Pathological Investigation of Meningioma Capsule with respect to Tumor Cell Invasion

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Research Article

Keywords: meningioma, prognosis, recurrence, tumor capsule, tumor invasion

Posted Date: October 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-945497/v1>

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Abstract

OBJECTIVE

No previous study has pathologically investigated whether the meningioma capsule presents with tumor cells. We investigated which types of tumor capsules include tumor cells to help decide the kind of capsules which can be left intraoperatively without recurrence risk.

METHODS

We investigated 22 specimens of 14 newly diagnosed meningiomas between February 2011 and June 2021. Capsules were classified into three types: tumor capsule (TC), capsule-like thickened arachnoid membrane (CAM), and extended membrane (EM). Capsule properties were scored as hardness (soft = 1, medium = 2, hard = 3) and transparency (high = 1, medium = 2, low = 3). Hardness, transparency, and score sum was compared between capsules with/without tumor invasion in CAM and EM types.

RESULTS

The mean follow-up duration was 28.1 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. 88.9% of TCs, 42.9% of CAMs, and 50% of EMs were invaded by tumor cells. Hardness, transparency, and score sum in CAM with tumor invasion was lower than in CAM without, but not significant ($p = 0.114$, $p = 0.114$, $p = 0.057$).

CONCLUSION

Thickened TC or soft and highly transparent CAM imply a high risk of tumor cell invasion, thus such cases should be followed up long and carefully. The hard and low transparent residual CAMs may have low risk of tumor invasion, thus these kinds of residual capsules might not increase the recurrence risk. Thus, leaving such capsules tightly adhered to the eloquent cortex is theoretically justified to avoid damaging the brain surface.

Introduction

Meningioma is the most common intracranial brain tumor, accounting for approximately 36% of primary brain tumors.[2, 8] Some meningiomas disrupt the arachnoid membrane and invade brain tissue, being diagnosed as malignant WHO grade II meningioma. On the contrary, most meningiomas are demarcated by a basement membrane that is collagen type 4-positive.[7] This basement membrane sometimes grows into thick connective tissue forming a capsule that can tightly adhere to the brain tissue.[6] When the capsule adheres to the eloquent cortex, it should be left to avoid damaging the brain tissue.[1, 5, 11] Even if the capsule adheres to the non-eloquent cortex, the less brain tissue damage the better. However, if the capsule includes tumor cells and they remain in the brain surface, there is a risk of recurrence. Thus, leaving the tumor capsule may be a trade off in tumor control necessary for protecting the brain surface. No previous study has pathologically investigated whether the meningioma capsule presents with tumor cells, and whether leaving the capsule increases the risk of recurrence. In

this study, we investigated whether some types of tumor capsule include tumor cells to assist on the selection of the capsules that can remain intraoperatively.

Methods

The study was approved by the institutional review board of Tokyo Medical and Dental University. All patients in this case series provided their informed consent for the inclusion of their clinical data in this manuscript.

We investigated 22 specimens of 14 newly diagnosed meningioma patients who underwent surgery in our hospital between February 2011 and June 2021. All these specimens were harvested from the partially remaining capsule on the brain surface because it was considered better to leave the capsule to maintain the brain surface intact. Only specimens where the accurate location could be identified by the surgical video were included.

These capsules were classified into three types based on intraoperative findings. Tumor capsule (TC): thickened capsule on the tumor surface (Fig 1a), capsule-like thickened arachnoid membrane (CAM): thickened membrane similar to the arachnoid membrane between the tumor and the brain surface (Fig 1b), and the extended membrane (EM): membrane extended along the surface of the dura mater around the tumor (Fig 1c). In CAM and EM types, the capsule properties were defined by intraoperative findings as follows: hardness (soft=1, medium=2, hard=3), transparency (high=1, medium=2, low=3). The hardness, transparency, and the sum of these two scores were compared between capsules with and without tumor invasion in both CAM and EM types.

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

The WHO grade and tumor cell invasion into the capsule were determined by a pathologist by hematoxylin-eosin staining, and the capsule type and properties by the surgeon.

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

Results

The characteristics of the 22 specimens from the 14 patients are summarized in Table 1. The mean age was 60.3 years (range, 36–83 years), and seven patients were male (50%). The tumor was 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 1 and three were grade 2; one patient with WHO grade 2 meningioma underwent adjuvant intensity-modulated radiation therapy of 60 Gy/30 Fr. The mean follow-up duration was 28.1 months (1-75), 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 nine TCs (88.9%, all but one) were invaded by tumor cells, and only one TC (11.1%) showed no tumor invasion. However, the TC capsule that did not show tumor invasion had tumor cells attached on the surface. Three of seven CAM (42.9%) and three of six EM (50%) were invaded by tumor cells, respectively (Table 2).

Among the three CAMs with tumor invasion, all three (100%) were soft, two (66.7%) had high transparency, and one (33.3%) medium transparency. On the other hand, among the four CAMs without tumor invasion, only one (25%) was soft, two (50%) had medium hardness, and one (25%) was hard, three (75%) had medium transparency, and one (25%) low transparency. As for EM, of the three EM with tumor invasion, one (33.3%) specimen each had a soft, medium, and hard capsule respectively, two (66.7%) had medium transparency, and one (33.3%) low transparency. Of the three EM without tumor invasion, one (33.3%) was soft and two (66.7%) had medium hardness, one (33.3%) had medium transparency, and two (66.7%) low transparency (Table 3). Typical intraoperative and pathological pictures of each type of capsule are shown in Fig. 1-3.

The hardness score in CAM with tumor invasion was lower than without tumor invasion (mean: 1 vs. 2), but not significantly different ($p=0.114$). Similarly, the transparency score and the sum of these two scores were lower in CAM with tumor invasion (1.33 vs. 2.25, 2.33 vs. 4.25), although not significantly different ($p=0.114$, $p=0.057$).

Discussion

Most meningiomas are demarcated by a basement membrane that is collagen type 4-positive,[7] and this basement membrane sometimes grows into thick connective tissue as a capsule formation and can adhere tightly to the brain tissue. This thick connective tissue is considered as the capsule of the defined TC. In the present study, almost all TCs (8/9, 88.9%; all but one) were invaded by tumor cells. Moreover, the one that did not show tumor invasion was attached to tumor cells on the surface of the capsule, which may indicate that the tumor had almost invaded the capsule.

Sometimes a thickened arachnoid-like membrane, which adheres to the brain surface, develops between the tumor and the brain surface. Such a kind of membrane cannot be determined intraoperatively whether it originates from the arachnoid membrane or a newly generated membrane and was defined as CAM in our study. In this study, soft and highly transparent CAM tended to be invaded by tumor cells. In general, malignant tumors are invasive and rarely form hard capsules.[10] In contrast, many benign tumors grow, pushing the surrounding tissue and creating a capsule between the tumor and the surrounding tissue.[4, 9] This evidence suggests that invasive meningioma does not develop a thick and hard capsule between the tumor and brain surface and can easily infiltrate the soft arachnoid membrane, and that the reason why hard CAM is not usually invaded by tumor cells is that the meningioma that formed it is not invasive. However, the number of samples in our study is too small precludes a definitive conclusion.

We sometimes experience the membrane extending along the surface of the dura mater around the tumor. This membrane was defined as the EM in our study. This EM can extend along the dura mater far from the tumor itself. Therefore, almost all this type of membrane ends up to be residual. Although half of EMs showed tumor invasion in our study, we could not find any difference between EMs with and without tumor invasion.

These results indicate that not removing TCs and soft and highly transparent CAMs has a high risk of leaving tumor cells. And this residual capsule may lead to recurrence of the tumor. Kamitani et al. 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 after surgery. [3] The patients in this study did not experience recurrence related to the residual capsule but the follow-up period was too short to conclude the relationship between the residual capsule and tumor recurrence. Therefore, we should follow up the patients long and carefully who had residual TCs or soft and highly transparent CAMs. However, the hard and low transparent CAMs may have low risk of tumor invasion, thus these

residual capsules may be justified in cases when the capsule tightly adheres to the brain surface, especially the eloquent cortex, to avoid damage to the brain surface.

The follow-up period was too short to conclude the relationship between the residual capsule and tumor recurrence. This is the main limitation to our study, and therefore, further research is warranted to examine this point.

Conclusion

A thickened capsule on the tumor surface and a soft and highly transparent membrane between the tumor and brain surface imply a high risk of tumor cell invasion. Although we did not find recurrence related to the residual capsule in this study, we should follow up these patients long and carefully. The hard and low transparent residual CAMs may have low risk of tumor invasion, thus not removing these kinds of capsules might not increase the risk of recurrence theoretically. When such a kind of capsule tightly adheres to the brain surface, especially to the eloquent cortex, avoiding removal might be better in order not to damage the brain surface. Because of the short follow-up period, the relationship between these remaining tumor-invaded capsules and tumor recurrence could not be clarified, and further investigation is required.

Declarations

Funding: This study is not receiving any funding.

Conflicts of interest: The authors declare no conflicts of interest associated with this manuscript.

Availability of data and material: The datasets during and/or analyses during the current study available from the corresponding author on reasonable request.

Code availability: Not applicable

Authors' contributions: Conceptualization: Takashi Sugawara; Methodology: Takashi Sugawara; Daisuke Kobayashi; Formal analysis and investigation: Takashi Sugawara; Writing - original draft preparation: Takashi Sugawara; Writing - review and editing: Takashi Sugawara, Taketoshi Maehara; Supervision: Takashi Sugawara, Taketoshi Maehara.

Ethical approval: Approval was obtained from the institutional review board of Tokyo Medical and Dental University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate: Informed consent for their participation was obtained from all individual participants included in the study.

Consent to participate: Consent to participate was obtained from all individual participants.

Consent for publication: Consent for publication was obtained from all individual participants.

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Tables

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Table 2: Definition of each capsule type and the proportion of capsules with tumor invasion in each type

Capsule type	Definition	No. of specimens	Tumor invasion (+) (%)	Tumor invasion (-) (%)
Tumor capsule (TC)	thickened capsule in tumor surface	9	8 (88.9)	1 (11.1)
Capsule like thickened arachnoid membrane (CAM)	thickened membrane having a property similar to arachnoid membrane between tumor and brain surface	7	3 (42.9)	4 (57.1)
Extended membrane (EM)	membrane extended along the surface of dura mater around tumor	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

Figures

Figure 1

Typical intraoperative (A, B) and pathological pictures (C, D, original magnification $\times 20$) of TC type. (A) and (C): Images of specimen 16. (A) residual thickened capsule tightly adhering to the brain surface after tumor removal. (C) tumor solid invasion into the fibrous capsule. (B) and (D): Images of specimen 20. (B) residual thickened capsule tightly adhering to the brain surface after tumor removal. (D) small tumor tissue invasion between hyalinized vessels in the tumor capsule. Arrowhead showing the location of the harvested specimen. TC: thickened capsule on the tumor surface.

Figure 2

Typical intraoperative (A, B) and pathological pictures (C, D, original magnification $\times 20$) 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 after tumor resection. The membrane is soft and high 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 the brain surface. The membrane is soft and medium transparent. (D) dense fibrous tissue with many vessels without tumor invasion. Arrowhead showing the location of the harvested specimen. CAM: thickened membrane with similar properties to the arachnoid membrane between the tumor and the brain surface.

Figure 3

Typical intraoperative (A, B) and pathological pictures (C, D, original magnification $\times 20$) of 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 and medium transparent. (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 was of medium hardness and medium transparent. (D) dense fibrous tissue with many vessels without tumor invasion. Arrowhead showing the location of the harvested specimen. EM: membrane extending along the dura mater surface around the tumor.

Supplementary Files

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- [Table1.docx](#)