

Original Article

Papillary meningioma: clinical and histopathological observations

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Abstract: Papillary meningioma is a rare subtype of malignant meningiomas, which is classified by the World Health Organization as Grade III. Because of lack of large sample size case studies, many of the specific characteristics of papillary meningioma are unclear. This study investigated by retrospective analysis the clinical, radiological and histopathological findings of 17 papillary meningioma patients who underwent surgical resection or biopsy, to assess the characteristics of papillary meningioma. Eight female and nine male patients were included, with a mean age of 40 (range: 6 to 55) years. Tumors were mostly located in the cerebral convexity and showed irregular margins, absence of a peritumoral rim, heterogeneous enhancement and severe peritumoral brain edema on preoperative images. Brain invasion was often confirmed during the operations, with abundant to exceedingly abundant blood supply. Intratumoral necrosis and mitosis was frequently observed on routinely stained sections. The average MIB-1 labeling index was 6.9%. Seven cases experienced tumor recurrence or progression, while seven patients died 6 to 29 months after operation. Radiation therapy was given in 52.9% of all cases. Univariate analysis showed that only the existence of intratumoral necrosis and incomplete resection correlated with tumor recurrence. The 3-year progression free survival was 66.7% after gross total resection and 63.6% for other cases. The 3-year mortality rate was 50% after gross total resection and 63.6% for other cases. Papillary meningioma has specific clinical and histopathological characteristics. Tumor recurrence (or progression) and mortality are common. Gross total tumor resection resulted in less recurrence and mortality.

Keywords: Papillary meningioma, clinical manifestations, histopathology, prognosis

Introduction

Meningioma is one of the most common tumors of the central nervous system (CNS) which accounts for 22.8%~34.7% [1-3] of all CNS tumors. Atypical and malignant meningiomas comprise a small fraction of the total ($\leq 5\%$) and have a slight male predominance [4], which also show higher rates of recurrence [5, 6]. According to the 2007 World Health Organization's (WHO) classifications [7], papillary meningioma is defined as a subtype of "malignant meningiomas" (WHO Grade III) which feature the presence of a perivascular pseudopapillary pattern of tumor cell growth, either entirely or more commonly in combination with other common histological compo-

nents of meningiomas [8, 9]. Tumors of this type frequently invade the brain and bone and may exhibit extracranial metastases [10]. Papillary meningioma tends to occur in young patients [9]. At the time of writing, only a limited number of papillary meningioma cases have been reported, most of which were seen in single case reports. Our analysis of 17 consecutive papillary meningiomas is the largest single institute retrospective case study to date.

Patients and methods

Between January 2005 and December 2010, 17 papillary meningioma patients underwent surgical removal or biopsy in the Department of Neurosurgery, Huashan Hospital, Fudan

University. Two of the 17 patients experienced tumor recurrence and underwent a second operation, prior to 2010. These two cases were not taken as new cases in this study.

Patient diagnosis was confirmed by two pathologists at the beginning of the study who were blind to the patients' clinical data. Clinical data were recorded by two clinicians and checked together for further analysis. The 2007 WHO classifications of CNS tumors [7] were used as guidelines for histopathological differentiation. Follow-up was performed by direct telephone inquiries or at clinical visits. The final follow-up took place in June 2012.

Routinely processed sections were stained with H&E. Immunohistochemical assays were conducted for epithelial membrane antigens (EMA), vimentin (Vim), broad-spectrum cytokeratin (CKs), S100 protein and glial fibrillary acidic protein (GFAP). The levels of Ki-67 antigen (MIB-1) expression were evaluated for each of the 17 tumor samples. A recheck of the histopathological sections was performed by two pathologists independently.

Statistical analysis was performed using commercially available computer software (SPSS 16.0 for Windows; SPSS, Chicago, Ill). Categorical variables were compared with the Pearson χ^2 -test, and continuous variables with the Student's *t* test. Comparison for the mean value of continuous variables was performed with ANOVA. Hazard ratio (HR) comparison was used in univariate analysis for correlations between follow-up outcome (new recurrence or death) and gender, age, recurrence, tumor volume, blood loss, resection completeness, necrosis, brain invasion, mitosis, MIB-1 (%), radiation therapy, KPS on admission and KPS at discharge. Unconditioned logistic regression was applied for multivariate analysis of those factors. Kaplan-Meier product-limit estimates were applied for analyzing the occurrence of recurrence (or progression) and death. Probability values of less than 0.05 were considered statistically significant.

Results

Gender and age

Eight female and nine male patients (female/male ratio: 0.89) were observed in the study

(**Table 1**). The mean age was 40 (male: 38.0; female: 42.3; range: 6 to 55) years. For comparison, we listed the female/male ratios and mean ages of WHO grade I and II meningiomas also operated on in our department during the same period of time (**Table 2**). Altogether, the three female/male ratios were significantly different ($P<0.001$), with differences also found in paired comparisons between papillary meningioma and WHO grade I meningiomas ($P=0.022$). Significant differences were observed in both multiple comparisons ($P<0.001$) and paired comparisons ($P_{1,2}<0.001$, $P_{1,3}<0.001$, $P_{2,3}=0.014$) of the mean ages of the three meningioma groups (**Table 2**).

Tumor locations

The tumor locations for the 17 cases were cerebral convexity ($n=14$), parasagittal ($n=1$), peritumoral ($n=1$) and sellar ($n=1$). The cerebral convexity was the most common site for papillary meningioma to be found. Interestingly, with three tumors showing midline growth, nine of the 17 cases were located on the left side, and the other five cases were on the right side (**Table 1**).

Patient history and comorbidities

Twelve patients complained of intermittent ($n=1$) or continuous ($n=11$) headache, with ($n=4$) or without ($n=8$) projectile vomiting. Seventeen percent (2/12) of which also complained of blurred vision. Four patients reported generalized seizures 2 days to 5 years prior to discovery of the meningioma. A 6-year-old female patient with a right parietal meningioma suffered two episodes of generalized tonic-clonic seizures when she was 8 months old and then again when she was 3 years old. The average duration of tumor relevant symptoms before operation was 8.8 months (range: 2 days to 5 years).

For gynecological conditions, only one patient (case 5) had a history of hysteromyomectomy; another (case 7) had oophorectomy. Routine preoperative chest x-rays and further meglumine diatrizoate enhanced chest CT scans discovered probable left lower lobe lung cancer with multiple intra-pulmonary metastasis in a 52-year-old male patient (case 6), concomitant with a left occipital papillary meningioma. No patients reported a history of severe

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Table 1. Summary of clinical and histopathological findings in 17 papillary meningiomas

Case	Gen-der	Age	Locations	Size (cm ³)	Blood Supply	Blood Loss (mL)	Resec-tion	Histopathological Findings							Post-operation Radiation	KPS		
								Necro-sis	Brain Invasion	Mito-sis	CKs	S100	GFAP	MIB-1 (%)		Admis-sion	Dis-charge	Follow-up
1	M	54	Left Parietal	8×9×5	n.a.	1400	2	Y	Y	Y	-	+	-	12	Y	90	80	90
2	M	29	Right Parieto-occipital	6×4×2	3	2400	1	Y	Y	Y	-	+/-	-	5	Y	80	80	0
3	M	34	Left Parieto-occipital	6×4×2	4	2600	2	N	Y	Y	-	n.a.	n.a.	10	Y	80	80	100
4	F	53	Left Temporo-occipital	10×6.5×5	3	300	2	Y	N	Y	+	n.a.	-	10	n.a.	50	90	Lost
5	F	55	Right Frontal	2.5×2.5×2.5	3	400	1	N	Y	Y	n.a.	n.a.	-	10	N	90	90	0
6	M	52	Left Occipital	n.a.	3	300	1	Y	N	Y	-	n.a.	-	5	N	90	90	0
7	F	47	Right Frontal	4×4×4	n.a.	300	1	Y	Y	N	-	+/-	-	15	N	90	90	100
8	F	52	Left Frontal	4×3×3	n.a.	200	1	Y	Y	N	n.a.	n.a.	n.a.	4	Y	90	90	100
9	M	33	Right Fronto-parietal	3×4×4	3	1200	2	Y	n.a.	Y	n.a.	n.a.	n.a.	8	n.a.	70	80	Lost
10	M	30	Peritorcular	2×2×4	3	400	1	N	n.a.	Y	n.a.	-	n.a.	3	Y	90	90	100
11	F	6	Right Occipital	6×6×5	3	600	2	Y	Y	N	+/-	+/-	+/-	5	Y	80	90	0
12	M	36	Left Temporal	3×2×1	3	400	2	Y	Y	Y	-	n.a.	-	4	n.a.	90	90	Lost
13	M	24	Suprasellar	n.a.	4	n.a.	5	n.a.	n.a.	Y	+/-	-	-	3	N	80	80	0
14	F	31	Left Parieto-occipital	n.a.	3	350	2	N	N	Y	n.a.	+/-	-	2	Y	80	80	90
15	F	54	Bilateral Frontal Parasagittal	6×7×6	3	1200	4	Y	Y	Y	n.a.	+/-	-	4	Y	50	40	0
16	M	50	Left Frontal	5×6×7	3	1000	2	N	Y	Y	n.a.	n.a.	-	10	N	70	70	0
17	F	40	Left Temporo-parietal	5×5×4	n.a.	250	2	Y	Y	Y	-	n.a.	+/-	8	Y	80	90	100

(The cases were arrayed by date of admission. M, male; F, female; Y, yes; N, no; n.a., not available).

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Table 2. Female/male ratios and mean ages of WHO grade I and II meningiomas and papillary meningiomas operated on at Huashan Hospital from January 2005 to December 2010

	Gender		Ratio	Age (years)	
	Female (No.)	Male (No.)		Mean	95% CI
WHO Grade I	3451	1338	2.58	51.8	(51.5, 52.1)
WHO Grade II	139	127	1.09	49.0	(47.3, 50.8)
Papillary Meningiomas	8	9	0.89	40.0	(32.9, 47.1)

(WHO, World Health Organization; CI, confidence interval).

head trauma or hypertension. Average Karnofsky Performance Status Scale (KPS) [11] for those patients on admission was 79.4 (range: 50~90) (**Table 1**).

Four tumors were recurrence or a progression of previously resected meningioma, each having had one (n=1) or two (n=3) past operations performed either at our institution or at another hospital. The Simpson resection grade or a pathological diagnosis for former operations was not available for three of the four cases. In one case (case 4), the patient had undergone two former operations on tumors at the same location. Those were performed 12 and 16 years ago. The pathological diagnosis of the tumors was meningothelial and fibrous meningioma. Both tumors were recorded given Simpson grade I resection.

Radiological findings

Using MR and/or CT scans, the preoperative diagnosis was confirmed as meningioma in 13 of the 17 cases, although not every case mentioned considerations of tumor malignancy. Three cases (cases 12, 13, and 14) were diagnosed before operation as glioma. One case (case 11) was diagnosed as a primitive neuroectodermal tumor (PNET).

In cases where data were available, all presented with irregular tumor margin (6/6), heterogeneous enhancement with gadolinium (7/7) and severe peritumoral brain edema (PTBE) (8/8). Four out of five tumors showed absence of a peritumoral rim. There was only scattered minor interspace along the border of the one other tumor. Typical MR manifestations of a papillary meningioma are shown in **Figure 1**.

Operations

Tumor blood supply was evaluated as either grade 1 (low), 2 (medium), 3 (abundant) or 4 (exceedingly abundant). Except for four cases

without valid information, all tumors (13/13) had abundant (n=11) to exceedingly abundant (n=2) blood supply (**Table 1**). For the suprasellar papillary meningioma patient (case 13), which was diagnosed before operation as glioma, only a biopsy was taken. Complete or partial tumor removal was abandoned for that patient because of too turbulent blood supply disclosed after dissecting only a minor part of the tumor. Average intraoperative blood loss was 831.3 mL (range: 250~2600 mL) for all 17 patients (**Table 1**).

Aggressive invasion into the adjacent brain was observed in 64.7% (11/17) of cases, all of which were confirmed during operations. Bone invasion was observed in two left frontal meningiomas (cases 8 and 16). Intratumoral necrosis and/or obsolete hemorrhaging were seen in six cases during tumor resections. Three of the 17 cases were observed with intratumoral cystic changes. A typical case is shown in **Figure 1**.

The completeness of the operations was graded using routine Simpson grading [12]. Simpson grade 1 tumor resection was achieved in 35.3% (6/17) of cases. Nine other cases were recorded as Simpson grade 2 resection. One patient (case 15) had undergone two previous operations at the same location prior to our operation. This patient was only given a Simpson grade 4 resection this time. A biopsy (Simpson grade 5 resection) was performed for one patient, as mentioned above. Evaluation of resection completeness was made intraoperatively and was not confirmed with postoperative contrast-enhanced MR images. Pre- and postoperative gadolinium enhanced MR images of two tumors that were given Simpson 1 (case 8) and 2 (case 1) resections respectively are shown in **Figure 2**.

Postoperative course

Postoperative hospital stays were uneventful in 64.7% (11/17) of cases. All 12 patients who

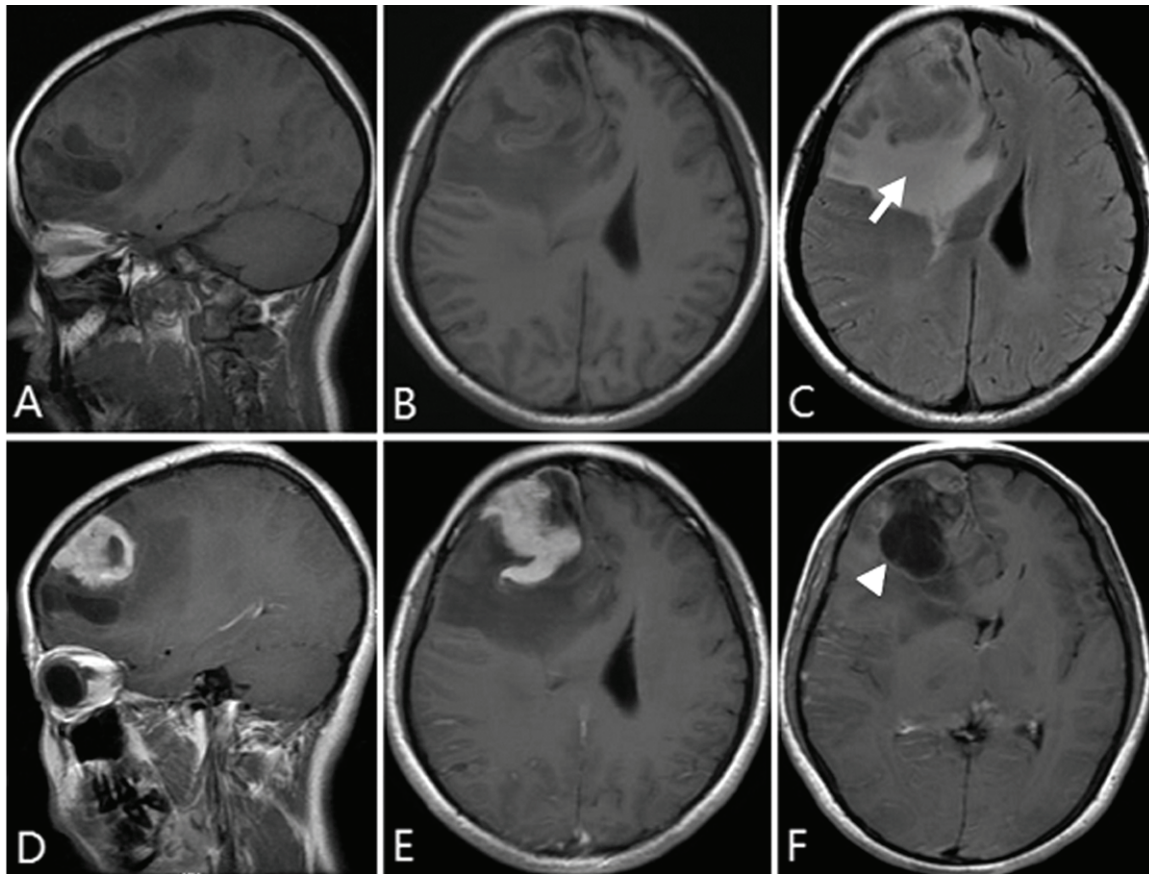


Figure 1. Sagittal and axial T1 (A and B), axial T2 (flair) (C) weighted, Sagittal and axial gadolinium enhanced (D, E and F) MR images of a right frontal papillary meningioma (case 7) with cystic change and large scale of PTBE (ar-row). The tumor showed an irregular tumor margin with no peritumoral rim, and was heterogeneously enhanced. The cyst wall was not enhanced (arrowhead).

had complained of headaches and/or vomiting pre-operation reported alleviation of their symptoms before discharge. Paralysis of varying severities (n=4, with grade 0 to IV muscle strength of affected extremities), upper digestive tract symptoms (n=2, nausea or upper gastrointestinal hemorrhaging), pneumonia (n=1), urinary tract infection (n=1), subcutaneous hydrops (n=1), delayed wound healing (n=1) or generalized seizure attack (n=1) were observed during the 17 papillary meningioma patients' hospital stays following their surgical procedures.

A 54-year-old female patient (case 15) with a bilateral frontal parasagittal recurrent meningioma experienced an episode of generalized tonic-clonic seizure 5 days after tumor resection (Simpson grade 4). The patient's state deteriorated remarkably after the seizure attack, with the Glasgow Coma Score [13] (GCS) decreasing from 15' to 7'. Although no

hemorrhage was found, a CT scan revealed severe brain edema around the operation field, worse than before the operation.

Impairment of motor function occurred only in those cases where the tumor was located close to the motor cortex or subcortex conducting pathways, because papillary meningiomas frequently had no clear border and invaded the adjacent brain. That growth pattern made damage to the surrounding cortex inevitable if complete tumor removal was attempted.

A 53-year-old female patient who had a recurrent left temporo-occipital meningioma suffered right side hemiparalysis and "was able to carry on normal activity" (cases 11) (KPS: 90) at the end of her hospital stay.

Average KPS for the 17 patients at discharge was 82.4 (range: 40~90) (Table 1). Compared with the patients' status before the operations

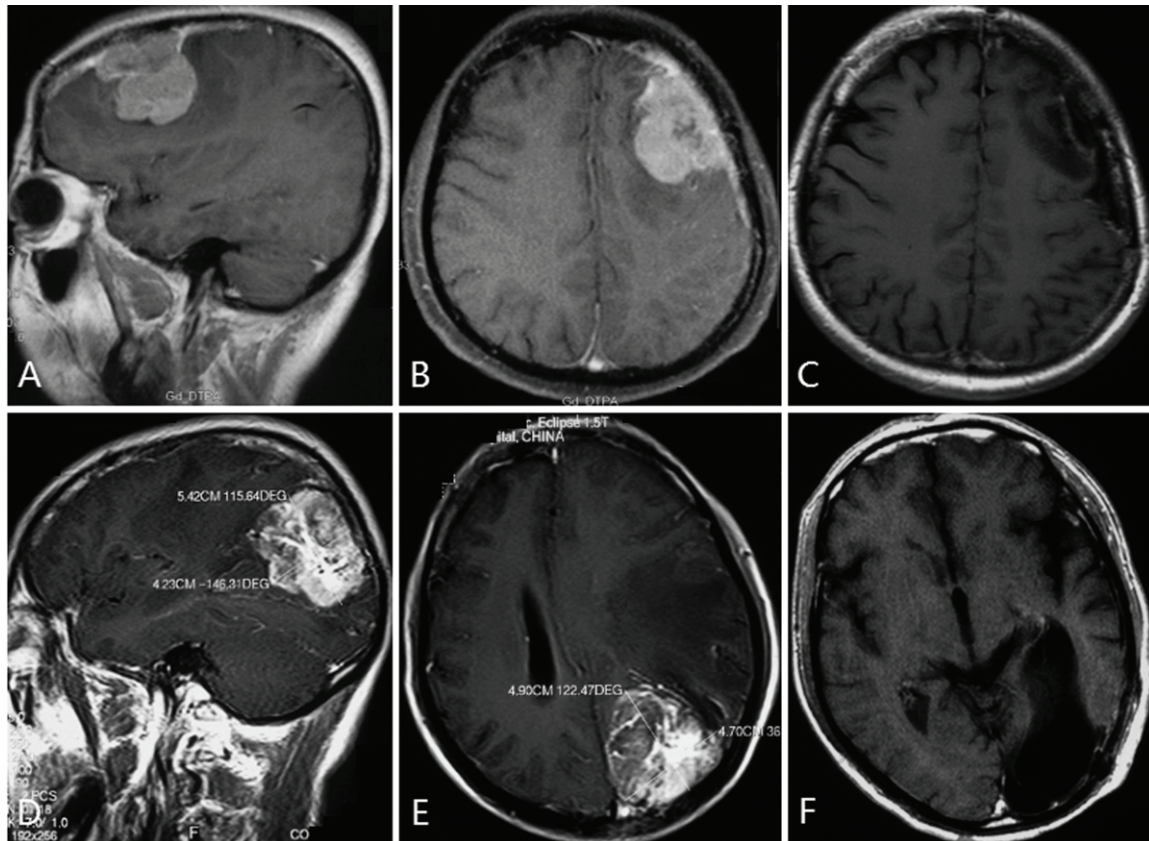


Figure 2. Preoperative sagittal and axial gadolinium enhanced MR images (A, B and D, E) and follow-up axial MR images (C and F) of two papillary meningiomas. A, B and C (6 months after operation), case 8; D, E and F (11 months after operation), case 1.

(average KPS: 79.4), symptoms correlated with intracranial hypertension (headache and projectile vomiting, $n=4$) and were usually alleviated after resection of the tumor.

Histopathological findings

Intraoperative frozen pathological processing was performed for three cases. However, two cases were mistakenly diagnosed as grade II or III gliomas. Only one of the three cases was identified as a tumor with fusiform cells (case 12), although it was not further determined to be a type of malignant meningioma either.

Tumor necrosis was observed in 68.8% (11/16) of the sections. The patient who was given a biopsy only was excluded because the available sample was not sufficient to find tumor necrosis. In 82.4% (14/17) of cases, obvious mitosis was found.

For cases where there was a processed section available, immunohistochemical assay for CKs

was positive in 30% (3/10) of cases, protein S100 was positive in 75% (6/8) of cases, and GFAP was positive in only 15% (2/13) of cases.

The average MIB-1 labeling index was 6.9% for all 17 cases (range: 2%~15%). A summary of the histopathological findings is listed in **Table 1**. Typical microscopic manifestation of a papillary meningioma is arrayed in **Figure 3**.

Postoperative treatment and follow-up

Three patients (17.6%) did not participate in follow-ups. Seven patients experienced tumor recurrence or progression at a mean of 13 months (range: 1 to 36 months). They were given either another operation ($n=4$), radiation ($n=1$) or only conservative treatment ($n=2$). Seventy-five percent (3/4) of the cases who were given another operation died 6 to 27 months (mean: 19.7 months) after their first operation at our institute. Those included the patient who had a tumor biopsy for suprasellar papillary meningioma. This patient died 6

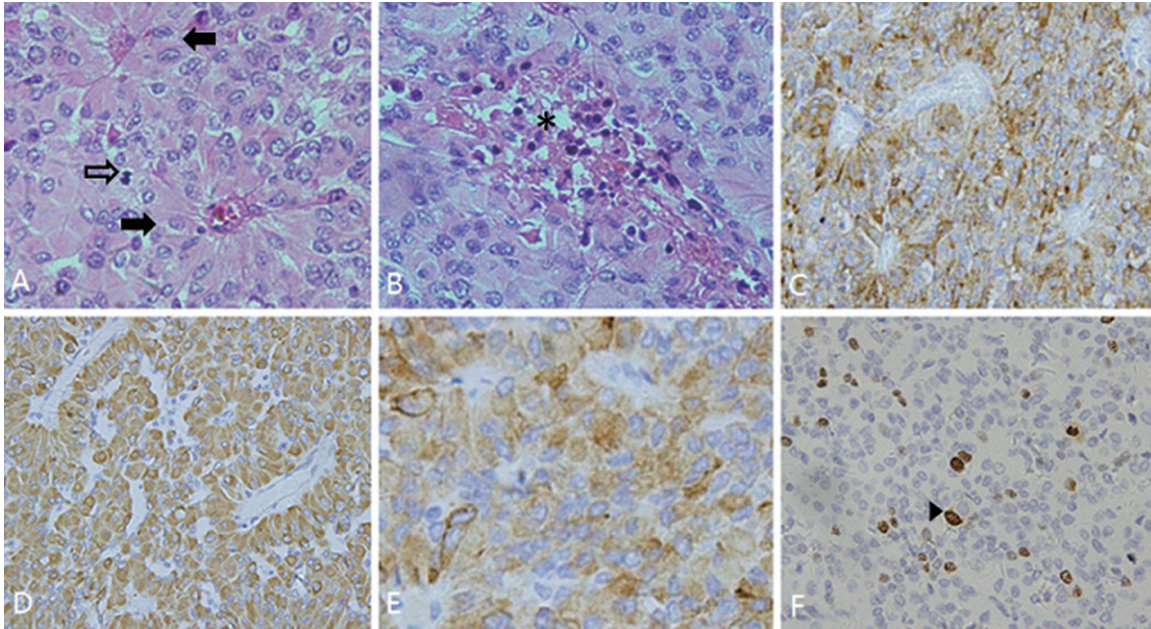


Figure 3. Microscopic manifestation of a papillary meningioma (case 4). A. perivascular pseudopapillary pattern (arrows) and mitosis (hollow arrow) shown on H&E sections; B. focal necrosis (*) shown on H&E sections; C. labeling of EMA; D. labeling of Vim; E. labeling of CKs; F. positivity with Ki-67 labeling (arrow head). Original magnification: $\times 400$ for all sections.

months after the biopsy. The patient who was given conventional radiation therapy following his second operation at our institute showed no signs of residual tumor at the 6-year follow-up. The three patients who received radiation only or no further treatment died 15 to 29 months (mean: 23 months) after their operations. In total, seven patients died 6 to 29 months (mean: 19.1 months) after operation. Six of those cases are mentioned above. The patient with advanced stage lung cancer died 6 months after operation because of multiple organ failure, as reported by his family.

As there were only two cases with Simpson grade 4 and 5 resections (no grade 3 resection) in this series, we stratified the 17 cases into two groups: group 1 with a Simpson grade 1 tumor resection (gross total resection); and group 2 with a Simpson grade 2 to 5 resection. Survival analysis revealed no significant difference in rates of recurrence ($P=0.707$) or death ($P=0.575$) between the two groups.

Univariate analysis of the correlations between follow-up outcomes (new recurrence or death) and gender, age, recurrence (history of meningioma resection), tumor volume, blood loss, resection completeness (Simpson grade 1 to

5), necrosis (yes/no), brain invasion (yes/no), mitosis (yes/no), MIB-1 (%), radiation therapy (yes/no), KPS on admission and KPS at discharge, showed that only the existence of intratumoral necrosis ($P=0.023$, HR 0.023) and incomplete resection ($P=0.032$, HR 0.032) correlated with tumor recurrence. Multivariate analysis was not performed for further investigation. No significant correlation was found between mortality and those factors listed above.

The 3-year PFS was 66.7% for cases after gross total resection and 63.6% for other cases (no significant difference). The 3-year mortality rate was 50% for cases after gross total resection and 63.6% for other cases (no significant difference).

Discussion

A Pubmed online literature search was performed using the following key words: "papillary [All Fields] and meningioma [All Fields] and English [lang]" and "papillary meningioma [Title/Abstract] and English [lang]". The last search was finished on 25 June 2012. Other relevant articles that had been acquired using the Google search engine were included. In

total, 24 articles with full text (n=13) or with a meaningful abstract only (n=11) were taken into consideration.

Papillary meningiomas are more commonly seen in male patients [14] and tend to occur in younger patients [14-25]. In our series, papillary meningiomas showed a female/male ratio significantly less than lower grade meningiomas, especially when compared with WHO grade I meningiomas. The patients with papillary meningiomas were also younger than other groups with lower tumor grades (**Table 2**). Patients with papillary meningiomas usually manifest symptoms caused by intracranial hypertension, such as severe headache and vomiting and blurred vision, which are notably alleviated after resection of the tumor. Papillary meningiomas with cystic changes have been seen in eight reported cases at the time of writing [19, 26, 27]. In our series of 17 cases, three cases showed intratumoral cystic changes. Papillary meningiomas are most frequently seen in the supratentorial compartment [15]. Our series is consistent with this finding. The literature review reported the other areas for tumors to locate as being the posterior fossa, the jugular foramen and the oculomotor nerve [20, 21, 28, 29].

High-grade meningiomas usually have unclear tumor margins, heterogeneous gadolinium enhancement and a larger scale of PTBE [30, 31]. The available cases in our series showed irregular tumor margins without a peritumoral interface and were enhanced heterogeneously, which represents rapid tumor growth and non-uniform pathological features caused by intratumoral necrosis [32]. Severe PTBE, caused by extravasation of plasma water and macromolecules through a damaged blood-brain barrier [31], were also observed in these cases.

Extracranial metastasis is reported to occur in approximately 0.1% of meningiomas of all grades [29, 35]. This is especially so in malignant meningiomas, which can arise from various cell dissemination paths [35, 36].

Papillary meningioma was frequently mentioned as the origin of metastatic meningiomas in the pleura [14], lung [37, 38] and liver [10], or most commonly diffuse cerebrospinal metastasis [8, 22-24, 39, 40]. However, we did not

observe any CNS or distant metastasis in the 17 patients studied. All six patients who experienced recurrence and later died were hospitalized in local health centers and did not provide us with detailed information about their exact clinical manifestations. This may possibly be why no tumor metastasis is reported in this series. The patient (case 6) who had multiple intrapulmonary lesions suspected to be lung cancer with metastasis, died 6 months after resection of the left parietal papillary meningioma. There was no pathological evidence available which could remove the possibility of metastatic papillary meningioma to the lung.

As a malignant, fast growing tumor, papillary meningiomas were all found to have abundant to exceedingly abundant blood supplies during operations in our series. Brain invasion was also frequently encountered during the surgical procedure, making damage to the adjacent cortex or subcortex structure inevitable for those patients. This resulted in a high rate of postoperative functional abnormalities which were mostly absent before the operation.

As the largest series of papillary meningiomas previously reported, Ludwin et al. [10] mentioned in their clinicopathological analysis of 17 cases, that mitoses were seen in 7/17 (41%) of cases, brain invasion in 8/17 (47%) of cases, local recurrence in 10/17 (59%) of cases and extracranial metastasis in 4/17 (23.5%) of cases. The presence of papillary pattern growth in the meningiomas was argued to correspond with the histopathological and clinical aggressiveness of the tumors [33]. Lesions with papillary patterns were known to have an aggressive character with typical and atypical mitoses, necrosis and pleomorphism [33, 41]. Other researchers, however, have suggested that these papillary structures were no more than secondary manifestation of vasotropism and a weak cohesion between the cellular perivascular "crowns" [34]. It appears likely that the papillary pattern of meningioma is not always an expression of anaplasia when no other clinical or histological signs of malignancy are present [34]. However, heteromorphism of the neoplasm from originated cells is itself an independent characteristic for evaluating tumor malignancy.

The aggressive behavior of papillary meningioma associated with poor clinical prognosis

requires a timely diagnosis [14]. Our analysis of 17 cases showed that only intratumoral necrosis and incomplete resection predispose the patient to tumor recurrence (or progression). Hence, more aggressive resection of the tumor is required once the tumor is recognized as a probable high grade meningioma. Though univariate analysis showed the Simpson resection grade (grade 1 to 5) was correlated with new recurrence of the tumor, no significant difference was found when we compared the 3-year PFS and 3-year mortality in cases with gross total resection and all other cases. This may be because of the small sample size in this study. Gross total tumor resection resulted in less recurrence (3-year PFS: 66.7% vs. 63.6%) and mortality (3-year mortality: 50% vs. 63.6%) than that after less aggressive operations performed on patients, although the differences were found with no statistical significance.

In conclusion, papillary meningioma is an uncommon malignant subtype of meningiomas. It has specific clinical and histopathological characteristics, such as a comparative male predominance, younger patient age, irregular tumor shape on CT or MR images, heterogeneous enhancement with gadolinium, tumor invasion into the adjacent brain, abundant blood supply to the tumor and a higher MIB-1 index. Tumor recurrence (or progression) and mortality were common among patients. Gross total tumor resections seemed to result in less recurrence and mortality. Studies with a larger sample size are needed to further clarify the characteristics of papillary meningioma.

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Conflict of interest

The authors have no conflicts of interest.

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