



## Follow-Up and Treatment of Patients with Coexisting Brain Tumor and Intracranial Aneurysm

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■ **OBJECTIVE:** The association of primary brain tumors with coexisting unruptured intracranial aneurysms (UIAs) has been debated, and treatment strategies have not yet been established. We evaluated the flow association between brain tumors and coexisting UIAs and the outcomes of patients with brain tumor who did not receive treatment of coexisting UIAs.

■ **METHODS:** The medical records of patients with coexisting UIAs and brain tumors who had undergone surgical tumor resection were retrospectively analyzed to evaluate the incidence of UIAs according to tumor type, association of arterial feeder vessels and coexisting UIAs, and the occurrence of subarachnoid hemorrhage during the follow-up period for patients who had not receive treatment for the UIAs.

■ **RESULTS:** Of the 55 patients, 21 (38.9%) had undergone treatment of UIAs and 33 (61.1%) had received regular follow-up examinations without UIA treatment. Two patients (6.1%) developed subarachnoid hemorrhage. Of the 33 patients with astrocytic or oligodendroglial tumors who had not undergone treatment of UIAs, 2 had experienced an interval increase. Flow-related UIAs were found to be significantly more common in patients with astrocytic or oligodendroglial tumors than in those with tumors of other histological types ( $P = 0.01$ ).

■ **CONCLUSIONS:** The incidence of UIAs among patients with primary brain tumors appears to be greater than that in the general population. An interval increase in aneurysm

size and aneurysmal rupture was observed in 2 patients with astrocytic or oligodendroglial tumors. We would recommend perioperative treatment of flow-related UIAs in patients with astrocytic or oligodendroglial tumors and noninvasive evaluations such as magnetic resonance angiography if coexisting UIAs remain untreated.

### INTRODUCTION

Patients with a diagnosis of a brain tumor who also have coexisting unruptured intracranial aneurysms (UIAs) require special considerations during treatment to avoid complications caused by the UIAs. However, because the prevalence of UIAs in patients with a brain tumor has not been well studied, no consensus has been reached in the treatment strategy of coexisting UIAs in patients with a brain tumor. Also, the flow association between these 2 entities has remained unclear.

In the present study, we reviewed the patients' medical records, including the radiological examination findings of patients with both UIAs and brain tumors, the treatment decisions made to address coexisting UIAs, and the outcomes of untreated UIAs to evaluate the flow association of UIAs with brain tumors and suggest the treatment strategies.

### METHODS

#### Patient Inclusion Criteria and Data Collection

We performed a single-center retrospective observational study, complemented by a review of the medical records. We reviewed

#### Key words

- Astrocytoma
- Brain tumor
- Intracranial aneurysm
- Meningioma
- Oligodendroglial tumor
- Subarachnoid hemorrhage

#### Abbreviations and Acronyms

- CT:** Computed topography
- DSA:** Digital subtraction angiography
- MRA:** Magnetic resonance angiography

**MRI:** Magnetic resonance imaging

**UIA:** Unruptured intracranial aneurysm

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**Table 1.** Primary Brain Tumor Pathology of 1128 Patients

Pathological Entity	All Patients (n, %)	Patients with Coexisting UIAs (n, %)
Meningioma	551 (48.8)	33 (6)
Astrocytic, oligodendroglial tumors	300 (26.6)	10 (3.3)
Pituitary adenoma	133 (11.8)	3 (2.3)
Intracranial schwannoma	64 (5.7)	4 (6.3)
Craniopharyngioma	28 (2.5)	4 (14.3)
Hemangiopericytoma	12 (1.1)	1 (8.3)
Neuronal-glia	8 (0.7)	0 (0)
Ependymal tumor	7 (0.6)	0 (0)
Choroid plexus tumor	5 (0.4)	0 (0)
Embryonal tumor (medulloblastoma)	3 (0.3)	0 (0)
Other (intracranial epidermoid cyst, Rathke's cleft cyst)	17 (1.5)	0 (0)

the patients' medical records to identify the presence of coexisting UIAs in patients who had undergone surgical resection of primary brain tumors from January 2014 to December 2017, with post-operative follow-up data available until December 2018. The institutional review board of our facility approved the present study. Patients aged >18 years of age who had undergone surgical resection for brain tumors by 1 surgeon (J.H.K.) were included. The patients' medical records were reviewed to identify their sex, age, underlying disease conditions, pathological diagnosis of the brain tumor, size and location of the UIAs, treatment modalities for UIAs performed in the treated cases, and the occurrence of aneurysmal rupture during the follow-up period.

Patients with metastatic brain tumors were excluded to avoid potential comorbidities such as cancer-related coagulopathy or vasculopathy. Patients with a diagnosis of UIAs before the detection of brain tumors were also excluded.

### Preoperative Assessment of UIAs

All patients who had undergone tumor resection had also had undergone a preoperative evaluation using computed tomography (CT) angiography. For the patients identified with coexisting UIAs, 4-vessel intra-arterial digital subtraction angiography (DSA) was also performed to define the characteristics of the UIAs. The UIA characteristics included the size (defined as the maximum width of the dome), location, and the UIA relationship to the parent artery.

### Definitions of Flow-Related Aneurysms

In the present study, we defined flow-related aneurysms as 1) aneurysms that had arisen in the artery and given off pial feeders to the brain tumor; or 2) aneurysms that originated in the artery 1 segment proximal or distal to the artery that had given off tumor feeders. For example, when the malignant glioma in the temporal lobe was supplied by a cisternal segment of the anterior choroidal artery, the UIA in the anterior choroidal artery of the same side, which had been found to be coexistent, was considered flow related. Another example of a flow-related UIA is a UIA one in the

anterior communicating artery in a patient with a low-grade glioma fed by A2 of the anterior cerebral artery. We defined flow-unrelated aneurysms as UIAs located in a different region, such as when separated by the tentorium, from the tumor or when the parent artery of the UIA had not given off feeders to the brain tumor.

### Treatment of UIAs

Coexisting UIAs were treated by either surgical clipping or coil embolization when the patient's life expectancy was expected to be  $\geq 5$  years after consideration of the patients' comorbidities and the average annual rupture rate of UIAs. The average annual rupture rate of UIAs has been estimated to be >1% according to data from Japan Society of Neurosurgery.<sup>1</sup> The timing of the treatment was determined by the location and estimated annual rupture rate of the UIAs. For example, surgical clipping of coexisting UIAs was performed during tumor resection when the UIA was located in the same cerebral hemisphere as the brain tumor and could be accessed via the same craniotomy flap used for tumor resection. However, when the coexisting UIA seemed to carry a high risk of rupture, as determined by the shape of aneurysmal dome, including the presence of blebs, and when the pathology of the tumor was considered benign by the World Health Organization classification,<sup>2</sup> surgical clipping or coil embolization of the UIA was performed before tumor resection.

### Patient Follow-Up and Outcomes Assessment

All patients who had undergone treatment for UIAs, including those who had undergone surgical clipping during the procedure for tumor resection, were followed up with postoperative CT angiography. Postoperative examination of resected site was performed using magnetic resonance imaging (MRI) with gadolinium enhancement or CT with contrast enhancement for patients with meningioma and advanced MRI with gadolinium enhancement, including perfusion and diffusion protocols<sup>3</sup> for patients with astrocytic or oligodendroglial tumors. The follow-up examinations of untreated UIAs were performed using either CT

**Table 2.** Clinical Characteristics and Treatment Modalities of Patients With Coexisting Unruptured Intracranial Aneurysms With Preoperative Data Available

Variable	Patients With Flow-Related UIAs	Patients with Flow-Unrelated UIAs	P Value
Patients (n)	26	29	
Patient age (years)	58.75 ± 9.98	59.68 ± 10.03	0.7
Sex			0.48
Male	3	6	
Female	23	23	
Hypertension	12 (42.9)	14 (42.4)	0.9
UIAs (n)	29	33	
UIA dome size (mm)	3.37 ± 1.51	3.54 ± 1.42	0.7
Location of UIA (n; %)			0.01
Distal ICA (paraclinoid, AChA, PcomA)	11 (37.9)	19 (57.6)	
MCA	7 (24.1)	10 (30.3)	
ACA (Acom, A1, A2, A3)	11 (37.9)	2 (6.1)	
Posterior circulation (basilar, PCA)	0 (0)	2 (6.1)	
Coexisting UIAs per brain tumor (n; %)			0.01
Meningioma	18 (62.1)	20 (60.6)	
Astrocytic or oligodendroglial	10 (34.5)*	2 (6.1)	
Pituitary adenoma	1 (3.4)	2 (6.1)	
Schwannoma	0 (0)	4 (12.1)	
Craniopharyngioma	0 (0)	4 (12.1)	
Hemangiopericytoma	0 (0)	1 (3)	
Treated coexisting UIAs (n; %)			0.004
Surgical clipping	14 (48.3)†	4 (12.1)	
Concurrent tumor resection and clipping	14	1	
Clipping before tumor resection	0	2	
Clipping after tumor resection	0	1	
Coil embolization	0 (0)	4 (12.1)	
Before tumor resection	0	2	
After tumor resection	0	2	

UIA, unruptured intracranial aneurysm; ICA, internal carotid artery; AChA, anterior choroidal artery; PcomA, posterior communicating artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; Acom, anterior communicating artery; PCA, posterior cerebral artery.

\*Coexisting flow-related UIAs were significantly more common than were flow-unrelated UIAs in astrocytic or oligodendroglial tumors.

†Surgical clipping of coexisting UIAs was significantly more common for flow-related UIAs than for flow-unrelated UIAs at the same time as tumor resection.

angiography or magnetic resonance angiography (MRA) to detect interval changes. Interval changes were defined as an increase in the size or a change in the shape of the coexisting UIAs.

### Statistical Analysis

SPSS, version 22.0 (IBM Corp., Armonk, New York, USA) was used for statistical analysis. The normality of the data was tested using the Kolmogorov-Smirnov method. The Mann-Whitney U test was used to evaluate the statistically significant differences between the mean values of the continuous variables. The  $\chi^2$  test was

performed to determine the significance between the categorical variables. P values <0.05 were considered to indicate statistical significance.

## RESULTS

### Patient Characteristics and Clinical Outcomes

From January 2014 to December 2017, 1213 cases of surgical resection of primary brain tumors had been performed in 1128 patients at our institution. The most common primary brain tumor

**Table 3.** Follow-Up Results for 31 Untreated Coexisting Unruptured Intracranial Aneurysms in 29 Patients Who Had Undergone Surgical Resection of Primary Brain Tumor

Variable	Flow-Related UIAs (n = 13)	Flow-Unrelated UIAs (n = 18)
UIA without rupture (n)		
Interval increase of UIA size	2	0
UIA location		
MCA	1	0
AcomA	1	0
Pathology of coexisting tumor		
Glioblastoma	1	0
Diffuse astrocytoma	1	0
Aneurysmal rupture during follow-up (n)	2	0
Aneurysm location		
AChA	1	0
A1–A2 junction	1	0
Pathology of coexisting tumor		
Glioblastoma	1	0
Oligodendroglioma	1	0

UIA, unruptured intracranial aneurysm; MCA, middle cerebral artery; AcomA, anterior communicating artery; AChA, anterior choroidal artery.

was meningioma, followed by astrocytic or oligodendroglial tumors (Table 1).

Of the 1128 patients with surgically treated primary brain tumors, 55 (4.5%) had had 62 coexistent UIAs. Of the 62 UIAs, 29 were flow-related UIAs in 26 patients and 33 were flow-unrelated UIAs in 29 patients (1 patient had had 2 UIAs; 1 flow-related and 1 flow-unrelated UIA).

Meningiomas and astrocytic or oligodendroglial tumors were the 2 most common primary brain tumors in which coexisting flow-related UIAs were found. Flow-related UIAs were significantly more common in patients with astrocytic or oligodendroglial tumors than in patients with tumors of other histological types ( $P = 0.01$ ; Table 2).

Treatment of the UIAs was performed for 22 coexisting UIAs in 18 patients. Surgical clipping was performed for 18 UIAs in 15 patients, including 15 UIAs from 13 patients in whom clipping of the UIAs had been performed at the same surgery for tumor resection. Coil embolization was performed in 4 patients for 4 UIAs.

The mean follow-up duration was  $30.9 \pm 29.1$  months (range, 1–120). For the 40 untreated UIAs in 36 patients, angiographic follow-up data were available for 31 UIAs from 29 patients. The remaining 9 UIAs in 7 patients had been lost to follow-up. Of the 31 untreated UIAs, 2 were from patients with glioblastoma and diffuse astrocytoma and had shown an interval increase in UIA size. Aneurysmal subarachnoid hemorrhage occurred in 2 patients

in whom flow-related UIAs had ruptured at 35 months. The rupture had occurred after tumor resection in 1 patient with glioblastoma and at 32 months after tumor resection of an oligodendroglioma in another patient. The locations of the ruptured aneurysms and UIAs that showed interval increases are described in Table 3. No interval increases in UIA size or aneurysmal ruptures were identified in the flow-unrelated UIAs.

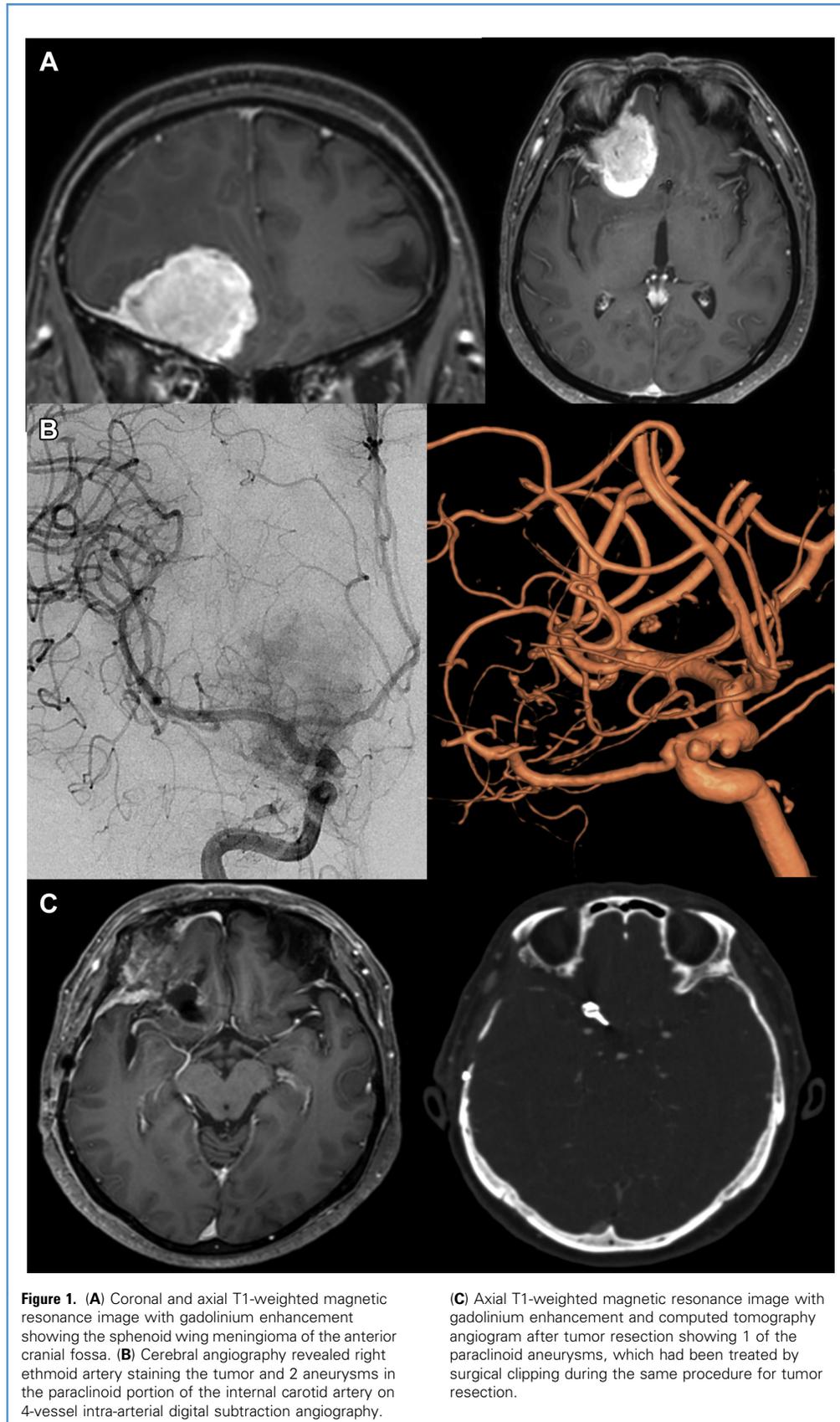
### Case Description of Initially Undetected UIAs and Ruptured UIA During Follow-Up

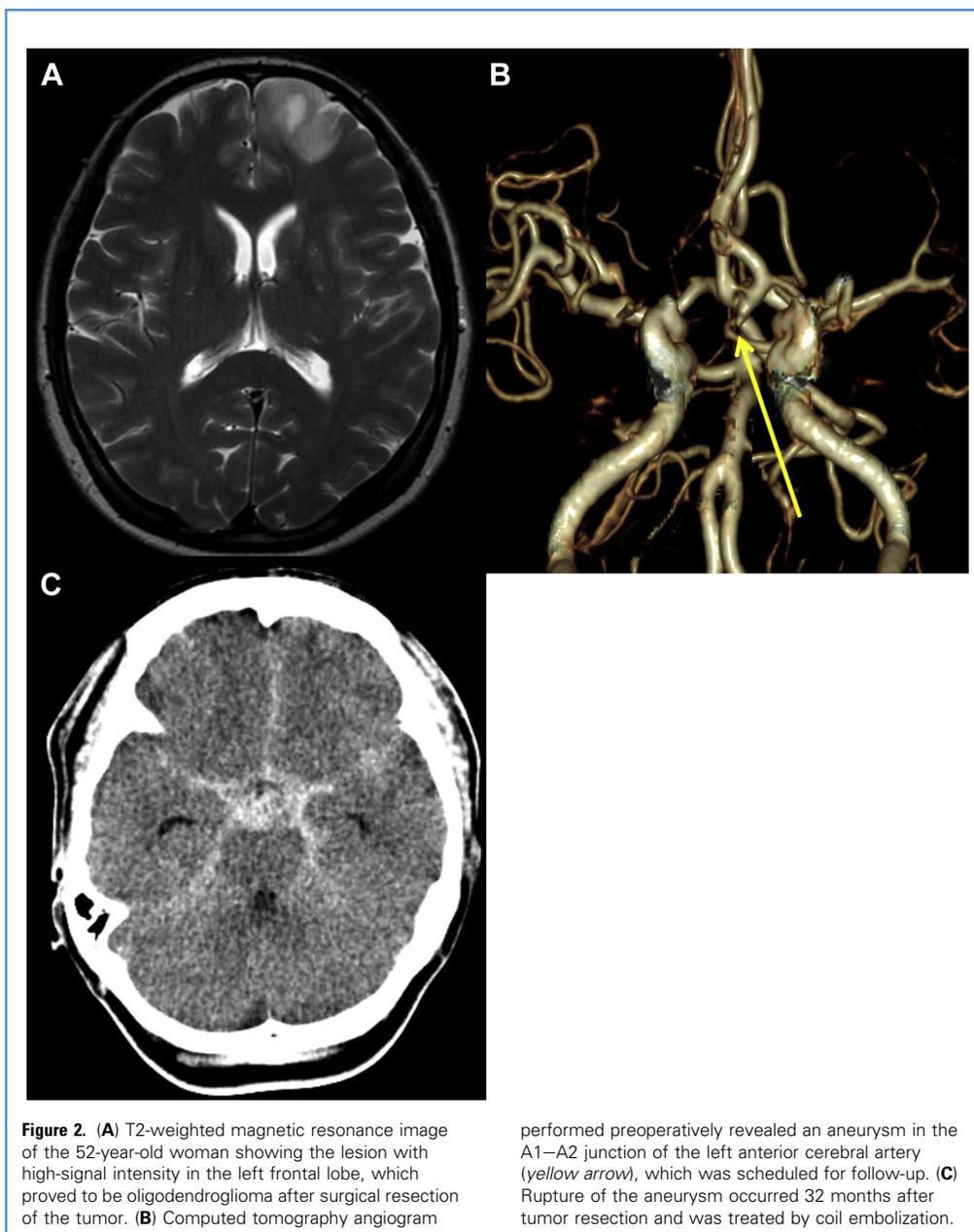
**Patient 1.** A 61-year-old woman had visited the outpatient clinic reporting a headache that had gradually worsened over several weeks. Brain MRI with gadolinium enhancement was performed and identified a  $4.5 \times 5$  cm hypervascular extra-axial tumor in the right anterior cranial fossa with dural attachment to the sphenoid bone, compatible with a diagnosis of meningioma (Figure 1A). The CT angiogram showed a hypervascular tumor with high enhancement in the arterial phase; however, no abnormal findings in the major intracranial vessels were observed. The patient underwent 4-vessel intra-arterial DSA to evaluate the tumor feeding vessels and also received preoperative tumor embolization. The tumor was strongly stained by the middle meningeal artery and a pial feeder that was constituted by the right ophthalmic and anterior ethmoidal artery on cerebral angiography. Intra-arterial DSA revealed 2 small aneurysms in the ophthalmic segment of the right ICA and 1 supraclinoid aneurysm with a superior direction (Figure 1B). The patient underwent tumor resection, with surgical clipping of the supraclinoid aneurysm at the same surgery after the tumor had been removed (Figure 1C).

**Patient 2.** A 52-year-old woman had been referred to our hospital to undergo surgical resection of an intra-axial tumor of the left frontal lobe (Figure 2A). Preoperative CT angiography revealed an UIA in the A1–A2 junction of the left anterior cerebral artery (Figure 2B). After tumor resection, the tumor was identified to be an oligodendroglioma. The patient was followed up for 2 years without evidence of tumor recurrence. However, the aneurysm had ruptured 32 months after tumor resection; thus, the patient underwent coil embolization for the ruptured aneurysm (Figure 2C).

### DISCUSSION

Although the coexistence of UIAs in patients with primary brain tumors has been described,<sup>4,7</sup> no clinical guidelines are available for the management and follow-up of these patients. In general, the treatment decisions for these patients has been determined by the patient's physical status and life expectancy and the risk of rupture presented by the UIAs.<sup>1</sup> Although life expectancy and physical status after surgical resection might not justify the treatment of coexistent UIA in some patients with high-grade tumors, management of coexisting UIAs should be considered because of the improved postoperative survival outcomes for patients with high-grade tumors<sup>8,9</sup> and the fatality resulting from ruptured UIAs during follow-up.<sup>10</sup> The rate of aneurysmal rupture of coexisting UIAs in patients with primary brain tumors has not been studied previously. However, several cases have been reported of aneurysmal rupture after surgical resection or





decompression of brain tumors, suggesting that decompressive surgery might increase the risk of aneurysmal rupture.<sup>11–13</sup> Moreover, clinicians should give special attention to UIAs contained in the postoperative radiation field, because these aneurysms could become more fragile and prone to rupture.<sup>14</sup> Reviewing the follow-up results from our study, all the UIAs that had demonstrated an interval increase in aneurysm size or aneurysmal rupture had been flow-related UIAs in patients with astrocytic or oligodendroglial tumors. In contrast, no UIAs had ruptured in patients treated for meningioma within the follow-up period. Unlike surgical resection of extra-axial tumors such as

meningioma in which the plane of surgical dissection is between the arachnoid membrane and tumor capsules, intra-axial tumor resection should be performed by subpial dissection, breaking the arachnoid layer,<sup>15</sup> which can result in coexisting UIAs becoming more vulnerable to rupture. Our findings have shown that flow-related UIAs in patients with astrocytic or oligodendroglial tumors might entail more risk of aneurysmal rupture after brain tumor resection compared with flow-related UIAs coincident with extra-axial tumors such as meningioma. Also, special attention should be given to the UIA location in patients undergoing adjuvant radiotherapy postoperatively. Therefore, with the recent

documentation of the safety and favorable outcomes of clipping surgery of UIAs,<sup>16</sup> we would cautiously recommend surgical clipping of UIAs at tumor removal if it can be performed in the same surgical field. When that is not feasible, perioperative coil embolization can also be considered for the treatment of coexisting UIAs, especially for patients for whom postoperative adjuvant radiotherapy has been scheduled.<sup>7</sup>

The study by Lee et al.,<sup>17</sup> which included data from the Korean national health-claim database, reported that the annual detection rate of UIAs in the Korean population was 20 cases per 100,000 persons and the rate of rupture was 2.7% among those with UIAs. However, the coexistence of UIAs has been reported in 0.19%–5.4% of patients with brain tumors.<sup>6,18,19</sup> The overall UIA detection rate in our study was 4.5% in patients with primary brain tumors, similar to those reported by previous studies.<sup>6,19</sup> The 4-year detection rate of coexisting UIAs in the patients with a primary brain tumor was 4.5% (55 of 1213 patients) in our study, slightly >1% annually and greater than the annual UIA detection rate of 0.02% in the general population in Korea reported by Lee et al.<sup>17</sup>

Confining the detection rate of UIAs to flow-related UIAs, the rate in the patients with meningioma was 3.3% (18 of 551 patients), and the rate in those with astrocytic or oligodendroglial tumors was 3.3% (10 of 300 patients). The actual incidence of coexisting UIAs in patients with meningioma might be lower than we have reported because patients with small-size tumors who were not candidates for surgical resection at the first diagnosis and those who had undergone radiosurgery were excluded.

In the patients with astrocytic or oligodendroglial tumors such as glioblastoma, almost all of whom had undergone surgical resection after the initial radiological diagnosis, the greater detection of flow-related UIAs in the present study compared with that for the general population seems more reliable. Therefore, considering the higher detection rate of flow-related UIAs compared with that in the general population and the observed cases of interval increases in UIA size or ruptured aneurysms in patients with astrocytic or oligodendroglial tumors, we would recommend noninvasive angiographic evaluations for both the initial radiological workup and during follow-up. Moreover, owing to the negative effects of postoperative adjuvant radiotherapy on the vasculature that result in UIAs becoming more fragile and the report of radiotherapy-induced UIAs,<sup>14</sup> we would also recommend MRA in the postoperative follow-up period if the coexisting UIAs have remained untreated in patients with astrocytic or oligodendroglial tumors. Recently, brain MRI scans with advanced techniques, including diffusion and perfusion studies, have been used for the accurate diagnosis of brain tumors by revealing tumor characteristics, such as permeability and diffusion restriction, in the enhancing region.<sup>3</sup> However, noninvasive angiographic evaluation such as MRA were not included in the follow-up brain MRI protocol in our hospital. It is possible that 2 cases of ruptured UIAs could have been avoided if follow-up imaging with MRA had been performed after tumor removal.

In some cases, when the contour of the major vessels have been shaded or deviated by the tumor, abnormalities in the intracerebral arteries can remain undetected, such as occurred with our patient 1. In such cases of large hypervascular tumors with numerous pial arterial feeders from intracerebral arteries

accompanied by deviation of the intracranial arteries, cerebral angiography should be considered preoperatively.

### Study Limitations

The present study had several limitations. Because 13 of 55 patients had undergone treatment of their UIAs at tumor resection and the UIAs of 2 patients had been treated before surgical resection of the brain tumor, the incidence of intraoperative rupture could not be elucidated. Also, the rate of aneurysmal rupture during follow-up was less reliable. Moreover, the natural course of untreated UIAs after surgical resection of a brain tumor remains inconclusive in the present study owing to the limited follow-up duration. Therefore, the long-term follow-up results of patients with untreated UIAs should be analyzed in future studies, in addition to the systematic review of previously reported case series. The present study also had a potential for bias in patient selection because older patients who were not candidates for surgical resection of the primary brain tumor were excluded.

We defined flow-related UIAs as those that had arisen from the continuum of the parent vessel of the feeding artery. However, a quantitative assessment of the flow through the artery from which the UIAs had arisen could not be performed, except for cases in which flow to the aneurysm can be presumed by the extent of tumor staining from the feeding arteries as assessed by cerebral angiography. To confirm the hypothesis that UIAs detected by noninvasive methods such as MRA would be associated with increased flow to the parent artery, we suggest that more patients with a coexisting brain tumor and UIAs who have undergone preoperative cerebral angiography should be evaluated in future studies. Also, the effect of vasoactive mediators such as overexpression of vascular endothelial growth factor in patients with malignant glioma should be investigated in future studies to evaluate whether it plays an independent role in aneurysm formation, aside from its effect of increasing blood flow.<sup>20,21</sup> Despite these limitations, to the best of our knowledge, our study is the first to compare coexisting UIAs according to the tumor pathology with follow-up of untreated UIAs in patients who had undergone surgical resection of the primary brain tumor. Further research is warranted to establish the clinical guidelines for patients with coexisting both brain tumors and UIAs.

### CONCLUSIONS

It is difficult to estimate the incidence of UIA in patients with primary brain tumors, especially when stratified by the tumor pathological features. In the present study, we found that the rate of coexistence of UIAs with tumors was greater than that of UIAs in the general population. We also found that patients with astrocytic or oligodendroglial tumors were more likely to have coexistent UIAs. Despite the rare occurrence of aneurysmal rupture, follow-up and adequate treatment of UIAs should be performed owing to the risk of mortality from subarachnoid hemorrhage. Therefore, when feasible, we recommend the perioperative treatment of UIAs, especially when they are considered to be flow-related in patients with astrocytic or oligodendroglial tumors. Perioperative treatment should consist of either surgical clipping at tumor resection or perioperative endovascular

treatment. Moreover, for patients who require follow-up for untreated coexisting UIAs, noninvasive follow-up modalities such as MRA should be included in the protocol of MRI studies for the postoperative follow-up of patients with primary brain tumors.

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