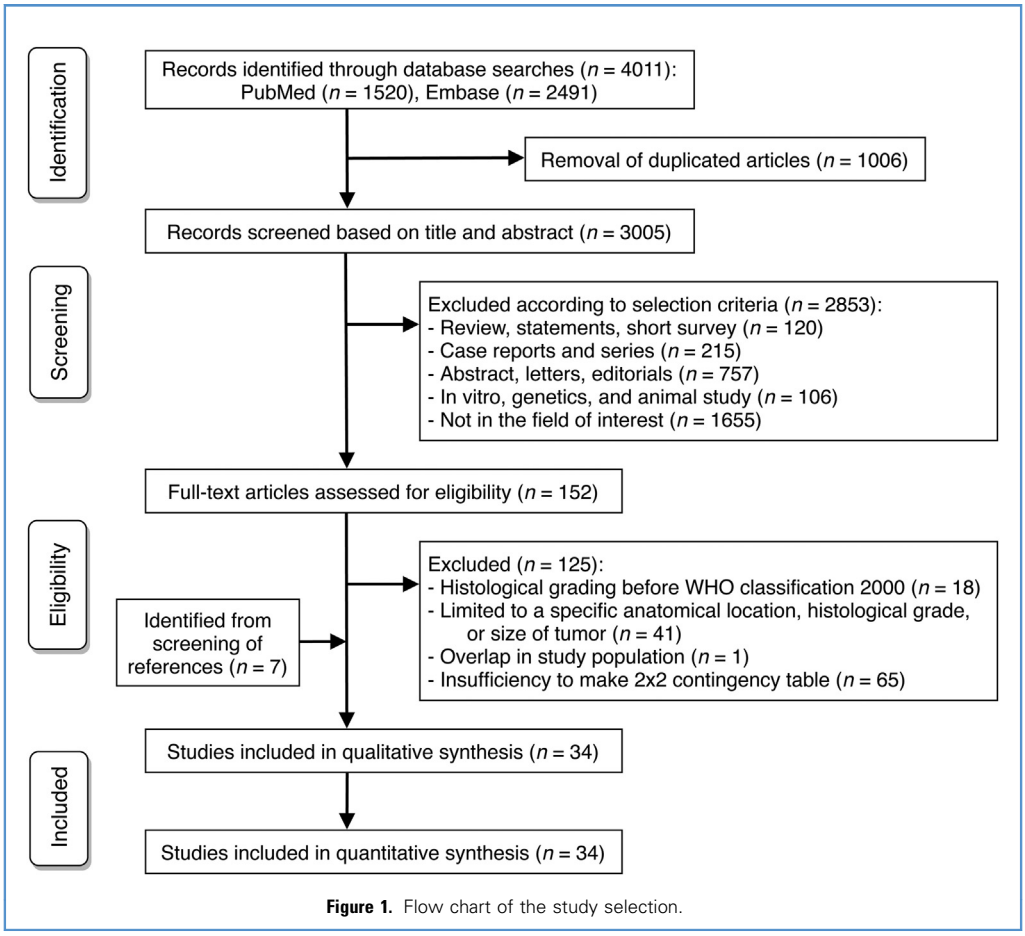

Figure 1. Flow chart of the study selection.

meningioma.[1,17,18] Another study suggested that spinal meningiomas tend to have less aggressive behavior compared with intracranial meningiomas.[19]

In this study, we aimed to perform a systematic review and meta-analysis of the published literature to delineate whether the histologic grade of meningiomas differs between the brain and spine and the relationships among recurrence, location, and sex.

MATERIALS AND METHODS

This study was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20] We performed a systematic review and meta-analysis of clinical studies concerning the epidemiologic data of meningiomas of the brain and spine.

Search Strategy

We searched records in PubMed and Embase from their inception through February 4, 2020. Search queries included synonyms and related terms for meningioma, World Health Organization (WHO), and grade as follows: (meningioma OR MGM) AND (WHO OR "World Health Organization") AND (grade OR Gr). In addition, the reference lists of the identified articles were checked to find additional relevant papers. There were no language restrictions on study eligibility. The literature search and selection were performed independently by 2 reviewers. Any discrepancies among the reviewers were solved through consensus and discussion.

Study Selection

The following inclusion criteria were applied: 1) histologically proven meningioma; 2) studies that were not limited to specific anatomic locations, histologic grade, or sizes of the tumors; 3) histologic grading after WHO classification 2000; and 4) sufficient information available to make 2 × 2 contingency tables. Non-original articles were excluded, and only the largest study was included for overlapping study populations.

Data Extraction and Quality Assessment

The following study and clinicopathologic characteristics were extracted using a standardized form: the study characteristics included the study author, publication year, country, and number of patients, and the clinicopathologic characteristics included the patient age, sex, WHO grade according to the tumor histology, location of the tumor, and recurrence during follow-up. The methodologic quality of the included studies was assessed using

Table 1. Baseline Characteristics of the Included Studies

Authors and Year	WHO Grade Classification	Country	Location	Number of Patients		Histologic Grade		Age (Mean)	Sex	
				Subtotal	Total	Grade I	High Grade		Male	Female
Amano et al., 2018[23]	2016	Japan	Brain	138	138	108	30	66.2	39	99
Barresi et al., 2012[33]	2007	Italy	Spine	58	58	55	3	59.2	10	48
Bayoumi et al., 2020[34]	2016	Turkey	Spine	61	61	57	4	60.5	13	48
Boström et al., 2008[35]	2007	Germany	Spine	61	61	61	0	61	11	50
Celtikci et al., 2018[24]	2007	Turkey	Brain	448	448	336	112	NR	NR	NR
Cornelius et al., 2013[45]	2007	Germany	Brain	1663	1663	1580	83	54.8	369	1294
Davies et al., 2017[36]	2016	UK	Spine	31	31	29	2	NR	NR	NR
Ding et al., 2014[25]	2007	China	Brain	93	93	89	4	NR	30	63
Ehresman et al., 2018[26]	2016	USA	Brain	572	572	534	38	54.9	153	419
Foda et al., 2019[2]	2016	Egypt	Brain	120	134	120	0	NR	28	92
			Spine	14		14	0	NR	3	11
Hoefnagel et al., 2014[27]	2007	The Netherlands	Brain	581	581	468	113	56.2	180	401
Hua et al., 2018[4]	2016	China	Brain	9806	10289	9263	543	53.8	2873	6933
			Spine	483		461	22	53.8	99	384
Hwang et al., 2016[46]	2007	USA	Brain	144	144	118	26	55.5	40	104
Kane et al., 2011[18]	2000	USA	Brain	378	378	309	69	54	100	278
Kasuya et al., 2006[16]	2000	Japan	Brain	342	342	296	46	NR	89	253
Kasuya et al., 2012[28]	2007	Japan	Brain	132	132	120	12	NR	NR	NR
Ko et al., 2007[29]	2000	Korea	Brain	487	487	436	51	NR	NR	NR
Kuo et al., 2019[30]	2016	Taiwan	Brain	77	77	61	16	NR	32	45
Liang et al., 2014[47]	2007	China	Brain	1239	1239	1048	191	51.8	355	884
Lin et al., 2014[31]	2007	Taiwan	Brain	120	120	90	30	58.6	36	84
McGovern et al., 2010[17]	2000	USA	Brain	187	199	164	23	NR	NR	NR
			Spine	12		11	1	NR	NR	NR
Moradi et al., 2008[12]	2007	Iran	Brain	378	378	329	49	49.1	140	238
Mubeen et al., 2019[37]	2007	India	Brain	205	254	180	25	NR	80	125
			Spine	49		49	0	NR	3	46
Nakamura et al., 2012[38]	2007	Japan	Spine	68	68	67	1	56	12	56
Raco et al., 2017[39]	2007	Italy	Spine	173	173	170	3	55.6	35	138
Riad et al., 2013[40]	2007	France	Spine	15	15	15	0	67.6	2	13
Sade et al., 2007[1]	2000	USA	Brain	718	794	656	62	NR	NR	NR
			Spine	76		75	1	NR	NR	NR
Sandalcioglu et al., 2008[41]	2007	Germany	Spine	131	131	129	2	69	17	114
Sayagués et al., 2006[19]	2000	Spain	Brain	141	155	127	14	58	49	92
			Spine	14		14	0	64	1	13
Schaller et al., 2005[42]	2000	Germany	Spine	33	33	33	0	63	3	30
Setzer et al., 2007[43]	2000	USA	Spine	80	80	69	11	61.9	22	58

WHO, World Health Organization; NR, not reported.

Continues

Table 1. Continued

Authors and Year	WHO Grade Classification	Country	Location	Number of Patients		Histologic Grade		Age (Mean)	Sex	
				Subtotal	Total	Grade I	High Grade		Male	Female
Sicking et al., 2018[48]	2016	Germany	Brain	817	817	708	109	58	237	580
Stenzel et al., 2004[32]	2000	Germany	Brain	152	152	121	31	NR	NR	NR
Zham et al., 2016[44]	2007	Iran	Spine	39	39	34	5	51.6	14	25

WHO, World Health Organization; NR, not reported.

the modified form of the Newcastle-Ottawa Scale for nonrandomized studies (Appendix).[21] Data extraction and quality assessment were independently performed by 2 reviewers; any disagreements were resolved by discussion.

Statistical Analysis

To analyze the relationship regarding pooled outcomes, we calculated the proportion and odds ratio (OR) with 95% confidence interval (CI) for comparative studies, using 2 × 2 tables. If there was no event in the groups (i.e., a "zero cell" in the 2 × 2 table), 0.5 was added to each cell of the table (continuity correction) so that the OR could be calculated. The proportions and ORs were meta-analytically pooled using a random-effects model (DerSimonian-Laird method) for calculating weights. Heterogeneity among the results of the individual studies was evaluated with the Cochran Q test and the Higgins I^2 test ($I^2 > 50\%$ was used as a threshold to indicate significant heterogeneity).[22] Subgroup analyses and metaregression were performed to investigate the possible causes of heterogeneity using several clinically relevant covariates. All tests were 2-sided, and a P value <0.05 was considered statistically significant. Statistical analyses were performed with R software (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Literature Search

An initial literature search using the subject headings yielded 1520 studies in PubMed and 2491 studies in Embase. Among these 4011 studies, 1006 were duplicates and were therefore removed. After screening the remaining 3005 titles and abstracts, 2853 were excluded according to the selection criteria. Full-text reviews were performed for the remaining 152 studies, and 125 were excluded for the following reasons: histologic grading before WHO classification 2000 ($n = 18$), limited to a specific anatomic location, histologic grade, or size of tumor ($n = 41$), overlap in study population ($n = 1$), and insufficiency to make 2 × 2 contingency table ($n = 65$). Seven papers were added during a manual screening of references. Finally, a total of 34 studies were included in the meta-analysis.[1,2,4,12,16-19,23-48] Detailed results of the selection process are shown in Figure 1.

Study Characteristics

The baseline characteristics of the included studies are summarized in Table 1. All included studies were retrospective. Overall, the studies included 20,336 meningiomas (18,938 meningiomas in the brain and 1398 meningiomas in the spine). Among the 34 articles we identified, for histologic grading, 8 studies used the 2016 WHO guidelines, 17 the 2007, and 9 the 2000. Six studies investigated meningiomas in both the brain and spine, 17 included only those in the brain, and 11 included only those in the spine.

Quality Assessment

The results of the quality assessment with the modified form of the Newcastle-Ottawa Scale for nonrandomized studies appear in Supplementary Table S1. The included studies had a low to moderate risk of bias in terms of sample representativeness, sample size, unspecified diagnosis, ascertainment of the WHO grade, and quality of the descriptive statistics reporting. Specifically, all studies (34/34) fulfilled the criterion for sample representativeness, 67.6% (23/34) met the sample size criterion, 94.1% (32/34) met the unspecified diagnosis criterion, 100% (34/34) established the ascertainment of WHO grade criterion, and 44.1% (15/34) met the criterion for quality of descriptive statistics reporting.

Proportion of High-Grade Pathology in Brain/Spine

Thirty-four studies investigated the proportion of high-grade meningiomas in the brain and/or spine. For all 34 studies combined, the pooled proportion of high-grade meningioma was 9.0% (95% confidence interval [CI], 7.3–10.7%). The subgroup analysis showed that the pooled proportion for high-grade meningioma was higher in the brain than in the spine (proportion, 12.8%; 95% CI, 10.5–15.1% and proportion, 2.4%; 95% CI, 1.0–3.7%, respectively), and this was statistically significant ($P < 0.01$) (Figure 2).

Intracranial Location

Eight studies assessed the proportion of high-grade meningiomas in both skull base and non–skull base locations. For all 8 studies, the pooled proportion of high-grade meningiomas in the brain was 13.1% (95% CI, 9.8–16.3%). The subgroup analysis showed that the proportion of high-grade meningiomas was lower in skull base than non–skull base tumors (proportion, 8.7%; 95% CI,

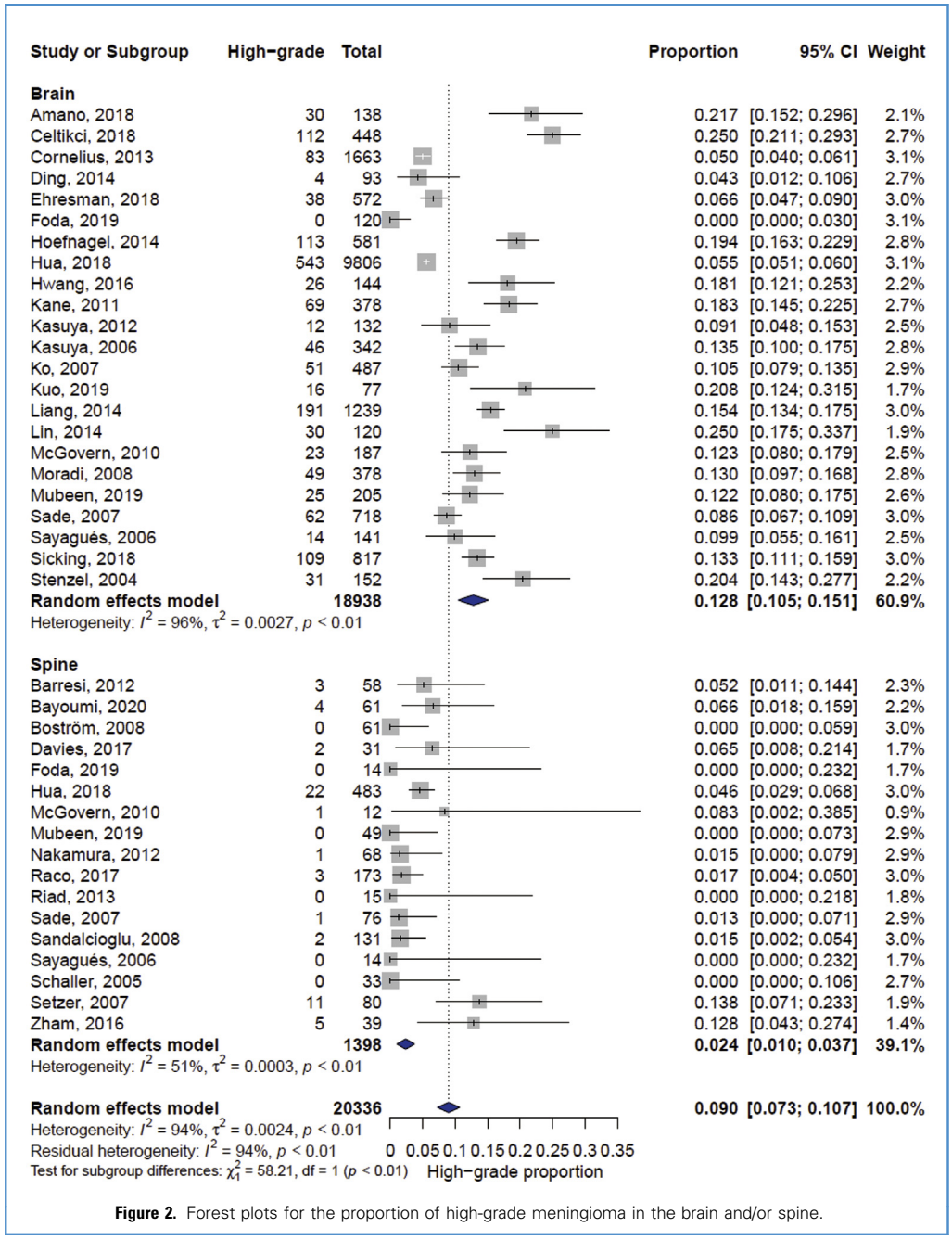

Figure 2. Forest plots for the proportion of high-grade meningioma in the brain and/or spine.

5.8—11.6% and proportion, 16.5%; 95% CI, 11.9—21.1%, respectively), and this was statistically significant (P < 0.01) (Figure 3).

Sex

Ten studies evaluated the proportion of high-grade meningioma in male and female patients. The subgroup analysis suggested that the proportion of high-grade meningiomas was higher in male than female patients (proportion, 18.0%; 95% CI, 10.1%—25.9% and proportion, 7.0%; 95% CI, 3.5%—10.6%, respectively), and this was statistically significant (P = 0.01) (Figure 4).

Twenty-seven articles assessed the female proportion of meningiomas in the brain and/or spine. Meta-analytic pooling of all 27 studies regarding the female proportion indicated the pooled proportion was 74.8% (95% CI, 72.6%—77.1%). The subgroup analysis showed that the pooled estimate for female proportion was lower in the brain than the spine (proportion, 70.6%; 95% CI, 68.6%—72.7% and proportion, 82.8%; 95% CI, 79.1%—86.5%,

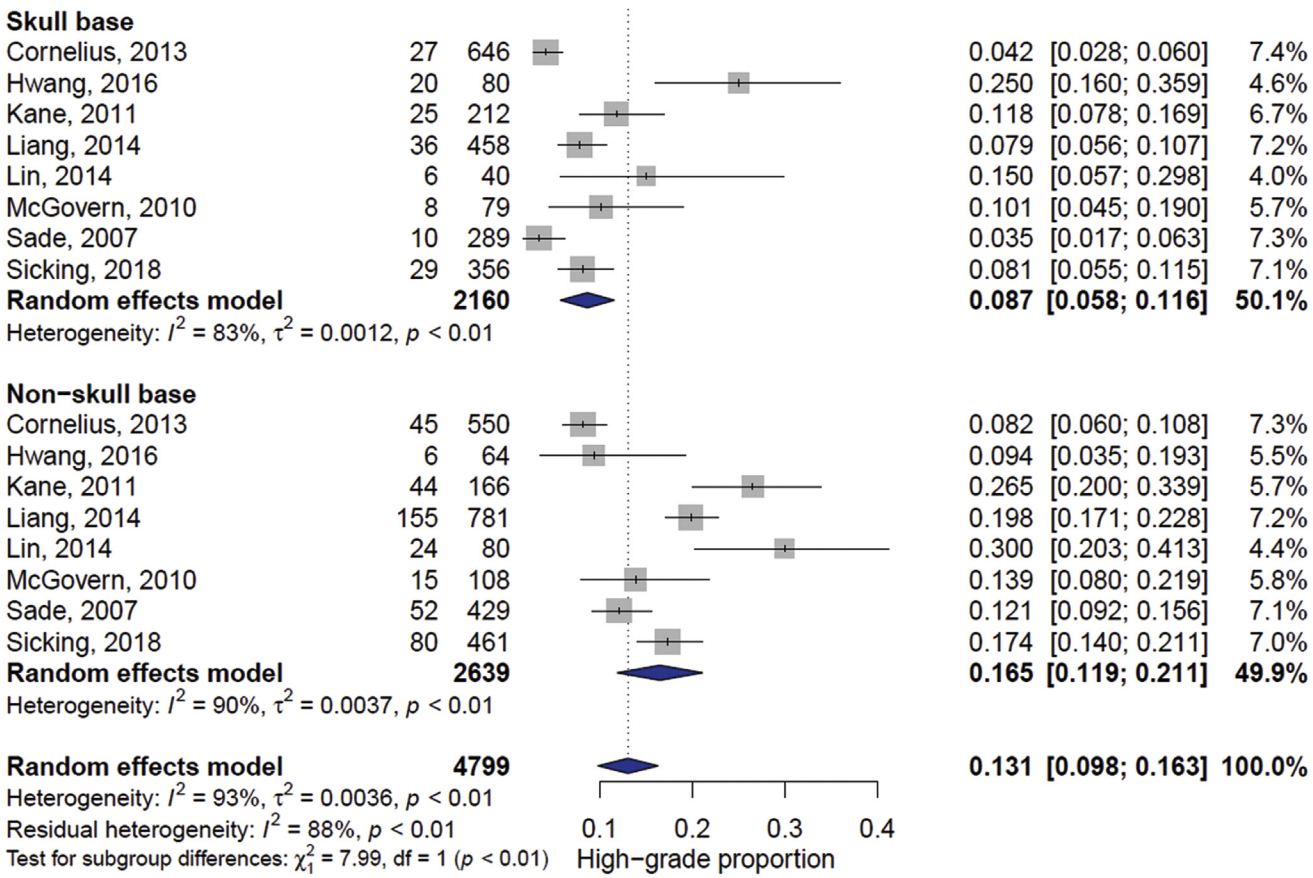

Figure 3. Forest plots for the proportion of high-grade meningioma in the skull base and non−skull base.

respectively), and this was statistically significant (P < 0.01) (Figure 5).

Odds Ratio of Recurrence (Depending on histologic Grade)

Seven studies reported the OR of recurrence in the brain or spine, depending on the histologic grade. Meta-analytic pooling of all 7 studies indicated that the pooled OR of recurrence in high-grade meningiomas compared with grade I meningiomas was 13.83 (95% CI, 4.10−46.65, P < 0.01). Subgroup analysis suggested that the OR of recurrence was 7.13 (95% CI, 2.45−20.70) in the brain and 31.63 (95% CI, 2.31−432.49) in the spine, though the subgroup difference was not statistically significant (P = 0.30) (Figure 6).

Meta-Regression

A meta-regression analysis revealed a statistically significant association between the proportion of male sex and the proportion of high-grade meningiomas (P < 0.001). The equation derived from the meta-regression analysis was $Y = -0.0483 + 0.5470 \times X$, where Y is the proportion of high-grade meningiomas and X is the proportion of male sex. In other words, there was a 0.54% increase in the proportion of high-grade meningioma for every 1% increase in the proportion of male patients (Figure 7).

DISCUSSION

Identifying the histologic grade of a meningioma is crucial for predicting outcomes, and it allows for planning the most appropriate management for individual patients. Although the specific proportion of high-grade meningiomas was different in each study, many studies have reported a different proportion of histologic grade depending on the location.[1,13,18,31,46,49] The reported rates of high-grade meningiomas are variable: 8.2% to 30.0% in non−skull base locations versus 3.5% to 25.0% at the skull base[1,17,18,31,45,46,48] but lower in the spine (0%−13.8%).[1,2,4,17,19,33-44] In this meta-analysis of 34 studies involving 20,336 meningiomas, we found a preponderance of high-grade meningiomas in the brain (12.8%) versus the spine (2.4%) and in non−skull base locations (16.5%) versus the skull base (8.7%).

There are several explanations for this different incidence of high-grade meningioma. Firstly, different embryologic origins of

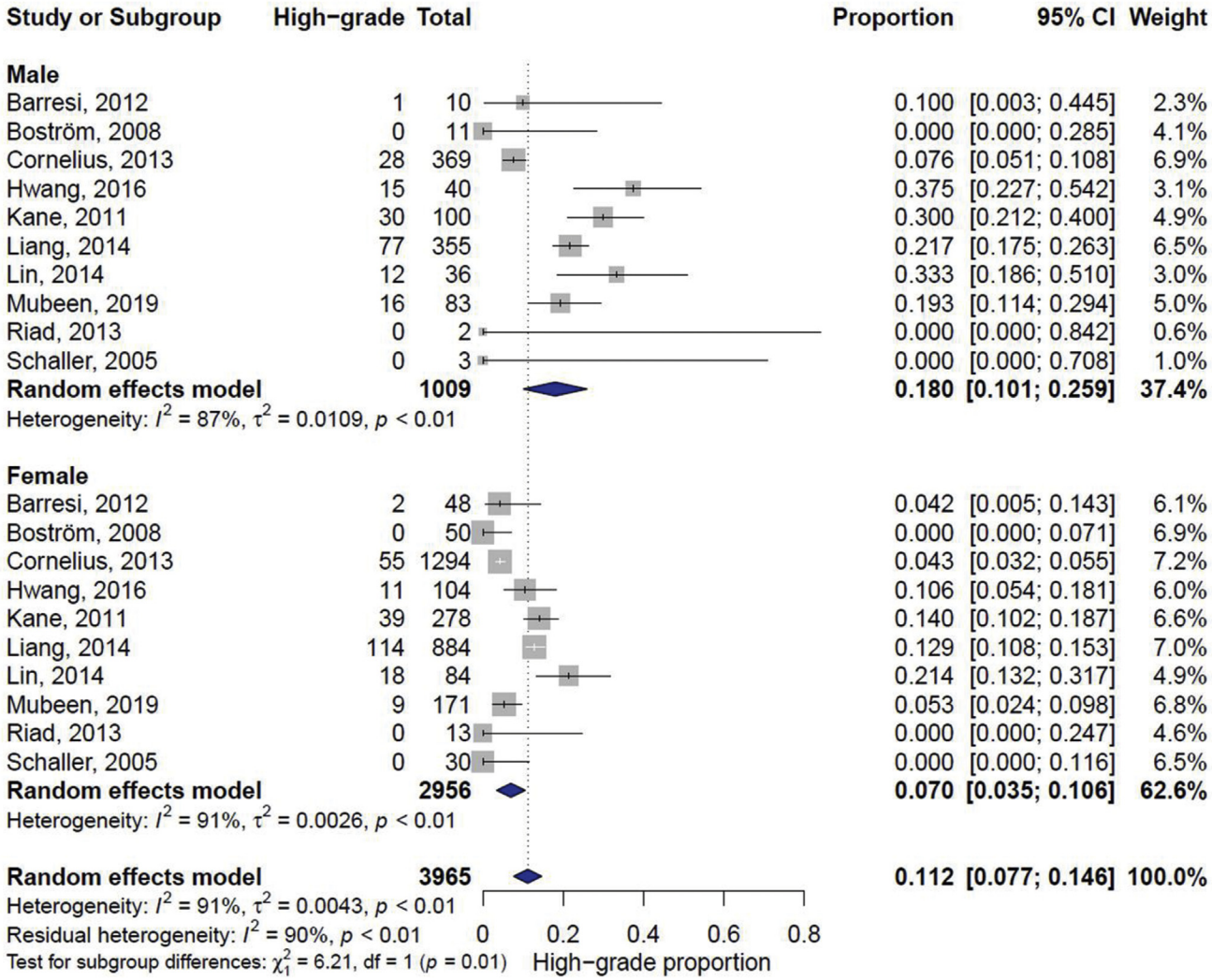

Figure 4. Forest plots for the proportion of high-grade meningioma in male and female patients.

the dura are considered to affect the high-grade proportion depending on the location. Non−skull base telencephalic meninges are thought to originate from the neural crest, which is derived from the ectoderm, whereas the meninges around the skull base and spine are believed to arise from the mesoderm.[50-52] In other words, embryologic differences of the meninges may result in their different histologic development and could produce various degrees of aggressive behavior.[1,53] Secondly, meningiomas in the skull base and spine could be more likely to present with signs and symptoms, while non−skull base meningiomas are relatively small without symptoms until they reach a large size. This could give the non−skull base meningiomas additional time to transform to high-grade meningioma.[1] In addition, genomic analysis has identified that meningiomas of the cerebral and cerebellar hemispheres are more frequently high grade and more commonly involve NF2 gene mutations and/or chromosome 22 loss than in other locations.[46,54] Sayagues et al[19] also demonstrated more heterogeneous chromosomal abnormalities in intracranial meningioma than in spinal meningioma, suggesting that intracranial meningiomas may genetically tend toward more aggressive behavior including relapse potential.

In our meta-analysis involving 10 studies, the proportion of high-grade meningiomas was higher in male (18.0%) compared with female (7.0%) patients. In addition, our metaregression analysis from 34 studies also confirmed a statistically significant association between the proportion of male patients and the proportion of high-grade meningiomas. These results are consistent with other articles showing a predominance of high-grade meningiomas in men. Kane et al[18] reported high-grade meningioma in males and females as 30% and 14%, respectively. Liang et al[47] also reported incidences as high as 21.7% and

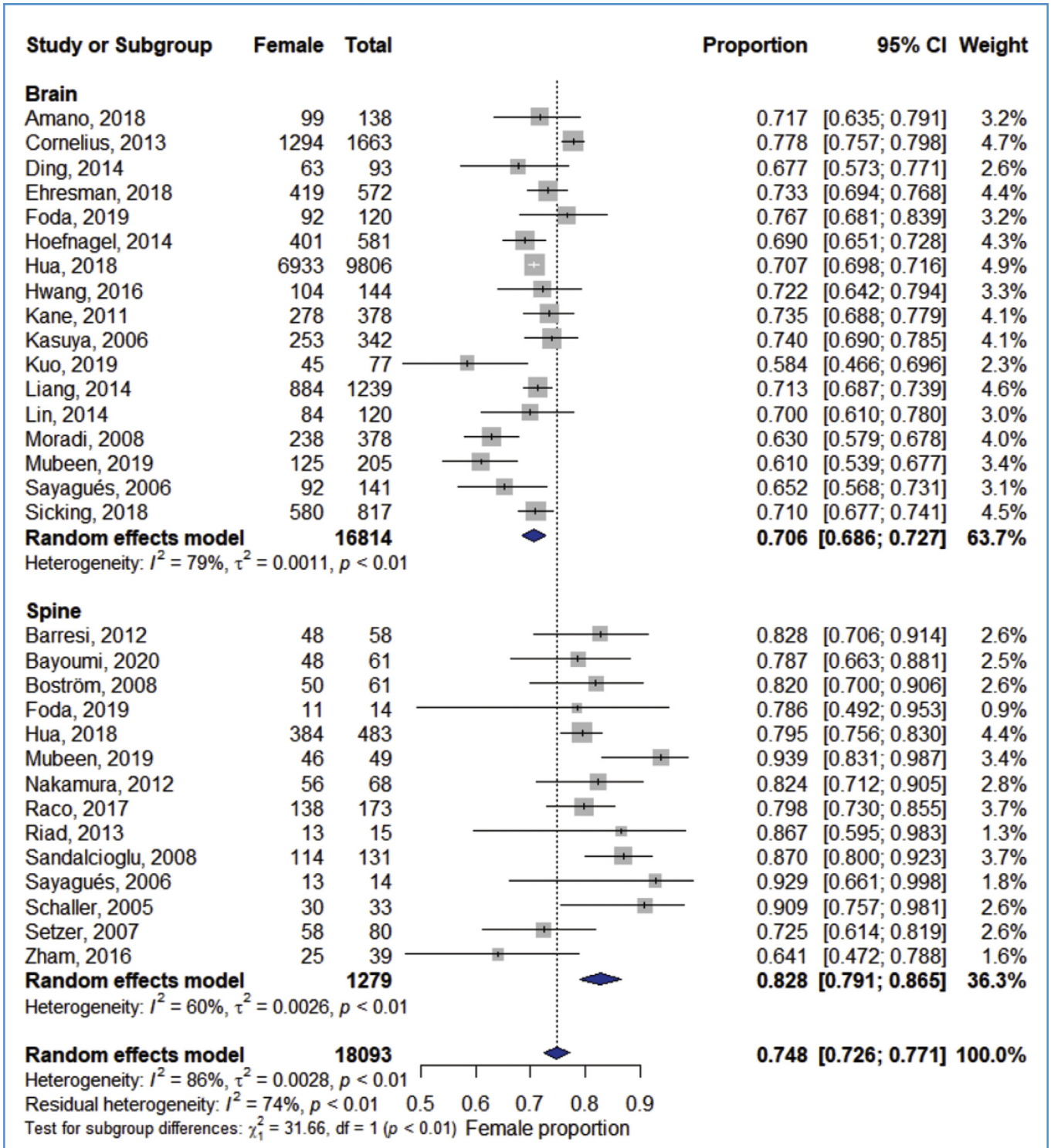

Figure 5. Forest plots for the female proportion of meningioma in the brain and/or spine.

12.9%, respectively. Cornelius et al[46] reported the OR of high-grade histopathology of men as 1.85 (95% CI, 1.155–2.961) in 1663 patients, which means high-grade meningiomas affected 7.6% of male and 4.3% of female patients, respectively. Although it is yet unclear, the background for the malignant tendency in men has been investigated in some clinical and histopathologic

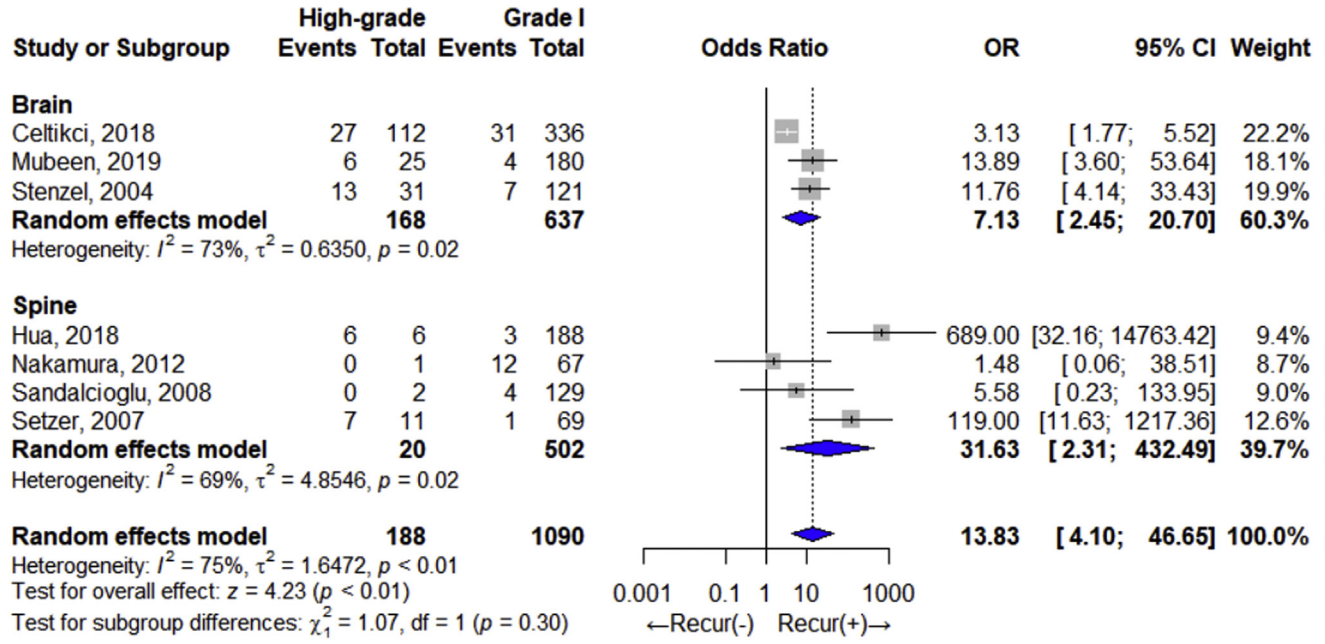

Figure 6. Forest plots for the odds ratio of recurrence in the brain or spine, depending on the histologic grade. A continuity correction of 0.5 was used.

studies. Meningiomas from male patients have lower levels of progesterone receptors, and high-grade meningiomas also have lower levels of progesterone receptors.[18,55-57] The influence of hormones on meningioma also exists in female patients. There are many studies about the close relationship between pregnancy and meningioma.[58-60] This relationship may be due to the growth acceleration of the meningioma from increased hormone levels during pregnancy. In addition, genetic studies have mentioned different gene expression patterns confined to the sex chromosomes in meningioma cells.[61]

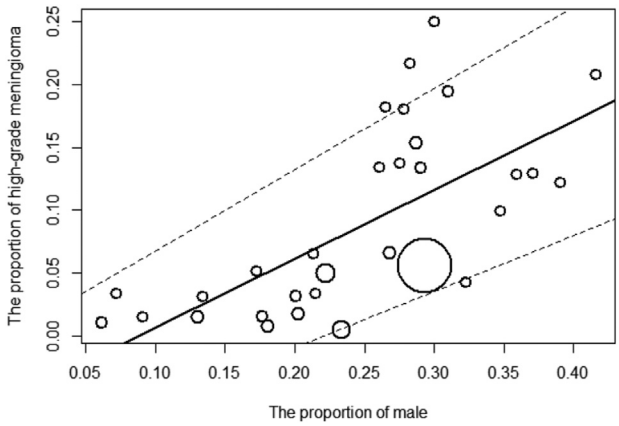

Figure 7. Bubble plot of meta-regression analysis to reveal the association between the proportion of male sex and the proportion of high-grade meningiomas. There was a 0.54% increase in the proportion of high-grade meningiomas for every 1% increase in the proportion of male patients (P < 0.001).

Interestingly, the female proportions of meningiomas are different between the brain and spine. Hua et al[4] reported that the female proportion of meningioma is 70.7% in the brain and 79.5% in the spine, respectively. Mubeen et al[37] also reported them as 61.0% and 93.9% in the brain and spine, respectively. When pooling all studies, the female proportion in the brain and spine were calculated as 70.6% and 82.8%, respectively. These results might help explain the benign dominant pathology in spinal meningioma.

It is obvious that high-grade meningiomas are more likely to recur than grade I meningiomas. Pooled from 7 articles, we also confirmed the higher recurrence rates (OR = 13.83) of high-grade meningioma than grade I meningioma (95% CI, 4.10–46.65) (P < 0.01).

Limitations

There were a few limitations in this meta-analysis. First, only histologically proven tumors through surgery are analyzed, although radiosurgery is a popular treatment option and many tumors are treated with radiosurgery. Recently, radiosurgery is preferred, especially when the tumors are present in the skull base, and therefore there might be an underestimation of skull base meningioma in the current analysis. Nevertheless, as far as we know, this is the first meta-analysis providing a general overview on this topic. Second, there was considerable heterogeneity among the studies. Therefore caution is needed in applying our pooled estimates. Although we found the proportion of male sex being a significant factor affecting heterogeneity in the meta-

regression analysis, some portion of heterogeneity remains unexplained. Third, a commonly used definition of skull base meningiomas is Al-Mefty's definition.[62,63] However, in our meta-analysis, the definition of skull base meningiomas was different among the included studies. In 1 study, posterior fossa meningioma was not included as a skull base meningioma,[48] while some others included it[17,18,45,46] and others did not mention that.[31,47] Fourth, because the data of the included studies were not sufficient to be classified according to the extent of resection and the recurrence rate, we could not reveal the relationship between the extent of resection and the recurrence rate. Fifth, the data analysis was restricted to epidemiologic data rather than regarding the clinical results. Lastly, there have been several changes to the WHO grading system in 2000, 2007, and 2016 requiring special attention when analyzing the pooled data.[64-66] Although the original classification was not changed, a few cases showed changes in histologic grading based on the changed grading system. However, this would not be expected to severely bias the statistical analysis.

CONCLUSION

Our systematic review and meta-analysis found that the incidence of high-grade meningioma (grades II and III) is different depending on the location and patient's sex. Intracranial meningioma (12.8%) is more prone to being high-grade than spinal meningioma (2.4%), and non−skull base meningioma (16.5%) is more apt to be high grade than skull base meningioma (8.7%). In addition, high-grade meningioma is more likely to occur in male (18.0%) than female (7.0%) patients. Furthermore, we confirmed the higher recurrence rates of high-grade meningioma relative to grade I meningioma (OR = 13.83). In conclusion, this meta-analysis indicates intracranial, non−skull base, and male sex are the risk factors for high-grade meningioma, and high-grade meningioma had higher recurrence rates than grade I meningioma.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Hong Kyung Shin: Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Jin Hoon Park:** Data curation, Writing - review & editing. **Young Hyun Cho:** Investigation, Writing - review & editing. **Young-Hoon Kim:** Formal analysis, Writing - review & editing. **Seok Ho Hong:** Validation, Writing - review & editing. **Jeong Hoon Kim:** Validation, Writing - review & editing. **Sung Woo Roh:** Validation, Writing - review & editing. **Sang Ryong Jeon:** Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing.

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APPENDIX

MODIFIED NEWCASTLE-OTTAWA RISK OF BIAS SCORING GUIDE

(1) Sample representativeness:

1 point: Population contained multiple histologic grades at multiple locations.
0 points: Population contained either a single histologic grade, a single location, or both.

(2) Sample size:

1 point: Sample size was ≥100 participants.
0 points: Sample size was <100 participants.

(3) Unspecified diagnosis

1 point: the diagnosis of "unspecified" was ≤5%.
0 points: the diagnosis of "unspecified" was >5%.

(4) Ascertainment of WHO grade

1 point: well-described and/or validated measurement tool.
0 points: poorly described measurement tool of uncertain validity.

(5) Quality of descriptive statistics reporting:

1 point: The study reported descriptive statistics to describe the population (e.g., age, sex) with proper measures of dispersion (e.g., mean, standard deviation).
0 points: The study did not report descriptive statistics or incompletely reported descriptive statistics or did not report measures of dispersion.

The individual components listed above are summed to generate a total modified Newcastle-Ottawa risk of bias score for each study. Studies were scored on quality on a 5-point scale; 0–1 High risk of bias; 2–3 Moderate risk of bias; 4–5 Low risk of bias.

Supplementary Table S1. Modified Newcastle-Ottawa Risk of Bias Scoring Guide

Authors and Year	Sample Representativeness	Sample Size	UnspecifiedDiagnosis	Ascertainment of WHO Grade	Quality of Descriptive Statistics Reporting	Total	Risk of Bias
Amano et al., 2018[23]	1	1	1	1	0	4	Low
Barresi et al., 2012[33]	1	0	1	1	1	4	Low
Bayoumi et al., 2017[34]	1	0	1	1	0	3	Moderate
Boström et al., 2008[35]	1	0	1	1	0	3	Moderate
Celtikci et al., 2018[24]	1	1	1	1	1	5	Low
Cornelius et al., 2013[45]	1	1	1	1	1	5	Low
Davies et al., 2017[36]	1	0	1	1	0	3	Moderate
Ding et al., 2014[25]	1	0	1	1	0	3	Moderate
Ehresman et al., 2017[26]	1	1	1	1	1	5	Low
Foda et al., 2019[2]	1	1	1	1	1	5	Low
Hoefnagel et al., 2014[27]	1	1	1	1	1	5	Low
Hua et al., 2018[4]	1	1	1	1	1	5	Low
Hwang et al., 2016[46]	1	1	1	1	1	5	Low
Kane et al., 2011[18]	1	1	1	1	1	5	Low
Kasuya et al., 2006[16]	1	1	1	1	0	4	Low
Kasuya et al., 2012[28]	1	1	1	1	0	4	Low
Ko et al., 2007[29]	1	1	1	1	0	4	Low
Kuo et al., 2019[30]	1	0	1	1	0	3	Moderate
Liang et al., 2014[47]	1	1	1	1	0	4	Low
Lin et al., 2014[31]	1	1	1	1	0	4	Low
McGovern et al., 2010[17]	1	1	0	1	0	3	Moderate
Moradi et al., 2008[12]	1	1	1	1	1	5	Low
Mubeen et al., 2019[37]	1	1	1	1	0	4	Low
Nakamura et al., 2012[38]	1	0	1	1	1	4	Low
Raco et al., 2016[39]	1	1	0	1	1	4	Low
Riad et al., 2013[40]	1	0	1	1	0	3	Moderate
Sade et al., 2007[1]	1	1	1	1	0	4	Low
Sandalcioglu et al., 2008[41]	1	1	1	1	0	4	Low
Sayagués et al., 2006[19]	1	1	1	1	1	5	Low
Schaller et al., 2005[42]	1	0	1	1	1	4	Low
Setzer et al., 2007[43]	1	0	1	1	1	4	Low
Sicking et al., 2018[48]	1	1	1	1	0	4	Low
Stenzel et al., 2004[32]	1	1	1	1	0	4	Low
Zham et al., 2016[44]	1	0	1	1	0	3	Moderate

WHO, World Health Organization.