Will an Asymptomatic Meningioma Grow or Not Grow? A Meta-analysis

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Abstract

Background The treatment strategy for patients with an asymptomatic meningioma is still controversial. Key to an optimal decision is a careful evaluation of the growth possibilities of the meningioma by taking the patient's clinicoradiologic factors into consideration. However, previous studies have disagreed about the risk factors relating to tumor growth.

Methods A comprehensive search of PubMed, Embase, and the ISI Web of Knowledge was performed. Using a meta-analysis with nine subsidiary studies including 777 patients, we analyzed the correlation of the growth pattern of meningioma with patient gender, tumor location, tumor calcification, magnetic resonance imaging (MRI) T2 signal intensity, and peritumoral brain edema.

Results The growth rate of meningioma was negatively correlated with tumor calcification (odds ratio [OR]: 0.23; 95% confidence interval (CI), 0.11–0.46; $p < 0.001$) but positively associated with MRI T2 signal intensity (OR: 2.75; 95% CI, 1.75–4.33; $p < 0.001$). No correlations were found between tumor growth and other factors such as gender (OR: 1.29; 95% CI, 0.84–1.99; $p = 0.24$), skull base location (OR: 0.80; 95% CI, 0.25–2.58; $p = 0.70$), and peritumoral brain edema (OR: 1.24; 95% CI, 0.29–5.27; $p = 0.77$).

Conclusions Two factors, tumor calcification and low MRI T2 signal intensity, indicate the possibility of a slow growth meningioma. In such cases of asymptomatic meningioma, a follow-up strategy can be preferentially considered.

Keywords
- asymptomatic meningioma
- natural history
- meta-analysis

Introduction

Meningioma is one of the most common benign types of intracranial tumors. It grows from arachnoid brain cells and clinically makes up 13–26% of all primary intracranial tumors.[1] Due to the compression of the tumor to adjacent vessels and nerves, various clinical symptoms may develop.[1] Depending on the location and the size of the tumor, surgery and stereotactic radiotherapy are the common treatments to control tumor growth, relieve symptoms, and improve quality of life.[1]

In recent years, with the extensive application of head computed tomography (CT) and magnetic resonance imaging (MRI) examination, more asymptomatic meningiomas have been detected incidentally.[2] The patients manifest no tumor-related symptoms or only show nonspecific symptoms such as mild headache and dizziness.[3] The decision to operate on such patients should be based on careful weighing of the

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surgical risks and benefits. At the early stage, the benefits of surgery are to achieve a lower Simpson grade resection and reduce operative risks associated with a relatively smaller tumor size compared with those at a later stage with obvious symptoms.[4] Now an important question arises: How does asymptomatic meningioma progress, or when will the symptoms develop?

Previous studies on the growth pattern of meningioma demonstrated that most meningiomas grew indolently or even no growth is observed for many years.[2,5–7] In the early 1990s, Firsching et al[5] studied the growth rate of asymptomatic meningioma by CT follow-up of 17 patients. In the follow-up period of $\sim$ 21 months, no growth or only minor growth was observed in most cases, and none of those patients underwent surgery.[5] Another follow-up study of 67 patients with asymptomatic meningioma was analyzed for at least 5 years. It showed that 42 of 67 cases ($\sim$ 62.7%) manifested no obvious growth.[4] Braunstein and Vick[6] even followed one parietal falx meningioma and one frontal convexity meningioma for up to 12.8 years, and still no growth of tumors was observed. An epidemiological study conducted in Germany demonstrated that from 1961 to 1986, there was an annual incident detection of meningioma of 1.85 per 100,000 population. Interestingly, up to half of the proportion was discovered by autopsies, suggesting that some patients did not even know they had a meningioma all their lives.[7] Therefore, asymptomatic meningioma may remain undiscovered because of the tumor's slow growth. In such cases, conservative follow-up is apparently a better choice than an operation because it avoids postsurgical complications.

The key to a conservative treatment decision is the careful evaluation of the growth possibilities of the meningioma that can be predicted using a patient's clinicoradiologic factors such as gender, tumor location, calcification, MRI T2 signal intensity, and peritumoral brain edema. However, so far the associations between tumor growth and the parameters just listed have not always been consistent. This study aimed to further clarify the meningioma growth-related factors with a meta-analysis. We compared our results with previous reports; consistencies and the inconsistencies are discussed.

Materials and Methods

Literature Search

The literature was searched via PubMed, Embase, and the ISI Web of Knowledge from January 1970 to August 2013. The following keywords were chosen for the electronic search: *asymptomatic meningioma, incidental meningioma, small meningioma, natural history, growth, conservative treatment, conservative therapy,* and *follow-up.* To cover the maximum number of eligible studies, different combinations of the keywords were applied to the literature search. The references of all eligible articles were searched again, in case they were not covered by the electronic searches the first time.

Selection Criteria

The following criteria were used to select the data for the meta-analysis: (1) The cohort or case-control original studies presented quantitative data on the association between clinical or radiologic factors and growth of meningioma; (2) tumor growth was demonstrated on serial MRI or CT imaging; (3) the language of the publications should be confined to English; (4) the studies would be excluded if the full text could not be found or if the published data were insufficient to estimate an odds ratio (OR) and a confidence interval (CI); and (5) when there were multiple articles by the same group based on similar patients, only the most recent article was included.

Data Extraction

Two independent investigators extracted all relevant data from the included studies including author, year, country, patient number, mean follow-up duration, growth measurements, cutoff score for tumor growth, and factors related to tumor growth. Disagreements about any data extraction by the two investigators were referred back to the original article to achieve consensus.

Statistical Analysis

Review Manager v. 5.2 was applied for data analysis. Comparisons of dichotomous measurements were performed with the pooled estimates of ORs, as well as the 95% CIs. A p value < 0.05 was considered statistically significant. Between-study heterogeneity was evaluated using the I^2 statistic. If $I^2 > 50\%$, it indicates statistically significant heterogeneity. If there was heterogeneity, the random model was adopted; otherwise the fixed model was used. Sensitivity analysis was performed to evaluate the stability of the pooled estimates by exclusion of specific studies. Publication bias was assessed by the Begg rank correlation and the Egger weighted regression. A p value < 0.05 was considered a statistically significant publication bias.

Results

Search Results and Study Characteristics

A total of 1,120 duplicates among the three databases and 203 non-English articles were removed from the initial 3,315 records, leaving 1,992 articles to review. According to the titles and abstracts, 33 of them were potentially eligible and the full texts were reviewed. Overall, 24 articles were excluded and 9 articles were included according to the selection criteria outlined earlier. ►**Fig. 1** shows a flowchart of the selection process. ►**Table 1** lists the details of the included studies.

Association between Tumor Growth and Clinicoradiologic Factors

The association between tumor growth and clinicoradiologic parameters is analyzed and illustrated in ►**Fig. 2**. It shows that tumor growth was negatively correlated with tumor calcification (pooled OR: 0.23; 95% CI, 0.11–0.46; $p < 0.001$; random effect; ►**Fig. 2A**) but positively associated with MRI T2 signal intensity, leading to a risk difference of 2.75 (95% CI, 1.75–4.33; $p < 0.001$; fixed effect; ►**Fig. 2B**). No association was found between tumor growth and other features such as sex (pooled OR: 1.29; 95% CI, 0.84–1.99;

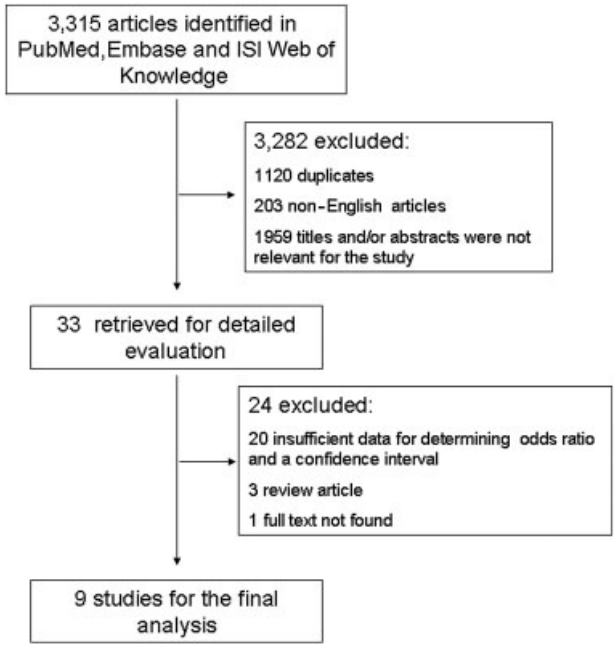

Fig. 1 Flowchart for selection of studies.

$p = 0.24$; fixed effect; ►**Fig. 2C**), skull base location (pooled OR: 0.80; 95% CI, 0.25–2.58; $p = 0.70$; random effect; ►**Fig. 2D**), and peritumoral brain edema (pooled OR: 1.24; 95% CI, 0.29–5.27; $p = 0.77$; random effect; ►**Fig. 2E**).

Subgroup and Sensitivity Analysis

To examine whether the pooled data of the growth-related factors were influenced by different growth measurements on serial imaging and to evaluate the potential source of heterogeneity, the subgroups of tumor volumetry and maximum diameter measurement were further classified, and the subgroup analysis was performed accordingly (►**Table 2**). Despite different methods of measurements, calcification and MRI T2 hyposignal still indicated a significantly slow growth of meningioma. Other factors such as sex and peritumoral brain edema nevertheless had no significant correlation with tumor growth. Only one previous study[8] adopting the method of volumetric analysis suggested a negative association between skull base location and tumor growth. The other three studies[4,9,10] using maximum diameter measurement found no correlation between them.

In addition, exclusion of one study at a time had no influence on the main effect. For instance, regarding the factor of tumor calcification, if the studies of Rubin et al and Oya et al were excluded from the group, the I^2 value decreased from 55.2% to 0.0%. However, the pooled OR is 0.24 (95% CI, 0.13–0.44; $p < 0.001$, fixed effect) and still indicates a significant association between calcification and slow tumor growth. Similarly, for the factor of MRI T2 signal intensity, random omission of any one study did not influence the positive correlation between MRI T2 signal intensity and tumor growth ($p < 0.001$; fixed effect).

Publication Bias

The *p* values of the Begg test varied from 0.22 to 1.00; those of the Egger test varied from 0.23 to 0.94 for all the previously mentioned meta-analyses. Because in both the bias estimation models the *p* values were > 0.05 and the total number of studies for each factor was limited (< 10), no funnel plot was applied.

Discussion

The clinical and radiologic characteristics of patients are important to identify the growth status of a meningioma and predict its development. Many articles have studied factors relating to tumor growth. However, many of their observations are inconsistent. With our meta-analysis we studied a total of 777 samples of meningiomas and analyzed the correlation between tumor growth potentials and clinical factors including gender, tumor location, calcification, MRI T2 signal intensity, and peritumoral brain edema.

The female hormones progesterone and estrogen play a role in the development of meningioma and are important for the

Table 1 Characteristics of included studies

Study	Year	Country	No. of patients	Mean FU, mo	Growth measurement	Cutoff score for growth definition
Yoneoka et al[26]	2000	Japan	37	50.4	Volumetry	1 cm^3/y
Kuratsu et al[19]	2000	Japan	63	36.6	Volumetry	NS
Hashiba et al[15]	2009	Japan	70	39.3	Volumetry	15%
Hashimoto et al [8]	2012	Japan	113	46.9	Volumetry	NS
Nirro et al[18]	2000	Japan	40	38.4	Maximum diameter	NS
Herscovici et al[30]	2004	Israel	51	67	Maximum diameter	2 mm
Yano and Kuratsu[4]	2006	Japan	67	> 60	Maximum diameter	NS
Rubin et al[9]	2011	Israel	63	65	Maximum diameter	NS
Oya et al[10]	2011	USA	273	45.6	Maximum diameter	2 mm

Abbreviations: FU, follow-up; NS, not specified.

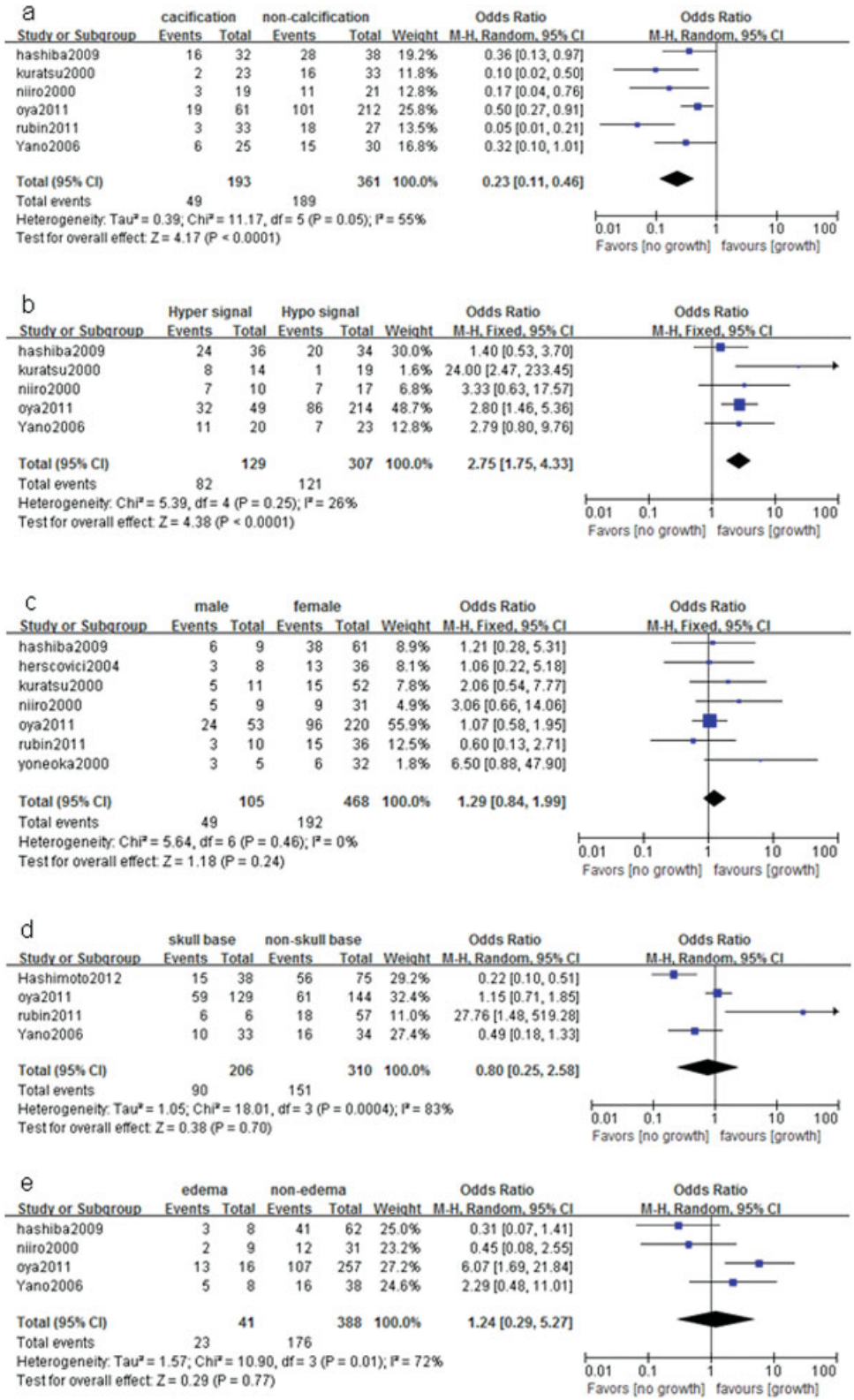

Fig. 2 Meta-analysis of the association between tumor growth on serial imaging and the clinicoradiologic factors of (A) calcification, (B) magnetic resonance imaging T2 signal intensity, (C) sex, (D) tumor location, and (E) peritumoral brain edema.

prognosis.[11] Does gender affect meningioma growth? One previous study found that the growth potential of meningioma cells of male patients was significantly higher than that of females.[12] However, Nakasu et al[13] and Hashiba et al[14,15] found no correlation between gender and tumor cell proliferation, which is consistent with the results of our meta-analysis.

Skull base meningioma accounts for a considerable proportion of asymptomatic incidental meningiomas.[8]

Table 2 Meta-analysis of factors related to tumor growth in subgroups classified according to different growth measurements on serial imaging

	Volumetric analysis	Maximum diameter
Male/female		
No. of studies	3[15,18,26]	4[9,10,18,30]
OR	2.08	1.12
95% CI	0.86–5.04	0.68–1.83
P	0.107	0.662
I^2	0.0%	0.0%
Skull base/non–skull base		
No. of studies	1[8]	3[4,9,10]
OR	0.22	1.24
95% CI	0.10–0.51	0.33–4.64
P	<0.001	0.753
I^2		75.5%
Calcification/noncalcification		
No. of studies	2[15,18]	4[4,9,10,19]
OR	0.23	0.22
95% CI	0.10–0.53	0.08–0.59
P	0.001	0.002
I^2	42.5%	67.4%
MRI T2 hypersignal/hyposignal		
No. of studies	2[15,18]	3[4,10,19]
OR	2.54	2.85
95% CI	1.12–5.76	1.66–4.92
P	0.026	<0.001
I^2	80.7%	0.0%
Edema/Nonedema		
No. of studies	1[15]	3[4,10,19]
OR	0.31	2.019
95% CI	0.07–1.41	0.47–8.76
P	0.129	0.348
I^2		64.3%

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio.

Because its deep location is adjacent to many important nerves and blood vessels, the operation is quite challenging and postsurgical complication rates are relatively high.[16] Accordingly, a decision to operate on an asymptomatic meningioma in the skull base should be made with caution. The correlation between tumor growth and skull base location remains controversial. Hashimoto et al[8] found a negative correlation of tumor growth with skull base location, whereas Rubin et al[9] found a positive correlation. No correlations between tumor growth and skull base location were demonstrated by Oya et al[10] and Yano and Kuratsu.[4] Our results show that skull base location does not correlate with tumor growth rate. This suggests that conservative treatment of a skull base tumor should be considered.

One significant factor negatively associated with tumor growth in our analysis is calcification, a common feature of meningioma.[17] Many previous studies also demonstrated this significant association.[9,18,19] For instance, Nirro et al followed up meningioma patients for an average of 38.4 months using serial imaging.[18] Overall, 16 of 19 cases of calcified meningiomas showed no growth; 11 of 21 noncalcified meningiomas grew significantly. Rubin et al[9] followed 33 patients with calcified meningiomas for a mean period of 65 months and observed growth in only 3 cases. Eighteen of 27 noncalcified meningiomas showed obvious growth.

The meta-analysis also indicates that MRI T2 signal intensity, which mirrors tumor texture, is significantly related to meningioma growth. Low T2 signal indicates a slow growth of

meningioma. The reasons for the low T2 signal include the following: (1) There is less water within tumor cells, (2) there are more fibrosis components, and (3) the texture of tumors is hard, such as calcification.[20,21] Therefore the prognostic significance of MRI T2 signal intensity is consistent with tumor calcification.

Peritumoral brain edema frequently accompanies meningioma and may indicate an invasive growth pattern as shown on MRI that the brain–tumor interface disappears.[22–24] However, in our analysis it was not a significant factor indicating tumor growth.

Do the methods of tumor size measurements influence the results? In the included studies, two methods were used to measure tumor growth: maximum tumor diameter measurement or tumor volumetry. Maximum tumor diameter is defined by the maximum linear diameter in any direction of the tumor. At least two views of axial, coronal, and sagittal planes should be used to check the value.[10] In tumor volumetry, image-analyzing software was used to trace the contour of the tumor in each slice image. The tumor volume was calculated by multiplying each tumor area by the slice thickness of the image.[10] It was demonstrated that both methods can effectively detect tumor growth. The volume method is relatively more sensitive than the maximum diameter method, especially for larger tumors or tumors located in the skull base.[25] Due to the different measurements for tumor growth, different studies may conclude distinct growth-related risk factors, thus leading to data heterogeneity of this study. Therefore, the subgroup analysis based on the respective growth measurement was performed again. However, the later results still confirmed tumor calcification and MRI T2 low signal as significant factors for slow tumor growth.

Our results can contribute to an optimal treatment choice for asymptomatic meningioma. For instance, if a patient has tumor calcification or a low signal in the MRI T2 sequence, a follow-up observation with neuroimaging and clinical monitoring can be preferentially considered. The follow-up interval can be as long as 6 months or 1 year.[4] However, if the imaging examination does not find calcification or low signal in the MRI T2 sequence, the possibility of rapid growth exists within such tumors. However, because the patient manifests no symptoms, follow-up imaging could still be suggested at the early stage, and the follow-up interval should be shorter. As suggested by several studies, the reexamination of imaging should be done 3 months after diagnosis to exclude atypical or malignant meningioma or other nonmeningioma lesions.[2,4,26,27] If the tumor still shows no obvious development, the follow-up period can be extended to 6 months or 1 year; the rate of tumor growth should be calculated every time.[2,4,26] In cases where the tumor grows at an annual rate > 1 cm^3 or tumor-related symptoms occurs, surgery needs to be considered.[26,28–30] Otherwise the follow-up observation can be continued every year.[2,4,26]

This study has some limitations. First, in the growth assessment with serial imaging, all meningiomas were diagnosed by image rather than by pathology. Some lesions, such as hemangiopericytoma or meningeal metastasis, can mimic typical meningioma on MRI, but the first two exhibit aggressive growth behavior.[2] Mixing of these nonmeningioma lesions in the meningioma group may lead to different factors related to tumor growth. Second, the included subsidiary studies did not adopt a unified criterion for definition of growth. For instance, Yoneoka et al[26] defined rapid tumor growth by an annual growth > 1 cm^3, whereas the criterion of Hashiba et al for rapid growth was an annual volume growth rate $> 15\%$.[15] Because each criterion of the respective study was made on its own standards to eliminate measurement bias, these diverse growth definitions were relatively comparable.[15] Third, the lengths of the follow-up periods in different studies were not totally identical. Finally, in the process of the literature retrieval, only nine articles matched the full inclusion criteria. Some studies were regretfully not included because no data with a format fit for meta-analysis were presented. Therefore, we hope that future studies adopt a unified definition of tumor growth and a consistent follow-up duration and that they provide adequate original data. Thus the meta-analysis may maximally reduce research heterogeneity and bias.

In conclusion, we have shown that two factors, tumor calcification and MRI T2 low signal, indicate slow growth or even no growth of meningioma. No significant correlation between gender, tumor site, peritumoral edema, and tumor growth was found in our study. The results are helpful to predict the growth pattern of asymptomatic meningioma and thus choose an optimal treatment for patients.

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