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Histopathological Investigation of Meningioma Capsule with Respect to Tumor Cell Invasion

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Abstract

No previous study has histopathologically investigated whether a meningioma capsule presents with tumor cells. We investigated which types of tumor capsules (TCs) included tumor cells to help intraoperatively determine those TCs that do not need to be removed and have a low recurrence risk. We investigated 22 specimens of 14 newly diagnosed meningiomas from February 2011 to June 2021. The capsules were classified into three types: TC, capsule-like thickened arachnoid membrane (CAM), and extended membrane (EM). Capsule properties were scored by hardness (soft = 1, medium = 2, hard = 3) and transparency (high = 1, medium = 2, low = 3). The hardness, transparency, and score sums were compared between capsules with and without tumor invasion in the CAM and EM types. The mean follow-up duration was 40.6 months, and there was only one recurrence in a remote location from the residual capsule. Nine capsules were classified as TC, seven as CAM, and six as EM. The tumor cells invaded 88.9% of TCs, 42.9% of CAMs, and 50% of EMs. The hardness, transparency, and score sums for CAMs with tumor invasion were lower than those for CAMs without tumor invasion, although not significant ($P = 0.114$, $P = 0.114$, $P = 0.057$, respectively). A thickened TC or soft and highly transparent CAM indicated a high risk for tumor cell invasion; thus, such cases require a careful and long-term follow-up. Hard and low transparent residual CAMs may have had a low risk for tumor invasion; therefore, leaving such capsules that tightly adhere to the eloquent cortex can be theoretically justified to avoid damaging the brain surface.

Keywords: histopathology, meningioma, recurrence, capsule, invasion

Introduction

Meningioma is the most common intracranial brain tumor, accounting for approximately 20%-36% of primary brain tumors.[1-4] Several meningiomas that disrupt the arachnoid membrane and invade the brain tissue are diagnosed as a malignant World Health Organization (WHO) grade II meningioma. Contrarily, most meningiomas are demarcated by a basement membrane that is collagen type 4-positive.[5] This basement membrane sometimes grows into thick connective tissue and forms a capsule that can tightly adhere to the brain tissue.[6] In the majority of cases, removal of these capsules is considered optimal. However, when the capsule adheres to the eloquent cortex, it should remain to avoid damaging the brain tissue,[7-9] even if the capsule adheres to the non-eloquent cortex. However, if a capsule includes tumor cells and remains on the brain surface, there is a risk of recurrence. Thus, leaving the tumor capsule (TC) may be a trade-off in tumor control necessary for protecting the brain surface. No previous study has histopathologically investigated whether meningioma capsules present with tumor cells and whether leaving the capsules increases the risk of recurrence. In this study, we investigated whether several types of TCs included tumor cells to assist with the intraoperative selection of the capsules that can remain.

Methods and Materials

The study was approved by the institutional review

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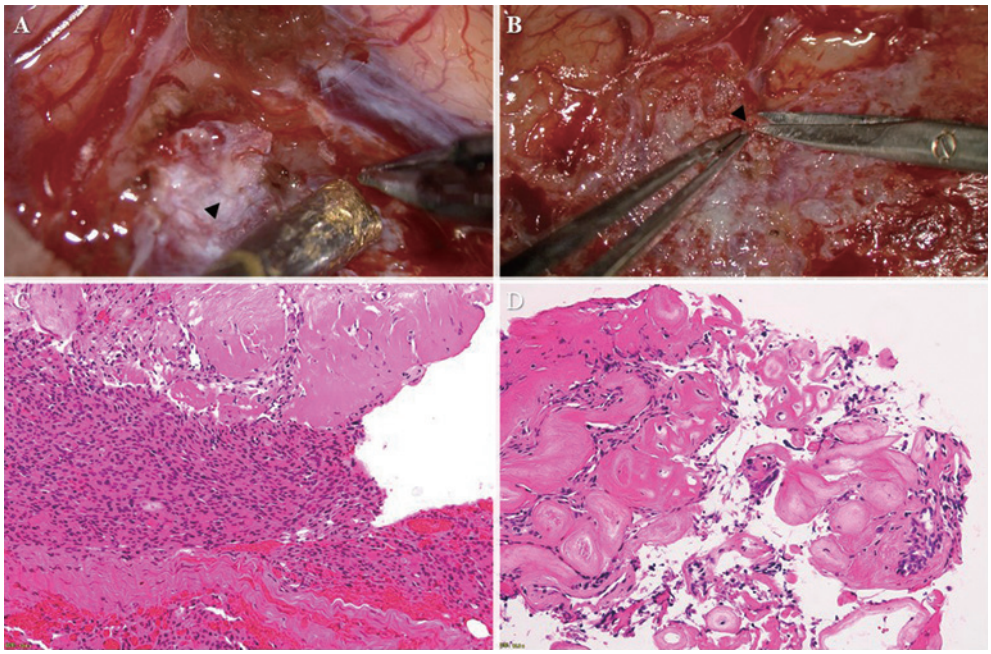

Fig. 1 Typical intraoperative (A, B) and pathological images (C, D, original magnification ×20) of the TC type. (A) and (C): Images of specimen 16. (A) Residual thickened capsule tightly adhering to the brain surface following tumor removal. (C) Solid tumor invasion in the fibrous capsule. (B) and (D): Images of specimen 20. (B) Residual thickened capsule tightly adhering to the brain surface following tumor removal. (D) Invasion of small tumor tissue between hyalinized vessels in the tumor capsule. Arrowhead shows the location of the harvested specimen. TC: thickened capsule on the tumor surface.

board of Tokyo Medical and Dental University. All patients in this case series provided informed consent for the inclusion of their clinical data in this manuscript.

We investigated 22 specimens from 14 patients newly diagnosed with meningioma who underwent surgery in our hospital from February 2011 to June 2021. All the specimens were harvested from the partially remaining capsule on the brain surface as it was considered optimal to leave the capsule to keep the brain surface intact. Only specimens that were harvested for the specific purpose of confirming tumor invasion were included, as the capsule properties and histopathological findings should have corresponded precisely. When the capsule properties and histopathological findings did not correspond precisely, the specimens were excluded.

The capsules were classified into three types based on the intraoperative findings: TC, thickened capsule on the tumor surface (Fig. 1A, B); capsule-like thickened arachnoid membrane (CAM), thickened membrane similar to the arachnoid membrane between the tumor or TC and the brain surface (Fig. 2A, B); and extended membrane (EM), the membrane extended along the surface of the dura mater without continuity with the dura mater, around the tumor (Fig. 3A, B). Regarding the distinction between TC and CAM, when the capsule between the tumor and brain surface was distinct from the thickened arachnoid membrane, the capsule was classified as TC; otherwise, the capsule was classified as CAM. In the CAM and EM types, the capsule properties were defined by the intraoperative findings as follows: hardness (soft = 1, medium = 2, hard = 3) and transparency (high = 1, medium = 2, low = 3). As for the hardness scoring, soft was defined as soft like the arachnoid membrane, hard was defined as hard like the pericranium, and when in between soft and hard, it was defined as medium. For scoring transparency, when the transparency was similar to the arachnoid membrane, it was defined as high; when the opposite side of the membrane was not seen through the membrane at all, it was defined as low; and when the transparency was in between high and low, it was defined as medium. The hardness, transparency, and sum of these two scores were compared between capsules with and without tumor invasion in both the CAM and EM types.

The following factors were retrospectively reviewed: age, sex, follow-up period, WHO grade, neurological deficit after surgery, presence of recurrence, capsule type (TC, CAM, or EM), presence of tumor cell invasion of the capsule, and capsule properties (hardness and transparency).

The pathological diagnosis and tumor cell invasion into the capsule were determined by a pathologist using hematoxylin-eosin (HE) staining. When the pathologist could not determine the presence or absence of tumor invasion only from HE staining, immunohistochemistry such as EMA and somatostatin receptor 2a were checked to determine the tumor invasion. The capsule type and properties were assessed by one surgeon who reviewed the surgi-

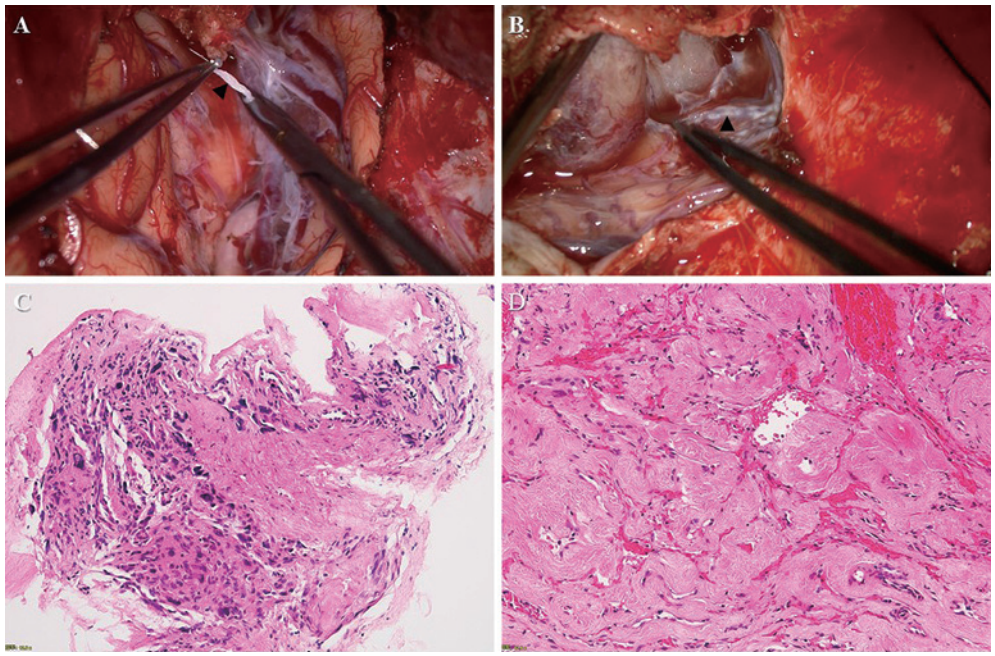

Fig. 2 Typical intraoperative (A, B) and pathological images (C, D, original magnification ×20) of the CAM type. (A) and (C): Images of specimen 3. (A) Thickened membrane with similar properties to the arachnoid membrane on the brain surface following tumor resection. The membrane is soft and highly transparent. (C) Crushed tumor tissue in the fibrous capsule. (B) and (D): Images of specimen 10. (B) Thickened membrane with similar properties to the arachnoid membrane between the tumor and brain surface. The membrane is soft with medium transparency. (D) Dense fibrous tissue with many vessels without tumor invasion. Arrowhead shows the location of the harvested specimen. CAM: thickened membrane with similar properties to the arachnoid membrane between the tumor and brain surface.

cal videos.

Statistical analyses were conducted using SigmaStat 10.0, (Systat Software Inc., Palo Alto, CA, USA). The Mann-Whitney U test was employed to investigate the correlations between the CAM capsule properties and pathological tumor invasion. Statistical significance was set to $P < 0.05$.

Results

The characteristics of the 22 specimens from the 14 patients are summarized in Table 1. The mean age was 60.3 (range, 36-83) years, and seven patients were male (50%). The tumors were located at the convexity, parasagittal, falx, craniofacial, sphenoid ridge, and petrous apex in four, three, three, two, one, and one patient, respectively. Eleven meningiomas were WHO grade I (transitional 6, metaplastic 2, meningothelial 1, microcystic 1, and secretory 1), and three were grade II (atypical 3). One patient with a WHO grade II meningioma underwent adjuvant intensity-modulated radiation therapy of 60 Gy/30 Fr. The mean follow-up duration was 40.6 (6-131) months, and only one patient experienced recurrence in a remote location from the residual capsule (Table 1).

Nine capsules were classified as TC, seven as CAM, and six as EM. Eight of the nine TCs (88.9%) were invaded by tumor cells, and only one TC (11.1%) exhibited no tumor invasion. However, the TC capsule that did not exhibit tumor invasion had tumor cells attached to the surface. Three of the seven CAMs (42.9%) and three of the six EMs (50%) were invaded by tumor cells (Table 2).

Among the three CAMs with tumor invasion, all three (100%) were soft, two (66.7%) had high transparency, and one (33.3%) had medium transparency. However, among the four CAMs without tumor invasion, only one (25%) was soft, two (50%) had medium hardness, one (25%) was hard, three (75%) had medium transparency, and one (25%) had low transparency. Of the three EMs with tumor invasion, one (33.3%) specimen each had a soft, medium, and hard capsule, two (66.7%) had medium transparency, and one (33.3%) had low transparency. Of the three EMs without tumor invasion, one (33.3%) was soft, two (66.7%) had medium hardness, one (33.3%) had medium transparency, and two (66.7%) had low transparency (Table 3). The typical intraoperative and pathological images of each type of capsule are presented in Figs. 1-3. In addition, each typical immunohistochemistry picture of the presence and absence of tumor invasion is presented in Supplementary Figures 1 and 2.

The hardness scores of the CAMs with tumor invasion were lower than those without tumor invasion (mean: 1 vs. 2) but not significantly different ($P = 0.114$). Similarly, the

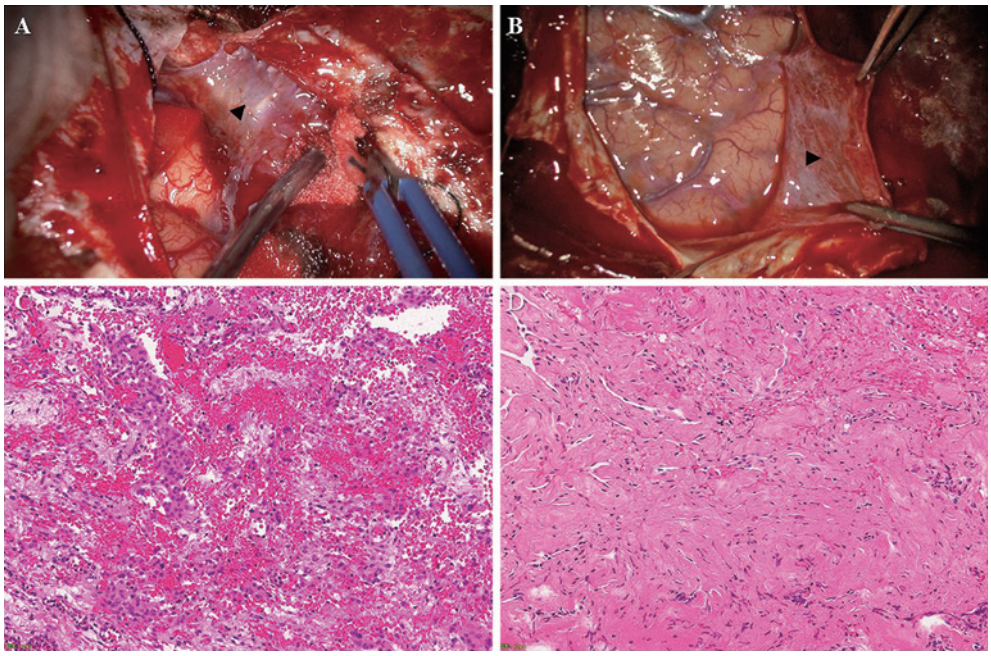

Fig. 3 Typical intraoperative (A, B) and pathological images (C, D, original magnification ×20) of the EM type. (A) and (C): Images of specimen 2. (A) Membrane extending along the dura mater surface around the tumor without brain surface adhesion. The membrane is soft with medium transparency. (C) Loose connective tissue with hemorrhage and tumor tissue clusters. (B) and (D): Images of specimen 7. (B) Membrane extending along the dura mater surface around the tumor without brain surface adhesion. The membrane is of medium hardness and medium transparency. (D) Dense fibrous tissue with many vessels without tumor invasion.
Arrowhead shows the location of the harvested specimen. EM: membrane extending along the dura mater surface around the tumor.

transparency scores and the sum of the hardness and transparency scores were lower in the CAMs with tumor invasion (1.33 vs. 2.25, 2.33 vs. 4.25), although not significantly different (P = 0.114, P = 0.057).

We investigated the relationship between the MIB-1 staining index (MIB-1) of the tumor and hardness of CAM. The MIB-1 tended to be higher in the tumor with soft CAM than that with medium and hard CAM (mean 3.75 vs. 1.1). However, the differences were not significant (P = 0.114).

Discussion

Most meningiomas are demarcated by a basement membrane that is collagen type 4-positive,[5] and this basement membrane sometimes grows into a thick connective tissue that forms a capsule and can tightly adhere to the brain tissue. This thick connective tissue is considered the capsule as defined for TC. In the present study, most TCs (8/9, 88.9%) had tumor invasion. Therefore, we believe that it is better to consider all TCs as having tumor invasion.

Sometimes, a thickened arachnoid-like membrane adheres to the brain surface and develops between the tumor and brain surface. Intraoperatively, a determination cannot be made whether this type of membrane originates from the arachnoid membrane or a newly generated membrane, defined as CAM in our study. In this study, soft and highly transparent CAMs tended to be invaded by tumor cells. In general, malignant tumors are invasive and rarely form hard capsules.[10] Contrarily, many benign tumors grow, pushing the surrounding tissue and creating a capsule between the tumor and the surrounding tissues.[11,12] This evidence suggests that invasive meningioma does not develop a thick and hard capsule between the tumor and brain surface and can easily infiltrate a soft arachnoid membrane; moreover, hard CAM is not usually invaded by tumor cells as the meningioma that formed it is not invasive. Our result indicating a higher growth rate tendency in soft CAM may support the aforementioned hypothesis. However, the number of samples in our study was too small for a definitive conclusion.

We have sometimes observed the membrane extending along the surface of the dura mater around the tumor. This membrane was defined as the EM in our study and can extend along the dura mater far from the tumor. Therefore, almost all these types of membranes result in being residual. Although half of the EMs had tumor invasion in our study, we could not find any difference between the EMs with and without tumor invasion.

The results indicated that not removing TCs and soft

Table 1 Clinical and pathological characteristics of patients and specimens

Case No.	Age (y/o)/ Sex	Location	Subtype (WHO grade)	MIB-1 staining index	Degree of resection (Simpson grade)	f/u duration (M)	Recurrence	Specimen No.	Capsule classification	Tumor invasion into capsule	Hardness of capsule	Transparency of capsule
1	36/f	lt. frontal convexity	Secretory (1)	1.0	1	131	–	1	TC	+	n/a	n/a
2	41/f	lt. frontal parasagittal	Metaplastic (1)	1.0	2	83	–	2	EM	+	soft	medium
3	76/f	rt. sphenoid ridge	Microcystic (1)	3.4	2	48	–	3	CAM	+	soft	high
4	68/m	lt. frontal falx	Transitional (1)	2.5	1	64	–	4	TC	+	n/a	n/a
								5	CAM	+	soft	high
5	73/m	rt. petrous apex	Meningothelial (1)	0.8	3	59	–	6	TC	+	n/a	n/a
6	59/m	rt. craniofacial (cavernous)	Transitional (1)	3.1	1	39	+ remote from capsule	7	EM	–	medium	low
								8	EM	+	medium	medium
7	66/m	lt. craniofacial (cavernous)	Atypical (2)	8.4	3	23	–	9	EM	–	medium	low
								10	CAM	–	soft	medium
8	77/m	rt. frontal falx	Transitional (1)	6.2	2	22	–	11	EM	+	hard	low
								12	TC	+	n/a	n/a
9	83/m	lt. frontal parasagittal	Transitional (1)	1.1	3	16	–	13	CAM	–	medium	medium
								14	CAM	–	medium	medium
								15	TC	–	n/a	n/a
10	57/f	lt. frontoparietal convexity	Metaplastic (1)	1.5	1	23	–	16	TC	+	n/a	n/a
11	50/f	rt. parietal parasagittal	Transitional (1)	16.7	2	24	–	17	TC	+	hard	low
12	42/m	lt. frontal falx	Transitional (1)	3.0	2	18	–	18	CAM	–	hard	low
13	55/f	lt. frontal convexity	Atypical (2)	4.1	1	12	–	19	TC	+	n/a	n/a
								20	TC	+	n/a	n/a
								21	CAM	+	soft	medium
14	74/f	lt. frontal convexity	Atypical (2)	10.0	1	6	–	22	EM	–	soft	medium
mean	61.2			4.5		40.6						

CAM, capsule-like thickened arachnoid membrane; EM, extended membrane; f/u, follow up; lt., left; n/a, not applicable; rt., right; TC, Tumor capsule

and highly transparent CAMs was a high risk of leaving tumor cells. Furthermore, this residual capsule may cause tumor recurrence. Kamitani et al.[13] reported that two meningiomas in which thick arachnoid membranes at the tumor margins were left in place at first surgery recurred at 6 and 12 years following surgery. The patients in this study did not experience recurrence related to the residual capsule maybe because of the short observation periods. In this study, the follow-up period was too short to draw a conclusion regarding the relationship between the residual capsule and tumor recurrence. Therefore, we should carefully conduct long-term follow-up in patients with residual

Table 2 The proportion of capsules with tumor invasion in each type

Capsule type	No. of specimens	Tumor invasion (+) (%)	Tumor invasion (–) (%)
Tumor capsule (TC)	9	8 (88.9)	1 (11.1)
Capsule-like thickened arachnoid membrane (CAM)	7	3 (42.9)	4 (57.1)
Extended membrane (EM)	6	3 (50)	3 (50)
total	22	14 (60.9)	8 (39.1)

Table 3 The properties of capsules in CAM and EM types

Capsule type	No. of specimens	Tumor invasion	No. of specimens	Hardness of capsule			Transparency of capsule		
				soft (%)	medium (%)	hard (%)	high (%)	medium (%)	low (%)
Capsule-like thickened arachnoid membrane (CAM)	7	+	3	3 (100)	0 (0)	0 (0)	2 (66.7)	1 (33.3)	0 (0)
		–	4	1 (25)	2 (50)	1 (25)	0 (0)	3 (75)	1 (25)
Extended membrane (EM)	6	+	3	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	2 (66.7)	1 (33.3)
		–	3	1 (33.3)	2 (66.7)	0 (0)	0 (0)	1 (33.3)	2 (66.7)

CAM, capsule-like thickened arachnoid membrane; EM, extended membrane

TCs or soft and highly transparent CAMs. In this study, it was implied that the hard and low transparent CAMs may have had a low risk for tumor invasion. Thus, in case of low transparent CAM, not removing the residual capsules may be justified when the capsule tightly adheres to the brain surface, especially the eloquent cortex, to avoid damaging the brain surface at the time of the initial surgery.

To the best of our knowledge, this is the first detailed histopathological investigation of tumor invasion into the capsule surrounding the meningioma. However, the follow-up period was too short, and the number of cases was too small to conclude a relationship between the residual capsule and tumor recurrence from our results. We harvested these specimens from residual tumors as much as possible, but the specimens were not harvested from the whole surface. Therefore, there is a possibility of tumor invasion in the different portions of the residual capsules. As the scoring of the capsule properties is, to some extent, based on the subjectivity of the surgeon, standardization is needed. These are the limitations of our study, and therefore, further study is needed.

Conclusion

A thickened capsule on the tumor surface and a soft and highly transparent membrane between the tumor and brain surface indicated a high risk for tumor cell invasion. Thus, a careful long-term follow-up of these patients is needed. Hard and low transparent residual CAMs may have a low risk for tumor invasion. The properties of CAM may reflect the growth rate of the tumor; however, its association with recurrence cannot be determined at this time. When a CAM type of capsule tightly adheres to the brain surface, especially to the eloquent cortex, it is preferable to avoid the removal of the tumor to avoid brain damage. Due to the lack of sufficient number of patients and the short follow-up period, the relationship between the remaining tumor-invaded capsules and tumor recurrence could not be elucidated, and further investigation is required.

Supplementary Material

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Conflicts of Interest Disclosure

The authors declare that there are no conflicts of interest. All authors who are members of the JNS have registered online the Self-Reported COI Disclosure Statement Forms through the website for JNS members.

References

1) Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV: An overview of meningiomas. *Future Oncol* 14: 2161-2177, 2018
2) Ostrom QT, Gittleman H, Fulop J, et al.: CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro Oncol* 17: iv1-iv62, 2015
3) Nakasu S, Nakasu Y: Natural history of meningiomas: Review with meta-analyses. *Neurol Med Chir (Tokyo)* 60: 109-120, 2020
4) Chiba K, Sugawara T, Kobayashi D, Sato A, Murota Y, Maehara T: Atypical histological features as risk factors for recurrence in

newly diagnosed WHO grade I meningioma. *Neurol Med Chir (Tokyo)* 61: 647-651, 2021
5) Nakasu S, Fukami T, Jito J, Matsuda M: Microscopic anatomy of the brain-meningioma interface. *Brain Tumor Pathol* 22: 53-57, 2005
6) Morisako H, Ohata H, Shinde B, Nagahama A, Watanabe Y, Goto T: Minimal anterior and posterior combined transpetrosal approach for large petroclival meningiomas. *J Neurosurg* 135: 1180-1189, 2020
7) Elzarief AA, Ibrahim MF: Long-term follow-up of motor function deterioration following microsurgical resection of middle third parasagittal and falx meningioma. *Egypt J Neurol Psychiatry Neurosurg* 54: 9, 2018
8) Ostrý S, Netuka D, Beneš V: Rolandic area meningioma resection controlled and guided by intraoperative cortical mapping. *Acta Neurochir (Wien)* 154: 843-853, 2012
9) Ottenhausen M, Rumalla K, Younus I, Minkowitz S, Tsiouris AJ, Schwartz TH: Predictors of postoperative motor function in rolandic meningiomas. *J Neurosurg* 130: 1283-1288, 2018
10) Jung S, Kim HW, Lee JH, et al.: Brain tumor invasion model system using organotypic brain-slice culture as an alternative to in vivo model. *J Cancer Res Clin Oncol* 128: 469-476, 2002
11) Rahmanzade R: Redefinition of tumor capsule: Rho-dependent clustering of cancer-associated fibroblasts in favor of tensional homeostasis. *Med Hypo* 135: 109425, 2020
12) Lubkin SR, Jackson T: Multiphase mechanics of capsule formation in tumors. *J Biomech Eng* 124: 237-243, 2002
13) Kamitani H, Masuzawa H, Kanazawa I, Kubo T: Recurrence of convexity meningiomas: Tumor cells in the arachnoid membrane. *Surg Neurol* 56: 228-235, 2001

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