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REVIEW ARTICLE

Prognostic significance of brain invasion in meningiomas: systematic review and meta-analysis

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Abstract

The WHO 2016 classification introduced brain invasion as a standalone criterion for grade II meningioma (GIIM). We systematically reviewed studies published after 2000 and performed a PRISMA-compliant meta-analysis of the hazard ratios (HRs) for progression-free survival (PFS) between brain-invasive and noninvasive meningiomas. In five studies that included both benign and higher-grade meningiomas, brain invasion was a significant risk factor for recurrence (HR = 2.45, $p = 0.0004$). However, in 3 studies comparing "brain-invasive meningioma with otherwise benign histology (BIOB)" with grade I meningioma, brain invasion was not a significant predictor of PFS (HR = 1.49, $p = 0.23$). Among GIIM per the WHO 2000 criteria, brain invasion was a significant predictor of shorter PFS than noninvasive GIIM (HR = 3.40, $p = 0.001$) but not per the WHO 2016 criteria (HR 1.13, $p = 0.54$), as the latter includes BIOB. Meta-regression analysis of seven studies of grade II meningioma showed that more frequent BIOB was associated with lower HRs ($p < 0.0001$). Hence, there is no rationale for brain invasion as a standalone criterion for grade II meningioma, although almost all studies were retrospective and exhibited highly heterogeneous HRs due to differences in brain–tumor interface data availability.

Keywords Brain invasion · Meningioma · Meta-analysis · WHO grade

Introduction

Meningiomas are usually benign, slowly growing tumors. Although most can be cured by gross total resection, postoperative recurrence is often life-threatening. Identifying tumors with such poor prognosis is important for treatment planning. Although the WHO grading system is one of the most reliable prognostic measures [1], even benign tumors can recur after total resection. Therefore, several studies have attempted to more accurately distinguish meningioma aggressiveness. Despite the progress of molecular studies, the WHO histological classification requires revision.

The WHO grading system for brain tumors has undergone several revisions. Notably, the meningioma grading criteria were substantially revised in 2000 [2]. At that time, atypical and anaplastic meningiomas were defined according to objective findings. Although brain-invasive meningioma with otherwise benign histology (BIOB) was not included within atypical meningiomas, it was described as being an aggressive tumor with the same biological activity as atypical meningioma. Therefore, according to the 2007 classification, such tumors were prognostically considered WHO grade II [3]. While several neuropathologists classified BIOB as an atypical meningioma after 2007, the WHO officially made this designation in 2016 [1].

Brain invasion is considered a sign of meningioma aggressiveness. Jellinger et al. [4] reported that the recurrence rate of brain-invasive meningiomas was high (40%), although the exact number of noninvasive meningiomas was unknown. Similarly, Böker et al. [5] reported that brain invasion was associated with a higher tumor recurrence rate. In contrast, several other studies did not find a significant prognostic difference between brain-invasive and noninvasive meningiomas [6–8]. Prior to the WHO 2000 criteria, Perry et al. [9] analyzed 581 patients with primary meningiomas. Although they demonstrated that brain-invasive meningiomas had a similar recurrence rate to noninvasive

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atypical meningiomas, the former included both BIOB and brain-invasive atypical meningiomas. Therefore, it remained unclear whether BIOB had a similar recurrence rate to atypical meningiomas. However, Perry et al. [10] subsequently found no significant difference in overall survival between 54 cases of atypical meningiomas and 20 cases of BIOB ($p = 0.61$).

After the publication of 2016 WHO meningioma classification, Brokinkel et al. [11] systematically reviewed brain-invasive meningiomas and showed that microscopic brain invasion was correlated with tumor progression in most series. Several researchers subsequently investigated the prognostic significance of brain invasion in meningioma grading [12–16], but most did not find a significant relationship between BIOB and benign meningioma or found that BIOB had a better prognosis than atypical meningioma excluding BIOB.

Because BIOB is relatively rare, its prognostic implications may be difficult to analyze without conducting multicenter studies. Therefore, we systematically reviewed the literature on BIOB and performed a meta-analysis to determine the prognostic significance of BIOB.

Materials and methods

Herein, we define "GI-00" as benign meningioma including BIOB per the 2000 WHO criteria, "GI-16" as benign meningioma without BIOB per the 2016 WHO criteria, "GII-00" as grade II meningioma per the 2000 WHO criteria, and "GII-16" as grade II meningioma per the 2016 WHO criteria.

Literature search

We performed this study in accordance with the PRISMA guidelines. The search flow diagram is outlined in Online Fig. 1. We searched the English literature in PubMed, Scopus, the Cochrane Library, and Google Scholar for relevant articles using the keywords "meningioma" AND "brain invasive" OR "brain infiltration," OR "cortical invasion" AND "human" AND "adult" (≥ 18 years). The authors searched the literature independently and determined the final selection by discussion. The literature after 2000 was searched because the WHO grading criteria were substantially revised in 2000, but remained very similar thereafter, except regarding the classification of BIOB. We excluded studies using criteria other than the WHO 2000 criteria or later versions.

Studies confined to anaplastic meningioma, neurofibromatosis, or restricted locations were excluded. Studies with less than 50 cases or less than 40 cases with grade II alone were also excluded. We selected articles that contained statistical data for progression/recurrence or the incidence of brain-invasive meningiomas. We perused multiple reports from a single institute to ensure that the data did not overlap. However, we included two studies with duplicate incidence data because only a small portion overlapped [17, 18].

Data extraction

For each study, we extracted the following data: WHO grade, the numbers of patients with each grade and BIOB, sex, mean (or median) age and follow-up, and statistics comparing progression-free survival (PFS) between brain-invasive and noninvasive tumors. We included BIOBs when calculating the percentage of brain-invasive tumors among WHO grade I tumors. We recorded the number of specimens that included brain–meningioma interface (B/M-I) for the diagnosis of brain invasion when available. We used the hazard ratio (HR) for PFS for meta-analysis but also recorded log-rank test results and odds ratios. For studies involving the log-rank test, we calculated HRs according to the method described by Tierney et al. [19] if the numbers of brain-invasive tumors and recurrences were available.

If required data were missing, we attempted to obtain them by contacting the authors of that study; three of the authors kindly responded to our inquiries and provided the required data [13, 20, 21].

Risk of bias

As all of the studies except one were retrospective observational studies, we did not use a specific method to assess the risk of bias. One important bias is that most studies lacked B/M-I data. Therefore, we carefully investigated study heterogeneity. We estimated publication bias using a funnel plot when 10 or more studies were included.

Statistical analysis

We used R for all statistical analyses. We applied the DerSimonian–Laird random-effects model to the meta-analysis. To evaluate the effect of brain invasion on the prognosis of meningiomas, we compared the HRs of PFS using EZR software in R [22]. To determine the relationships between brain invasion and clinical factors, we calculated odds ratios using forest plots. We used *metaprop* in R to perform a single-arm meta-analysis to determine the incidence of brain-invasive tumors for each WHO grade.

We tested the reviewed studies for heterogeneity. To determine factors related to heterogeneity, we also performed meta-regression analysis, calculating the following as covariates: B/M-I availability (number of cases with B/M-I case the information / total cases) as well as the proportions of male cases, skull base tumors, high-grade

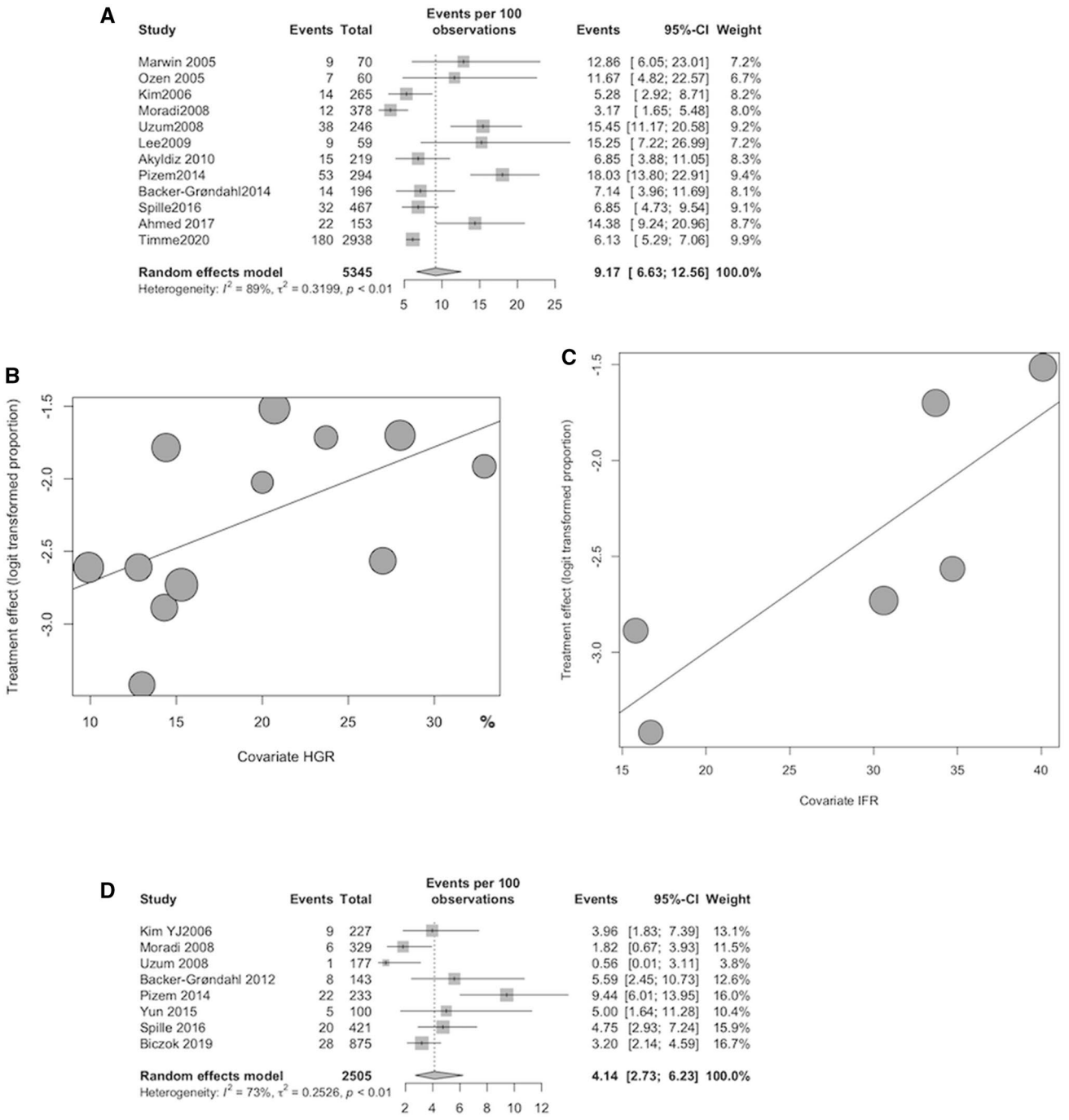


Fig. 1 **a** Forest plot showing the frequency of brain invasion in all meningiomas. **b** Bubble plot showing significant relation in the frequency of brain invasion by the rate of high-grade meningiomas (Meta-regression, $p = 0.033$). HGR, the rate of high-grade meningiomas in each study. **c** Bubble plot showing significant relation in the frequency of brain invasion by the rate of available brain/meningioma interface (Meta-regression, $p = 0.0006$). **d** Forest plot showing the frequency of brain invasion in benign meningiomas

(i.e., grade II and III) tumors, total resection (i.e., Simpson 1–3 removal cases), and brain-invasive tumors compared to the total. Two-sided p values less than 0.05 were considered statistically significant.

Ethical approval and informed consent

Because this review did not involve direct human investigation, informed consent was not required.

Results

We initially retrieved 129 articles after removing duplicates (Online Fig. 1). After full-text assessment, we selected 36 articles and added 3 through cross-referencing and manual searching. We analyzed 15 studies with HRs for recurrence between brain-invasive and noninvasive meningiomas [12, 15, 16, 21, 23–33], 14 studies with frequency analyses [18, 34–47], and 10 studies with both [13, 14, 17, 20, 48–53] (Online Table 1).

Incidence and associated factors of brain-invasive meningiomas

Twelve studies reported the frequency of brain-invasive meningiomas for all WHO grades [17, 18, 20, 30, 35, 38–42, 44, 48]. Single-arm meta-analysis indicated that the percentage of brain-invasive meningiomas was 9.17% [95% confidence interval (CI) = 6.63–12.56%; Fig. 1a]. Although the percentage was highly heterogeneous among studies [$I^2 = 88.9\%$, CI (82.5–92.9)], the heterogeneity was attributable to the different rates of higher-grade tumors included in each study (meta-regression $p = 0.033$; Fig. 1b). Although only six studies reported the number of specimens that contained B/M-I information [18, 20, 36, 39, 42, 45], the rate of available B/M-I information in each study was significantly associated with the frequency of brain invasion (meta-regression $p = 0.006$; Fig. 1c).

Among GI-00 cases, the frequency of BIOB was 4.14% [CI (2.73–6.23), $I^2 = 73.3\%$; test of heterogeneity; $Q = 26.19$, $p = 0.0005$; Fig. 1d] [14, 17, 20, 38, 41, 44, 46, 48]. The heterogeneity almost disappeared when the rate of available B/M-I information was incorporated into meta-regression analysis ($p = 0.0004$, $I^2 = 28.5\%$; test of heterogeneity, $Q = 4.20$, $p = 0.24$), although only five studies reported the number of cases with B/M-I information [14, 20, 41, 44, 48].

Most recent studies on atypical meningiomas reassessed specimens diagnosed as atypical meningioma according to the old histopathological criteria but did not review benign tumors. Accordingly, these studies might have failed to include some BIOBs as atypical meningiomas. Therefore, we calculated the frequency of brain invasion of GII-00 meningiomas ($n = 487$), which was 31.5% [CI (22.3–42.6), $I^2 = 79.9\%$] [20, 38, 44, 45, 50, 52, 53]. While we did not specifically include data on anaplastic meningioma, the frequency of brain invasion among anaplastic meningiomas ($n = 105$) was 59.9% [CI (43.8–74.2), $I^2 = 46.1\%$] within the literature of meningiomas of all grades and atypical ones [13, 17, 20, 34, 38, 40, 42, 44, 45, 52].

We performed a meta-analysis of the odds ratios of factors related to brain invasion with respect to sex and tumor location. Although meningiomas of all WHO grades exhibited a higher incidence of brain invasion among males ($p < 0.0001$) [17, 34, 43, 48], the incidence of brain invasion was not higher among males with only meningiomas of WHO grade I or above (Fig. 2a) [14, 46, 47, 51]. We observed a similar trend regarding tumor location (Fig. 2b) [14, 17, 18, 47, 48], although only one study each had data on WHO grade I and II meningiomas.

Prognostic value of brain invasion in meningiomas for all WHO grades

Five studies reported univariate analyses of HRs for PFS between brain-invasive and noninvasive meningiomas [17, 20, 26, 27, 48], two of which reported multivariate analyses [17, 27] (Table 1). Two of the studies included grade I and II meningiomas, and the other three included all three grades. We synthesized their data because HRs in both groups were comparable and the number of grade III tumor was small. Meta-analysis of HRs in univariate analyses showed that compared to noninvasive meningioma, brain-invasive meningioma was associated with a significantly higher risk of recurrence [HR = 2.45, CI (1.49–4.04), $p = 0.0004$; $I^2 = 74.3\%$; Fig. 3a]. Meanwhile, the results of two multivariate analyses that accounted for the degree of surgical removal and WHO grade or mitotic counts indicated that brain invasion was a borderline significant risk factor for recurrence [HR = 1.80, CI (0.998–3.23), $p = 0.0507$; Fig. 3b]. The high heterogeneity of HRs in univariate analyses was related to the rate of brain invasion in each study ($p = 0.005$; Fig. 3c) but was not related to high tumor grade ($p = 0.55$), total resection ($p = 0.24$), male sex ($p = 0.46$), or skull base location ($p = 0.59$) in meta-regression analysis (Online Table 2). Thus, the results of the meta-regression analysis indicate that the recurrence rate of invasive tumors exceeded that of noninvasive tumors when the rate of brain invasion in a given study was high. Meanwhile, we were unable to perform a meta-regression analysis on the B/M-I rate owing to a lack of data.

Four other studies reported statistics regarding the recurrence of brain-invasive and noninvasive meningiomas. Two reported that invasive meningiomas had a higher recurrence rate according to the χ^2 test ($p = 0.03$) [38] and log-rank test ($p = 0.0079$) [39], whereas the other two reported non-significant results according to Fisher's test ($p = 0.93$) [43] and the log-rank test ($p = 0.97$) [44].

Prognostic value of brain invasion in WHO grade I meningiomas

Three studies reported no significant difference in PFS between BIOB and GI-16 in univariate analysis [HR = 1.49, CI (0.78–2.86), $p = 0.23$] or multivariate

Table 1 Studies on the hazard ratio for recurrence between brain invasive and non-invasive tumors

Authors	Era	No	Follow (mo)	Grading criteria	WHO grade			Interface available	Brain invasive	BIOB	HR	CI	References
					I	II	III						
All grade (or grade I and II)													
Backer-Grøndahl 2014	1991–2000	196	8–18y	2007	135	59	2	68	14	8	Uni 1.75	0.67–4.55	[48]
Ho 2002	1976–1985	83	M158.5	2000	58	25	0	NA	11	NA	Uni 2.67	1.79–3.90	[26]
Lamba 2019	2001–2015	334	M52.2	2007	275	59	0	NA	8	NA	Uni 2.42 multi 2.28	Uni 0.95–6.14 multi 0.82–6.38	[27]
Pizem 2014	1999–2000 2009–2010	294	M51	2000	233	51	10	118	53	22	Uni 5.3	3.05–9.22	[20]
Spille 2016	1994–2009	467	M91	2016	401	60	6	NA	32	20	Uni 1.43 multi 1.60	Uni 0.98–2.09 multi 0.78–3.27	[17]
Pooled HR for all grade	Uni HR 2.45, CI 1.49–4.04, $p=0.0004$[a], $n=1374$, ref [17, 20, 26, 27, 48]								Multi HR 1.80, CI 0.998–3.23, $p=0.051$, $n=801$, ref [17, 27]				
WHO I													
Biczok 2019	2005–2014	875	M66.5	2007	875	0	0	170	28	28	Uni 0.596 multi 0.852	Uni (0.0001–2.6400) multi (0.27–2.710)	[14]
Pooled HR for GI-00	Uni HR 1.49, CI (0.78–2.86), $p=0.23$, $n=1509$, ref [14, 17, 20]								Multi HR 0.97, CI (0.39–2.39), $p=0.95$, $n=1276$, ref [14, 17]				
WHO grade II (4 studies including grade III)													
Barret 2019	1980–2018	97	M53	2016	0	97	0	NA	30	NA	Uni 1.288	0.656–2.529	[23]
Baumgarten 2016	NA	229	M22	2016	0	229	0	NA	NA	61	Uni 0.59	0.33–1.06	[12]
Bertero 2019	1994–2005	94	M3.9y	2016	0	85	9	NA	18	5	Uni 0.29 multi 0.27	Uni (0.09–0.99) multi (0.07–0.95)	[13]
Biczok 2018	1998–2014	87	M45	2016	0	72	15	NA	41	NA	Uni 3.44	1.93–6.13	[49]
Champeux 2016	2007–2015	194	M4.4y	2007	0	194	0	NA	80	NA	Uni 0.41	0.19–0.88	[24]
Champeux 2016	2000–2015	178	M3.6y	2007	0	178	0	NA	59	NA	Uni 1.16	0.52–2.56	[25]

Table 1 (continued)

Authors	Era	No	Follow (mo)	Grading criteria	WHO grade			Interface available	Brain invasive	BIOB	HR	CI	References
					I	II	III						
Fioravanzo 2020	NA/ multi-center	200	M53	2016	0	200	0	NA	94	46	Uni 0.70 multi 0.94	Uni (0.49–1.00) multi (0.62–1.43)	[15]
Jansen 2012	NA	86	> 5y	2000	0	86	0	NA	24	0	Uni 1.17	0.16–8.67	[50]
Kim D 2018	2007–2014	76	M52.6	2007	0	66	10	NA	22	NA	Uni 8.6	2.77–26.72	[28]
Klinger 2015	2000–2012	57	M43	2016	0	57	0	NA	NA	NA	Multi 1.74	0.49–6.14	[29]
Lee KD 2013	1999–2009	90	M48.7	2007	0	90	0	NA	NA	NA	Uni0.68	0.18–2.25	[30]
Li H 2019	2008–2015	302	M41.6	2016	0	302	0	NA	71	NA	Uni 1.613 multi 1.59	Uni (1.105–2.354) multi (1.12–2.26)	[51]
Shakir 2018	1992–2013	70	M69	2007	0	70	0	NA	25	NA	Uni 2.25 multi 1.46	Uni (1.19–4.26) multi (0.59–3.58)	[31]
Streckert 2019	1991–2018	138	NA	2016	0	138	0	NA	63	48	Uni 0.44 multi 0.37	Uni (0.25–0.79) multi (0.19–0.74)	[16]
Sun 2014	1993–2012	151	M45	2007	0	151	0	NA	32	22	Uni 4.1 multi7.1	Uni (1.3–12.9) multi (2.1–24.2)	[32]
Sun 2014	1993–2013	59	M67	2007	0	59	0	NA	NA	NA	Uni 1.5	0.5–4.6	[33]
Vranic 2010	1990–2005	86	M96	2000	0	76	10	37	25	0	Uni 7.2 multi 8.40	Uni (0.9–55.7) multi (1.02–69)	[52]

Table 1 (continued)

Authors	Era	No	Follow (mo)	Grading criteria	WHO grade			Interface available	Brain invasive	BIOB	HR	CI	References
					I	II	III						
Wang 2019	2009–2018	263	M41	2016/2007	0	263	0	NA	59	16	Uni 1.92 multi 1.15	Uni (1.15–3.20) multi (0.66–1.99)	[21]
Yoon 2015	2000–2010	158	M32	2000	0	158	0	144	35	0	Uni 2.2	1.08–4.5	[53]
Pooled HR for grade II	Uni HR 1.35, CI (0.93–1.95), $p=0.12$, $n=2590$, ref.[12–16, 20, 21, 23–25, 28–33, 50–53]								Multi HR 1.21, CI 0.74–1.98, $p=0.45$, $n=1361$, ref [13, 15, 16, 21, 29, 31, 32, 51, 52]				
GII-00	Uni HR3.40, CI (1.63–7.06), $p=0.001$[a], $n=467$, ref. [20, 28, 50, 52, 53]								Multi HR 8.4, CI (1.02–69.0), $p=0.048$[a], $n=86$, ref [52]				
GII-16	Uni HR 1.13, CI (0.76–1.70), $p=0.54$, $n=2062$, ref.[12–16, 21, 23–25, 31–33, 51]								Multi HR 1.11, CI (0.68–1.81), $p=0.67$, $n=1275$, ref [13, 15, 16, 21, 29, 31, 33, 51]				

MA meta-analysis: *mo* months, *y* year, *BIOB* brain invasive meningioma with otherwise benign histology, *HR* hazard ratio, *m* mean, *CI* 95% confidential interval, *M* median, *NA* not available, *uni* univariate analysis, *multi* multi-variate analysis, *Ref* reference number

GI-00 grade I meningiomas in the WHO 2000 criteria, *GII-00* grade II meningioma in the WHO 2000 criteria, *GII-16* grade II meningioma in the WHO 2016 criteria

[a]Statistically significant

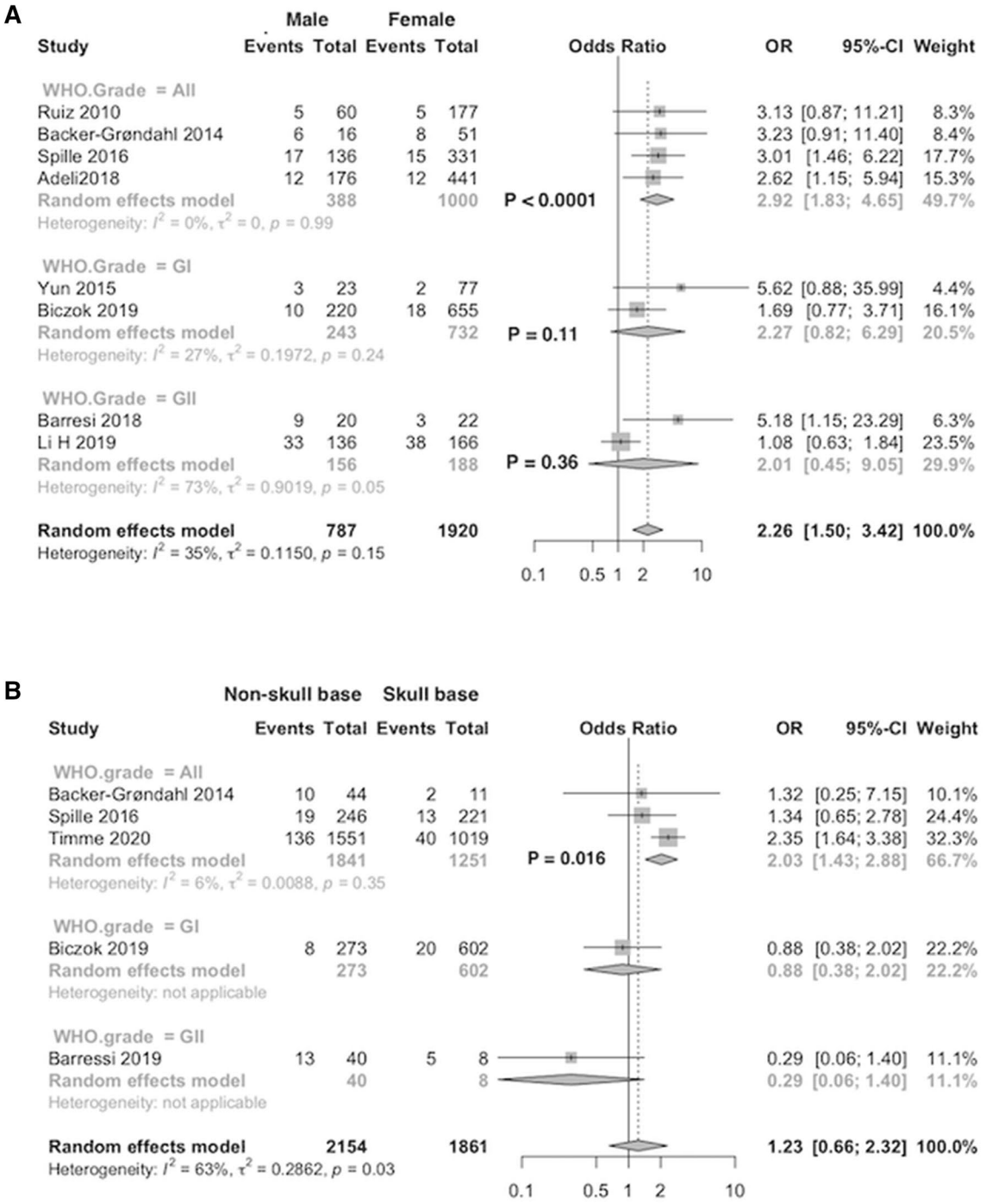


Fig. 2 Forest plots of the association between brain invasion and gender **a** or location **b** in each WHO grade. Asterisk, not including WHO III tumors

analysis [HR = 0.97, CI (0.395–2.39), $p = 0.95$; Table 1, Fig. 4a, b] [14, 17, 20]. Heterogeneity was very low in both analyses. Besides the above studies, Kim et al. [38] reported recurrence in none of the nine cases of BIOB and in 9% of benign meningiomas during a mean follow-up of 57 months. In addition, all four studies defined brain invasion as irregular projections of the tumor or tumor cells into the adjacent central nervous system parenchyma without an intervening layer of the leptomeninges.

Prognostic value of brain invasion in WHO grade II meningiomas

Nineteen studies compared recurrence between brain-invasive and noninvasive WHO grade II meningiomas by univariate analysis [12–16, 20, 21, 23–25, 28, 30–33, 50–53]. A meta-analysis of HRs revealed that brain invasion was not a significant predictor of recurrence [HR = 1.35, CI (0.93–1.95); of note, four studies included grade III tumors [13, 14, 28, 52]; Table 1]. The funnel plot showed an almost symmetrical distribution ($p = 0.42$, linear regression; Fig. 5a). However, the heterogeneity of the meta-analysis was high ($I^2 = 78.5\%$). We could not determine the reason for this heterogeneity by incorporating the proportion of brain invasion, total resection, and skull base location as covariates in meta-regression analysis but detected a difference between studies with different pathological criteria (Online Table 2). Eleven studies employed the GII-16 definition, which includes BIOB [12–16, 21, 23–25, 31–33, 51], 5 other studies employed the GII-00 definition, which does not include BIOB [20, 28, 50, 52, 53]; 1 study in which the classification of BIOB was not described was excluded from the analysis [30]. Brain invasion was a significant predictor of higher recurrence among GII-00 meningiomas [HR = 3.40, CI (1.63–7.06), $p = 0.001$], whereas in GII-16 meningioma it was not [HR = 1.13, CI (0.76–1.70), $p = 0.54$; Fig. 5b]. Meta-regression analysis showed a significant difference in recurrence between these groups ($p = 0.02$). Among the 11 studies that presented the number of BIOBs, meta-regression analysis showed a significant association between the HRs and BIOB rates among grade II and III meningiomas ($p = 0.0005$).

We further confirmed the prognostic effect of including BIOB among grade II meningiomas alone. As seven studies reported the number of BIOBs using the GII-16 definition [12, 15, 16, 21, 32, 50, 53], we performed meta-regression analysis of the HRs with the BIOB rate as a covariate. The bubble plot clearly showed a significant relationship between the BIOB rate and HRs among grade II meningiomas ($p < 0.0001$; Fig. 5c). Hence, our results indicated that an increase in the proportion of BIOB according to the GII-16 definition decreased the HR, thus prolonging PFS in cases of brain-invasive meningioma. Actually, two studies from the same institute reported a better prognosis of BIOB than other atypical meningiomas in both univariate (HR = 0.258, $p = 0.011$) [17] and multivariate (HR = 0.37, $p = 0.005$) analyses [16].

Nine studies that presented multivariate analysis results yielded similar findings (Table 1). One of them in GII-00 meningioma showed the significant prognostic difference between invasive and non-invasive meningiomas [HR 8.40, CI (1.02–1.69), $p = 0.048$) [52] but other 8 studies in GII-16 did not [HR 1.11, CI (0.68–1.81), $p = 0.53$] (Table 1) [13, 15, 16, 21, 29, 31, 33, 51].

Besides the above studies, two studies compared the prognostic significance between brain-invasive and noninvasive tumors among atypical meningiomas. One study reported no significant difference between brain-invasive and non-invasive atypical meningiomas diagnosed according to the WHO 1993–2007 criteria ($p = 0.22$, log-rank test) [54]. The other study reported a significantly higher recurrence rate among brain-invasive GII-00 and anaplastic meningiomas than among noninvasive ones ($p = 0.013$, log-rank test) [45].

Discussion

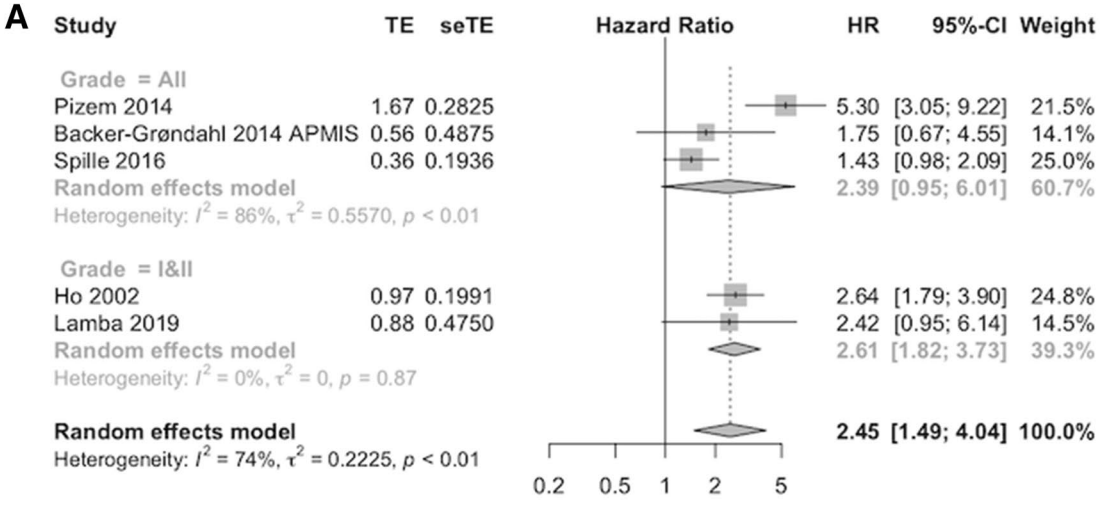
Our meta-analysis showed that brain invasion was a significant prognostic factor for recurrence in meningiomas for all grades as well as GII-00. However, it was not a significant prognostic factor using the GII-16 definition because the inclusion of BIOB in GII-16 cases decreased the HR for PFS between brain-invasive and noninvasive tumors. Furthermore, BIOB cases had similar PFS as other benign meningiomas. Therefore, there is no rationale for considering brain invasion as a standalone grading criterion for atypical meningioma.

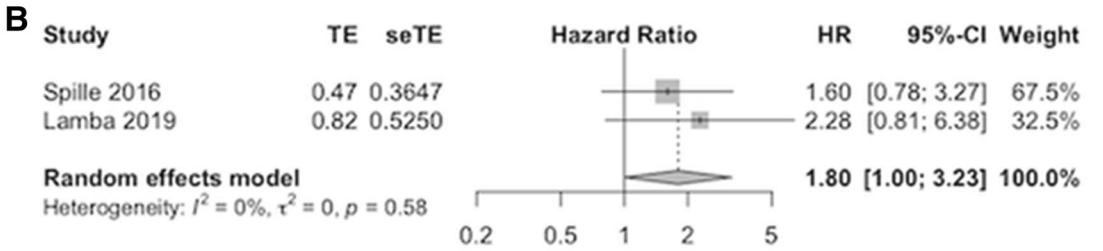
Definition of brain invasion

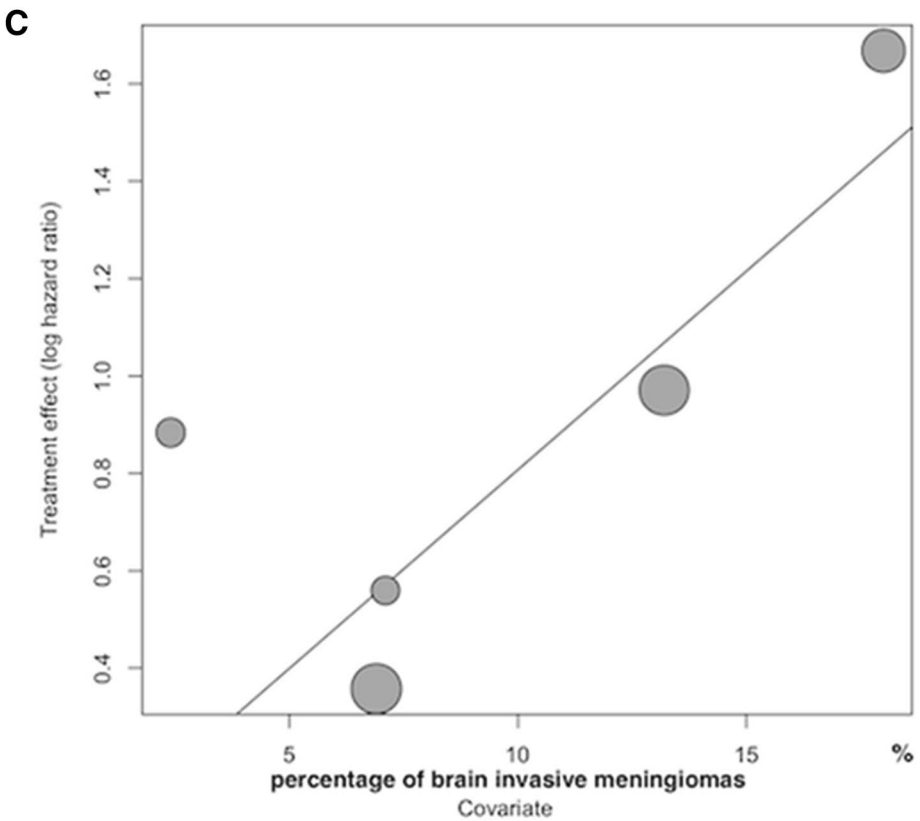
Almost all studies defined brain-invasive tumors as tumor tissue found within the adjacent brain without a separating connective tissue layer as proposed by Perry et al. [9] and did not include perivascular invasion. Burger et al. [55] stated that the significance of focal invasion—often perivascular and superficial cortical invasion—was unclear, as this feature was observed in typical meningioma. As the categorization was based on empirical criteria, we did not find studies that investigated the prognostic significance of perivascular invasion in meningiomas. In addition, it might be difficult to distinguish between tumor protrusion into the cortex and true invasion. Several reports described collagen type 4 immunostaining as being faded at the B/M-I in cases of true brain invasion while persisting when the tumor only pressed the cortex [56, 57]. Despite these difficulties, the interobserver concordance of brain invasion was reported to be higher ($\kappa = 0.76$) than that for other histopathological features [58].

Rate of brain invasion

Another issue regarding brain invasion is that its true rate is difficult to ascertain because of a frequent lack of brain tissue in surgical specimens [14, 20, 38, 44, 48]. This is because neurosurgeons aim to leave the arachnoid membrane


A
Study TE seTE Hazard Ratio HR 95%-CI Weight
Grade = All
Pizem 2014 1.67 0.2825 5.30 [3.05; 9.22] 21.5%
Backer-Grøndahl 2014 APMIS 0.56 0.4875 1.75 [0.67; 4.55] 14.1%
Spille 2016 0.36 0.1936 1.43 [0.98; 2.09] 25.0%
Random effects model 2.39 [0.95; 6.01] 60.7%
Heterogeneity: I^2 = 86%, τ^2 = 0.5570, p < 0.01
Grade = I&II
Ho 2002 0.97 0.1991 2.64 [1.79; 3.90] 24.8%
Lamba 2019 0.88 0.4750 2.42 [0.95; 6.14] 14.5%
Random effects model 2.61 [1.82; 3.73] 39.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87
Random effects model 2.45 [1.49; 4.04] 100.0%
Heterogeneity: I^2 = 74%, τ^2 = 0.2225, p < 0.01
0.2 0.5 1 2 5


B
Study TE seTE Hazard Ratio HR 95%-CI Weight
Spille 2016 0.47 0.3647 1.60 [0.78; 3.27] 67.5%
Lamba 2019 0.82 0.5250 2.28 [0.81; 6.38] 32.5%
Random effects model 1.80 [1.00; 3.23] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58
0.2 0.5 1 2 5


C
Treatment effect (log hazard ratio)
0.4 0.6 0.8 1.0 1.2 1.4 1.6
5 10 15 %
percentage of brain invasive meningiomas
Covariate

◂**Fig. 3** Forest plots showing hazard ratio (HR) for recurrence between invasive and non-invasive meningiomas of all grades and grade I and II meningiomas by univariate analysis **a** and multivariate analysis **b**. Meta-regression in HR by univariate analysis showing significant relationship against the rate of brain invasion ($p = 0.005$) **c**

intact during surgery to avoid damaging the brain. Although it might be possible to determine brain invasion based on intraoperative findings, some studies reported a discrepancy between histological and intraoperative cleavability [9, 20, 52]. Meningiomas are usually located above the arachnoid membrane and often wrapped in a "capsule" of fibroconnective tissue originating from the tumor stroma, arachnoid, and pia. However, meningiomas sometimes disrupt the membrane and invade the brain in rare cases [59]. The degree of arachnoid disruption is correlated with tumor grade and size [56]. Accordingly, dissection might become subpial when tumor cells attach directly to the pia mater, the tumor capsule fuses with the pia mater, or the tumor invades the brain. This is likely why the judgement of a non-cleavable tumor intraoperatively is discordant with brain invasion.

Our meta-analysis showed that brain invasion occurred in 9.17% of all meningiomas, specifically in 4.14, 31.5, and 59.9% of grade I, II, and III tumors, respectively. However, the analyses showed high heterogeneity that was most likely related to the rate of available B/M-I information in each study. Hence, the more specimens available, the more brain invasion observed, which might indicate a causal relationship. Pizam et al. [20] reported that the rate of brain tissue availability was correlated with the rate of brain invasion. Furthermore, they found that compared to the retrospective investigation, a prospective investigation produced higher rates of brain tissue in specimens and brain invasion. They speculated that the larger number of tissue blocks and GFAP staining in the prospective investigation affected the results. Moreover, the rate of brain invasion might actually increase when scrutinizing excised specimens. Backer-Grøndahl et al. [48] presented cases that were initially diagnosed as noninvasive but were ultimately invasive after further cutting of paraffin blocks; thus, the cutting level of paraffin-embedded tissue blocks was critical to correctly evaluate brain-invasive growth in 3 of 14 brain-invasive meningiomas. Although we expected a self-limiting relationship between B/M-I availability and the rate of brain invasion, we observed an almost linear (albeit exponential) relationship in the literature (Fig. 1c), indicating that not enough studies reported B/M-I with close scrutiny.

Factors related to brain invasion

Three studies reported that the brain invasion rate of meningiomas tended to be higher in males [17, 43, 48]. Our meta-analysis showed concordant results in meningiomas for all grades; however, the results were not significant for each WHO grade. Therefore, the higher brain invasion rate of meningiomas in males was likely due to the higher frequency of high-grade meningiomas in males; the same might hold true for the preponderance of brain invasion in tumors not located at the skull base [18]. Brain invasion was significantly more frequent in non-skull base tumors among all grades, although this might not hold true for each WHO grade given the small number of studies.

Brain invasion and recurrence

We showed that brain invasion was a prognostic factor for recurrence in meningiomas of all grades (pooled HR = 2.45) albeit with substantial heterogeneity ($I^2 = 74\%$), which was related to the varying frequencies of brain-invasive tumors among studies ($p = 0.006$). However, such variability, including the rate of high-grade tumors, did not fully explain the heterogeneity (Online Table 2). Brain invasion rates in the included studies varied greatly from 2–18%. Therefore, the heterogeneity of HRs was most likely due to the varying frequencies of assessable B/M-I, which could not be analyzed due to insufficient data.

When analyzing HRs between brain-invasive and noninvasive meningiomas, specimens without brain tissue on the analyzed slides were excluded in a few studies [20, 32, 48, 52] but were included as "noninvasive" and subjected to analysis in others [17, 29, 43]. When included, some brain-invasive tumors without B/M-I on the slides might have been labeled "noninvasive." Consequently, if true brain-invasive tumors have a higher recurrence rate, the calculated HR is expected to be smaller than the actual HR, because some true brain-invasive tumors are labeled noninvasive tumors. In fact, Vranic et al. [52] reported that the likelihood of progression/recurrence in brain-invasive versus noninvasive GII-00 meningiomas had an HR of 7.2 [CI (0.9–55.7)] when excluding cases without B/M-I, and an HR of 1.2 [CI (0.6–2.3)] when including them. Meanwhile, if brain-invasive and noninvasive GI-00 meningiomas indeed have similar prognoses as reported by Biczok et al. [14], the HR does not differ: excluding and including cases without B/M-I yielded HRs of 0.848 [CI (0.222–3.246)] and 0.852 [CI (0.268–2.71)], respectively.

In the benchmark study by Perry et al.[9], brain invasion was the strongest prognostic factor for recurrence in gross totally removed tumors. Brain invasive meningiomas ($n = 23$) including 10 BIOB showed a comparable recurrence rate to other atypical meningiomas. These results are mostly concordant with the results of this review. But Perry et al. did not analyze a recurrence rate of BIOB separately, probably due to the insufficient number of BIOB cases for a definite conclusion.

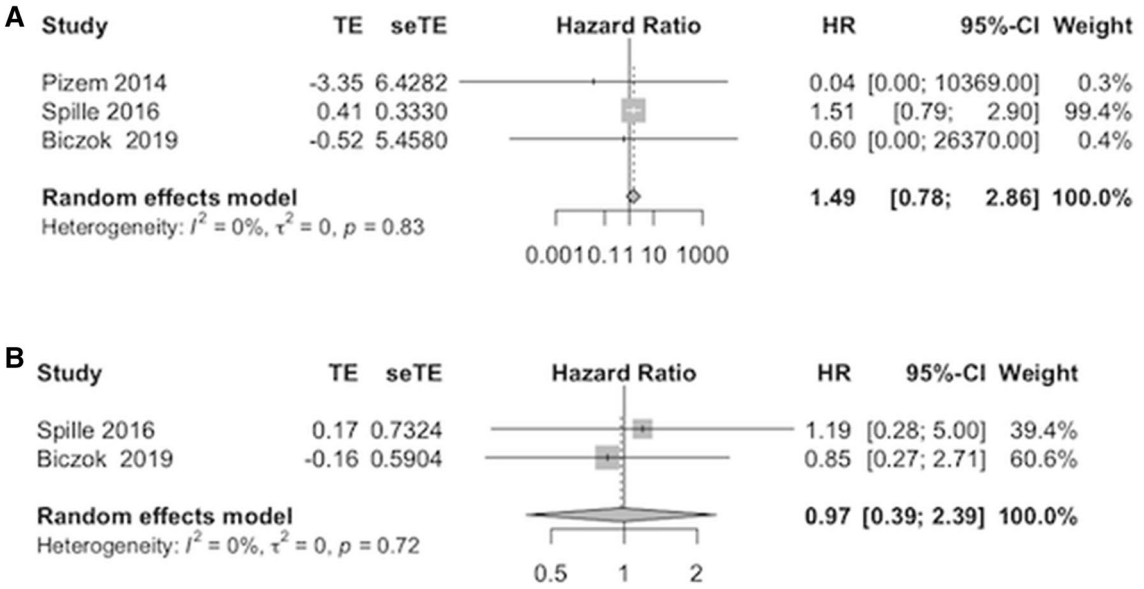


Fig. 4 Forest plots showing hazard ratio (HR) for recurrence between invasive and non-invasive meningiomas by univariate **a** and multivariate analysis **b** in WHO 2000 grade I meningiomas

Our study indicated that higher-grade meningiomas were more likely to invade the brain. Therefore, brain-invasive tumors had poorer prognosis overall. However, this might not hold true upon analyzing each grade separately. In our review, three studies found no significant difference in PFS between brain-invasive and noninvasive benign meningiomas [14, 17, 20] in univariate or multivariate analysis.

Another interesting finding of our review was that brain-invasive GII-00 meningioma had significantly shorter PFS than noninvasive GII-00 meningioma. Because atypical meningiomas per the WHO 2000 criteria are thought to be heterogeneous, our findings will be helpful for further categorizing this grade. In contrast, we found that brain invasion was not a prognostic factor for GII-16 meningioma. However, it might become a better prognostic factor if the inclusion rate of BIOB exceeds 20% (Fig. 5c). Therefore, we propose distinguishing BIOB from other atypical meningiomas.

Limitations

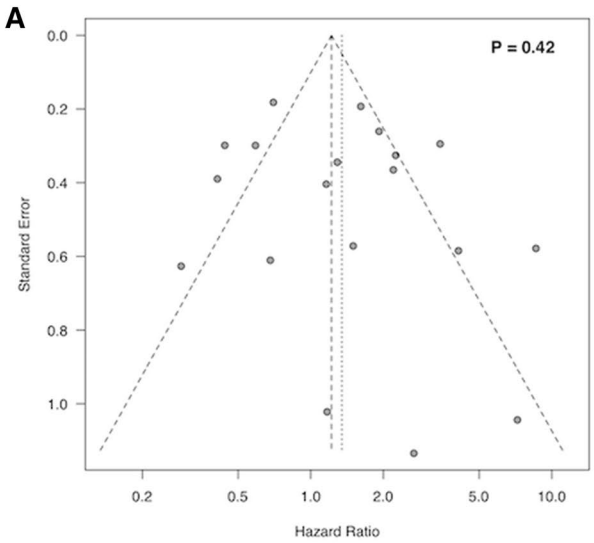
One limitation of our study is that the rate of brain invasion exhibited substantial heterogeneity among studies. Although this was partly attributable to the varying rates of high-grade tumors, it remained high even within tumors of the same grade. The availability of B/M-I information also affected the heterogeneity of the brain invasion rate owing to the retrospective nature of almost all included studies. Nevertheless, one prospective study reported the highest rates of both B/M-I and brain invasion. While that prospective study combined prospective and retrospective results, the prognoses of BIOB and GI-16 meningioma were comparable, and the HR of PFS was higher for invasive GII-00 meningioma than for noninvasive meningioma. Because relatively few studies reported the number of cases with B/M-I, we were unable to analyze the relationship between HRs and the observed heterogeneity.

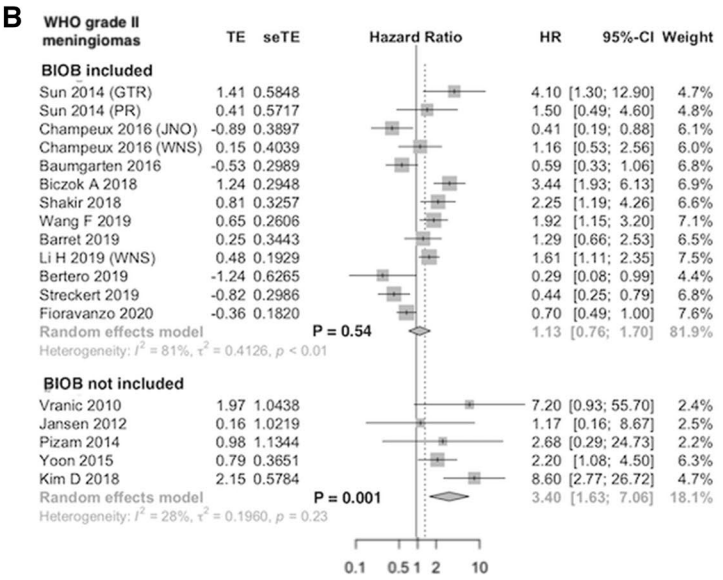
The analysis of the HRs of grade I meningioma had a potential risk of publication bias. All three studies included in the analysis were published after the WHO 2007 criteria [14, 17, 20] and were too small to be evaluated for publication bias, thus warranting further evaluation.

We presented the meta-analysis results for both univariate and multivariate analyses. In multivariate analysis, variability in the methods and variables used to derive the final multivariate model biased comparative analysis across studies. Therefore, we based our discussion mainly on the meta-analysis results of univariate analyses. Although there might be other factors related to the HR (e.g., the degree of resection or combined radiation therapy), the results of univariate and multivariate analyses were largely similar.

Conclusions

We conducted a meta-analysis of the prognostic significance of brain invasion in meningiomas. Although most included studies were retrospective with low evidence levels, brain invasion had significant prognostic implications for meningiomas, especially in GII-00. In contrast, pooled data showed that BIOB had a comparable prognosis to GI-00 meningioma and a better prognosis than GII-16. The lack of B/M-I histology in most studies often precluded precise





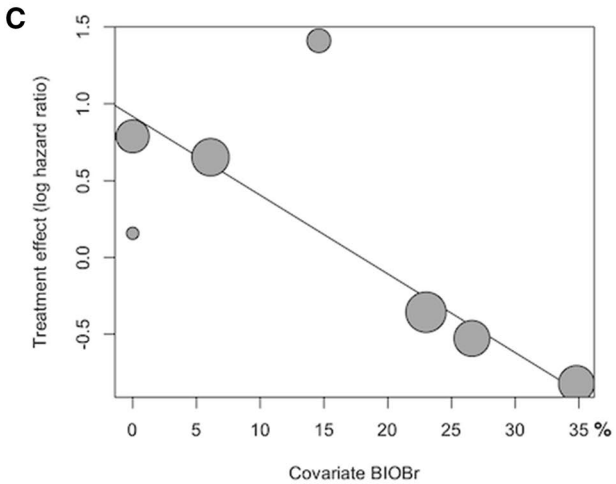


Fig. 5 **a** Funnel plot of hazard ratio (HR) in WHO grade II meningiomas showing symmetrical distribution ($p = 0.42$). **b** Forest plot of HR in grade II meningioma. Pooled HR showed brain-invasive tumors exhibited significantly higher recurrence rate than non-invasive ones in the tumor group without "brain invasive meningiomas with otherwise benign histology (BIOB)". Pooled HR is significantly higher in the tumor group without BIOB than that with BIOB (Meta-regression, $p = 0.02$). **c** Bubble plot showing meta-regression of HR in WHO grade II meningiomas by the inclusion rate of BIOB (BIOBr) ($p < 0.0001$)

data analysis. Therefore, additional data regarding the prognosis of BIOB together with information about B/M-I are required.

The pathology of B/M-I is not always available. However, the noninvasiveness of tumors can be determined in pathological specimens without sampling the surrounding brain tissue. If the surgical record describes a tumor as being removed while leaving the arachnoid membrane completely intact together with postoperative MRI confirmation, tumor invasion can be ruled out even without brain tissue. Meanwhile, if a specimen exhibits an arachnoid membrane over the tumor surface, the tumor does not invade the brain. Such information will enhance the precision of data analyses.

Hence, our review and meta-analysis collectively indicated no rationale for using brain invasion as a standalone criterion for atypical meningioma. Therefore, we recommend a diagnosis of BIOB until its definite prognostic value is determined.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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