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Reconsideration of So-Called "Invasive" Meningioma

—Definition and Surgical Strategy

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Abstract

For the purpose of histopathological diagnosis, so-called "invasive meningioma" is defined as a meningioma that has infiltrated the cerebral parenchyma, and such cortical infiltration raises the risk of recurrence. However, as the definition of "invasive" remains far from clear, we have attempted to redefine it. Tumors that were completely removed from 32 patients between April 2005 and September 2015 and that had been diagnosed as so-called "invasive meningioma" were classified by World Health Organization grade (Group I–III), and then further classified as: true invasion, involving invasion of the brain with breakdown of the pia mater; and pseudo-invasion, involving encroachment into the brain with the pia mater still intact. We then investigated recurrence rates in the brain or dura mater for each group. Rate of recurrence in the brain or dura mater was significantly higher for Group I meningioma classified as true invasion compared to that of the same group classified as pseudo-invasion. We redefined so-called "invasive meningioma" as Group I meningioma exhibiting true invasion, and considered that, when possible, wide resection of the areas of adhesion to the dura mater in addition to tumor extirpation along with the cerebral parenchyma increased the success rate for curative treatment.

Keywords

Invasive Meningioma, True Invasion, Pseudo-Invasion, Surgical Margin, Recurrence Rate

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1. Introduction and Background

Invasive meningioma is categorized as grade II by the World Health Organization (WHO), and is regarded as more highly malignant than low-grade meningioma [1] [2]. The diagnostic criteria for invasive meningioma are not necessarily clear; however, there has been little detailed discussion of the mode of invasion of the cerebral parenchyma. At our hospital, we have treated 32 patients with meningioma that had invaded into the cerebral parenchyma and for whose complete tumor extirpation was confirmed by surgical microscopy. We considered the pathological features of these cases, and investigated pathological findings that reflected the recurrence rate, as well as essential points for surgery to increase the success rate of curative treatment.

2. Materials and Methods

We treated 32 patients (7 men, 25 women; age range, 39 - 83 years; mean age, 46.6 years) at our hospital with meningioma growing in a non-eloquent area or for which focal symptoms had already appeared, with histopathological diagnosis of invasion to the cerebral parenchyma, and for whom complete tumor extirpation was confirmed by surgical microscopy between April 2005 and September 2015 (mean follow-up, 59.9 months; range, 11 - 126 months). The site of origin was the cerebral convexity in 17 cases, falx cerebri in 4, olfactory groove in 3, sphenoidal ridge in 3, cerebellar tentorium in 3, and para-superior sagittal sinus in 2. In all patients, the tumor was firmly adherent to the cerebral parenchyma, and tumor extirpation was performed by scraping away the brain surface, either because this site was in a non-eloquent area or because focal symptoms had already appeared. Dura mater adhering to the tumor was also resected across as wide an area as possible. Invasion of the cerebral parenchyma was diagnosed histopathologically in all cases, and was classified as Group I-III by the WHO classification. Group I represents WHO grade I meningioma with brain invasion, Group II represents WHO grade II meningioma (atypical meningioma) with brain invasion and Group III represents WHO grade III meningioma (anaplastic meningioma) with brain invasion. The mode of invasion into the cerebral parenchyma was further classified as either “pseudo-invasion”, involving encroachment into the cerebral parenchyma with the pia mater still intact (**Figure 1**), or “true invasion”, involving invasion of the cerebral parenchyma with breakdown of the pia mater (**Figure 2**). Retrospective analysis was then performed. SPSS Statistics version 22.0 software (IBM, USA) was used as statistical software, and values of $p < 0.05$ were regarded as statistically significant.

3. Results

The histopathological diagnosis was low-grade meningioma with brain invasion (Group I) in 26 cases (22

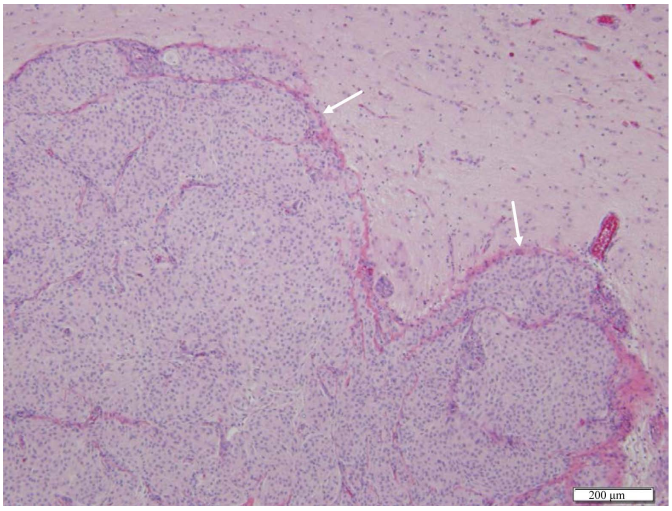


Figure 1. Pseudo-invasion (hematoxylin and eosin (HE) stain). The basic structure is that of meningothelial meningioma. The tumor is encroaching into the cerebral parenchyma, which is covered by pia mater (arrows).

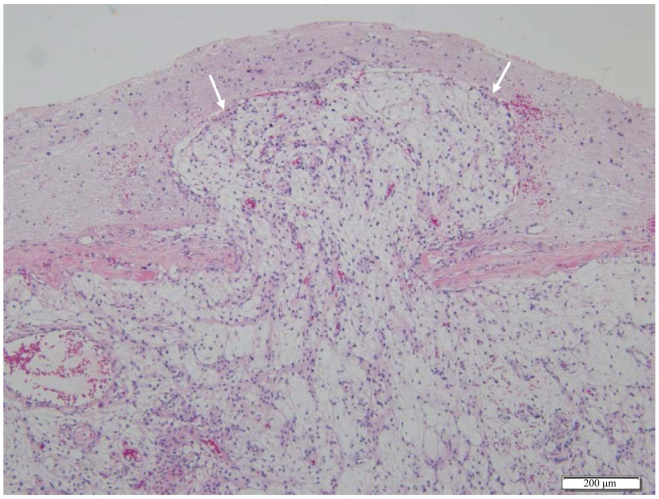


Figure 2. True invasion (HE stain). The basic structure is that of meningothelial meningioma. The tumor has broken through the pia mater to invade the cerebral parenchyma in a mushroom shape (arrows).

meningothelial type, 3 fibrous type, and 1 transitional type), atypical meningioma with brain invasion (Group II) in 4 cases, and anaplastic meningioma with brain invasion (Group III) in 2 cases, with invasion of the pia mater also evident in all patients. Twenty-one cases were classified as pseudo-invasion, comprising 18 Group I, 3 Group II, and 0 Group III. Eleven were classified as true invasion, comprising 8 Group I, 1 Group II, and 2 Group III. **Table 1** shows the association between recurrence, pathological grade, and pseudo-invasion or true invasion. In particular, MIB-1 staining index for Group I meningioma was 1% - 4% (mean, 2.2%) for pseudo-invasion and 1% - 5% (mean, 2.6%) for true invasion, showing no significant difference (t-test, $p = 0.91$). Recurrence may occur in dura mater adhering to the tumor, brain itself, or both, and we therefore also analyzed the site of recurrence (**Table 2**). No recurrence in any of the 18 Group I cases of pseudo-invasion, but recurrence was identified in 5 of the 8 Group I cases of true invasion, with the site of recurrence comprising the dura mater (D) in 2 cases and both the dura mater and brain itself (C) in 3. For Group II meningiomas, recurrence was evident in all 3 cases of pseudo-invasion and the 1 case of true invasion, with the site of recurrence in the 3 cases of pseudo-invasion comprising D in 2 cases and C in 1, and C in the 1 case of true invasion. All Group III meningiomas were cases of true invasion, and recurrence was evident in all of them, with the site of recurrence comprising D in 1 case and C in 1. Statistical analysis revealed a significant difference in the rate of recurrence for Group I meningiomas between pseudo-invasion (0%) and true invasion (62%; $p = 0.004$, χ^2 test).

4. Discussion

In terms of histopathological diagnosis, invasive meningioma corresponds to WHO grade II, and meningioma that invades into the cerebral parenchyma is believed to show a high rate of recurrence [2] [3]. In our experience, however, even for tumors diagnosed as invasive meningioma, recurrence rates for Group I tumor vary depending on the mode of encroachment into the cerebral parenchyma. That is, the recurrence rate for true invasion, in which invasion of the parenchyma occurs together with breakdown of the pia mater, is higher than that for pseudo-invasion, in which encroachment into the cerebral parenchyma occurs with the pia mater remaining intact. Only 3 patients with Group I meningioma classified as true invasion did not develop recurrence, and in 1 of those cases, Rosenthal fibers were apparent around the tumor. The presence of Rosenthal fibers and other degenerative signs around a tumor (**Figure 3**) suggests a slow-growing nature [4], and the large surgical margin secured around the tumor for which the presence of Rosenthal fibers was demonstrated may have helped to avoid recurrence. The fact that Rosenthal fibers, which may have formed as a result of long-term contact with glia after the tumor broke through the pia mater, were not observed in any other cases of true invasion may have been due to the method of preparing tissue sections, or to the action on Rosenthal fiber formation of protein degeneration by glial fibrillary acidic protein (GFAP) or other substances [4], and individual variation in this degenerative process may exist. We did not observe Rosenthal fibers in any of our cases of pseudo-invasion, and this may

Table 1. Mode of "invasion", *i.e.*, pseudo-invasion or true invasion in relation to pathological grade in 32 "invasive" meningiomas.

	Group I	Group II	Group III
Pseudo-invasion	18 (1% - 4%, 2.2%)	3 (20% - 30%, 23%)	0
True invasion	8 (1% - 5%, 2.6%)	1 (20%)	2 (15% - 20%, 18%)
Total	26	4	2

Group I: low-grade meningioma with brain invasion; Group II: atypical meningioma with brain invasion; Group III: anaplastic meningioma with brain invasion; Percentage in ( ): MIB-1 staining index range and MIB-1 staining index average.

Table 2. Incidence and site of recurrence in relation to both pathological grade and mode of "invasion".

	Group I	Group II	Group III
No. of recurrences/No. of pseudo-invasions	0/18	3 (D:2, C:1)/3	0/0
No. of recurrences/No. of true invasions	5 (D:2, C:3)/8	1 (C:1)/1	2 (D:1, C:1)/2

D: recurrence in dura mater; C: combined recurrence in brain and dura mater.

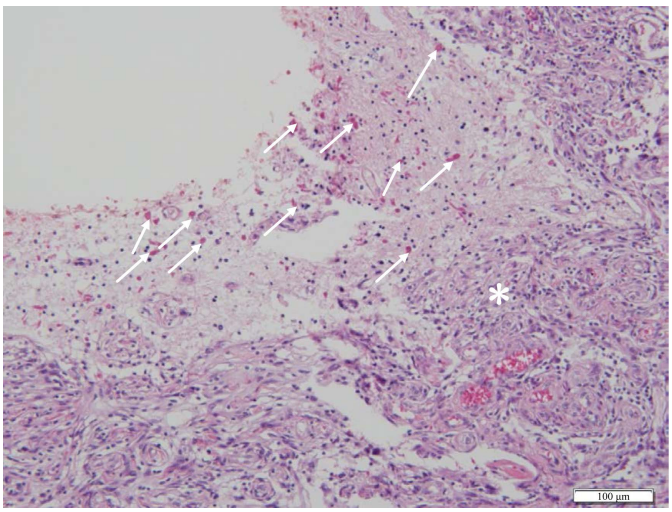


Figure 3. Brain invasion with Rosenthal fiber in a Group I true-invasion case. The presence of Rosenthal fibers (arrows) in tissue surrounding a tumor (*) that has encroached into the cerebral parenchyma suggests that the tumor may be slow-growing.

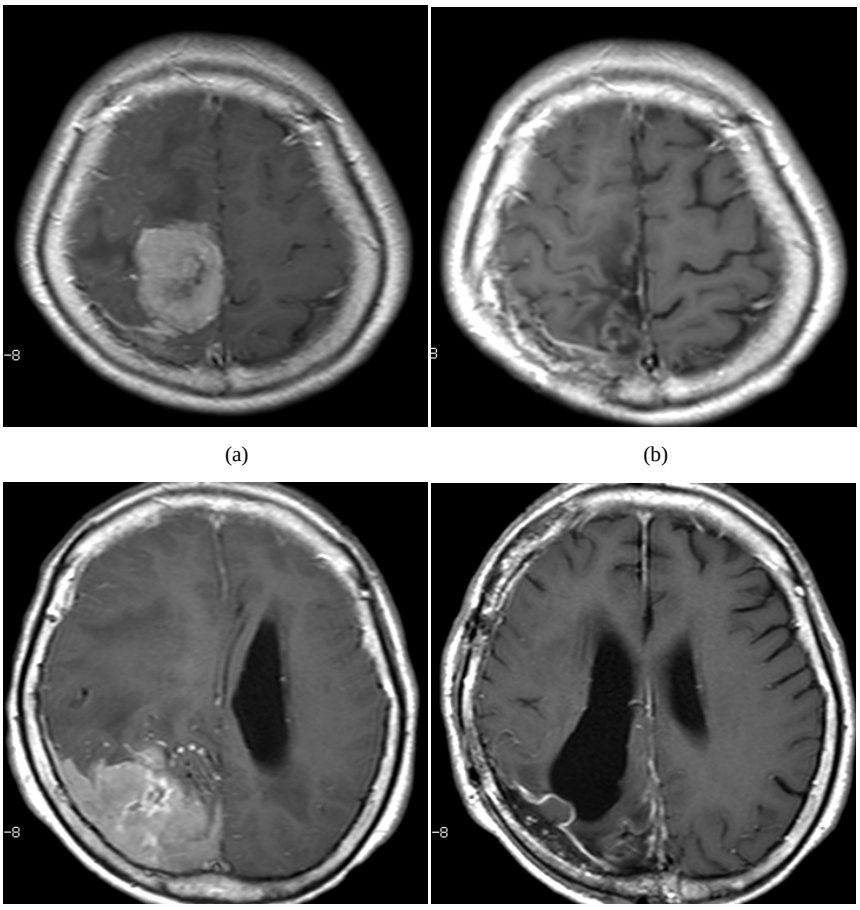
have been because the pia mater intervened between the tumor and glia, preventing degeneration from occurring. In the other 2 cases, follow-up periods were short (8 months and10 months after surgery), and these patients must be monitored for recurrence in future. Although few cases of Group II or III meningioma were identified, it is natural that given the underlying high malignancy of these histological types, should invasion of the dura mater or cerebral parenchyma occur then the risk of recurrence will be high even in the event of pseudo-invasion. As Group III meningiomas have even greater proliferative potential and their ability to break down tissue is more extensive, true invasion should logically tend to occur. Rosenthal fibers were not apparent in any cases of Group II or Group III meningioma, potentially because these tumors were rapidly growing, meaning that they recurred and surgery was performed before degeneration of the glia could occur. Further studies are required to clarify the significance of the appearance of Rosenthal fibers.

No difference in MIB-1 staining index was seen between cases of true and pseudo-invasion, and the question of whether any sort of difference in cellular activity exists between the two remains a matter for further study, although there are several reports up to now [5] [6].

Various proposals have been put forward for a reconsideration of WHO grades in light of the clinical course

[7] [8], but for the histopathological diagnosis of invasive meningioma, starting by strictly classifying tumors as exhibiting pseudo-invasion or true invasion and defining Group I tumors with true invasion as so-called "invasive meningiomas" (that is, WHO grade II) would provide a diagnosis reflective of the rate of recurrence.

In light of the above histopathological investigation, we then investigated the ideal technique for extirpating meningiomas that exhibit invasion of the cerebral parenchyma or firm adhesion to the brain surface. Patients with meningioma that has invaded the cerebral parenchyma or firm adhesions that have destroyed the arachnoid plane may sometimes be identified by means of preoperative imaging assessment [9], but distinguishing between pseudo-invasion and true invasion on surgical microscopy may be difficult. Despite the fact that in all our patients we resected the dura mater [10], which was regarded as the tissue of origin in all cases, as far as possible and also scraped away cerebral parenchyma that had been invaded by the tumor during tumor removal, recurrence was still evident in 11 cases. Meningioma recurred in 5 of the 8 Group I patients with true invasion, corresponding to WHO grade II. The site of recurrence was either the dura mater (2 cases) or the dura mater and cerebral parenchyma (3 cases) (**Figure 4**), but as tumors that exhibit true invasion have an inherent tendency to invade normal tissue, our results suggest that tumor cells may have persisted in the brain or dura mater even after good surgical margins had been secured to the point at which the dura mater or cerebral parenchyma appears



(a) (b)

(c) (d)

Figure 4. Recurrent meningioma in a Group I true-invasion case (enhanced magnetic resonance imaging). (a) Before initial surgery. Meningioma with adhesions from the parasagittal area to the cerebral falx; (b) After initial surgery. The tumor was removed together with the falx cerebri and the fornix to which it was adhering. An area of adhesion in the superior sagittal sinus was also completely extirpated and cauterized; (c) Before surgery for recurrence. Recurrent meningioma arising from the parasagittal area to the falx and cerebral parenchyma; (d) After surgery for recurrence. The tumor has been extirpated together with the cerebral parenchyma from which it was believed to have arisen, with the superior sagittal sinus wall and dura mater of the falx area.

normal on initial examination under surgical microscopy. However, no recurrence was seen when care was taken to follow this technique when extirpating Group I cases of pseudo-invasion, suggesting that if the site of invasion is a non-eloquent area, the tumor should be removed together with as much cerebral parenchyma as possible, and that the dura mater adhering to the tumor should also be resected as widely as possible [10] to give the greatest chance of successful curative treatment.

All Group II and Group III meningiomas recurred. One Group II and 2 Group III patients developed recurrence after the initial surgery and underwent radiotherapy, but the tumors subsequently regrew. High-grade meningioma that has invaded the cerebral parenchyma thus carries a high risk of recurrence whatever treatment is used. Only one patient died, however, and the cause of death was unrelated to the brain tumor. This suggested that it may be possible to reduce mortality using the technique described above to high-grade meningioma that has invaded the cerebral parenchyma.

5. Conclusion

The rate of recurrence of low-grade meningioma varies depending on the mode of invasion of the cerebral parenchyma, with tumors exhibiting true invasion having a higher recurrence rate in the dura mater as well as in the brain compared with those showing pseudo-invasion. Meningiomas in which true invasion of the cerebral parenchyma is evident should therefore be particularly identified as “invasive meningioma”, and if possible, intraoperative pathological diagnosis should be carried out with particular care by a neurological surgeon, as this may be useful for reducing the rate of recurrence. If invasion of the cerebral parenchyma or destruction of the arachnoid plane has occurred, a neurosurgeons may be recommended scraping away the tumor together with the surface of the brain, and at the same time should try to allow a good surgical margin when removing the dura mater attached to the tumor, as this may improve the success rate for curative treatment.

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