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Original Article

Secretory meningiomas: clinical, radiological and pathological findings in 70 consecutive cases at one institution

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Abstract: Secretory meningioma (SM) is a rare, benign subtype of meningioma. Between January 2005 and December 2010, 70 SMs were operated on at the Department of Neurosurgery, Huashan Hospital, Fudan University. We retrospectively analyzed the clinical data, radiological and immunohistochemical findings, and patient outcome to discuss the specific features of SMs. Cranial base preference, hyper-signal in T2 weighted MR image, "xenon light" gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) enhancement were frequently observed in the 70 cases. Non-skull base SMs, which received more complete resection ($p<0.01$) and had better short-term and long-term outcome, were observed with more severe peritumoral brain edema (PTBE) ($p<0.001$). In follow-up, only 1 cranial base SM case showed tumor progression. 3 cases died after operation, all with cranial base SMs. As for the 10 cases given Simpson grade 3 or 4 resection who were available at follow-up, 3 died, 5 received gamma-knife therapy, and the other 2 cases received no treatment at all. Only one of the 2 residual SMs without postoperative radiation presented minor progression at a median of 48 months follow-up. In conclusion, cranial base preference, hyper-signal T2 weighted MR image and "xenon light" GD-DTPA enhancement are specific for SMs. Prognosis of SMs is related with operation completeness and surgical risks, rather than the extent of PTBE. Residual SM grows slowly and reacts well to gamma-knife therapy.

Keywords: Location, prognosis, radiology, secretory meningiomas

Introduction

Secretory meningioma (SM) is an uncommon benign meningioma subtype (WHO grade I) [1], containing eosinophilic and periodic acid-schiff (PAS)-positive globular intracellular pseudopsamomas that are actually inclusions within intracytoplasmic lumina lined by microvilli [2-4]. The inclusions were also reported to be positive for cytokeratin (CK) [5] and carcinoembryonic antigen (CEA) [3, 5-9]. Moreover, the surrounding cells that might secrete and enclose the globules have both CK and CEA immunoreactivity [3-10]. Immunohistochemistry staining of progesterone receptor (PR) for the tumor also showed mostly positive [5, 7, 10]. SM was reported to account for 1.1-3.0% of all meningiomas [4, 5, 7, 9], while our 6 years series of 70 SMs accounted for 1.35% of all operated meningiomas in one institute. Female predominance, location preference, correlation with severe peritumoral brain edema (PTBE), and unique histopathological features had been repeatedly reported in previous articles, though all with comparatively few cases. With the largest series ever reported, this study aimed at exploring more of the clinical, radiological and immunohistochemical characteristics of SMs.

Methods

Series of 70 SMs

Between January 2005 and December 2010, 70 cases of SMs underwent surgical resection

in the Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University. That was 1.35% of the total 5184 meningioma patients operated in the institute during the same period of time. Prior to our further investigation, the 70 cases were confirmed by two pathologists who were blind to the patients clinical data, on the basis of the 2007 WHO classification of tumors of the central nervous system.

Clinical and radiological information

Information about hospital stay and histopathological study was obtained from archived medical records. An investigation about subsequent treatment, patient clinical status, follow-up and MRI was performed either at outpatient visit or through telephone inquiry. The ending point of follow-up was in May 2012.

The majority of the radiological files were primitive pictures taken with a camera during our follow-up process. Only a few were directly copied from the archived data of the radiological department. So adjustment of window level, window width or other features of MR images was infeasible in our study, reducing the question that those images were modified to look as what we wanted them to be. There was no intended designing of the radiological images during our study.

Completeness of the operations was graded by the Simpson grading scale. The results were further confirmed with follow-up MR images when available. Pre- and postoperative radiological files were collected during follow-up or by searching archived data of the radiological department. The radiological files were analyzed by 2 researchers independently. Preoperative images were evaluated for signal intensity on T1 and T2 weighted images, calcifications on CT scan, tumor size, tumor margin, peri-tumoral rim, signs of bone hyperostosis, and the extent of PTBE.

Tumor signal on T1 or T2 weighted (T2 flair) images was recorded as hypo-signal, iso-signal or hyper-signal, respectively. Size of the tumors was determined either by measuring on preoperative images or by reviewing operation records. MR imaging of the tumor after gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) enhancement was divided into 4 types: 1, weak enhancement; 2, heterogeneous strong enhancement; 3, homogeneous strong enhancement with small focal defects (less than 1/10 of the tumor); 4, homogeneous strong enhancement. Evaluation of enhancement was not made for cystic parts of the tumor in 2 cases.

PTBE manifested as massive change in the brain tissue adjacent to the tumor, which was typically low intensity on CT, hypo-signal in T1 weighted and hyper-signal in T2 weighted MR images [11, 12]. Grading criteria of PTBE was modified from those of Probst-Cousin, 1997 [5] and Regelsberger, 2009 [4]: Grade 0, no recognizable edema; Grade 1, edema smaller or equal to the tumor; Grade 2, edema exceeded the size of the tumor, but is less than half the hemisphere; Grade 3, a severe, nearly hemispheric edema.

The clinical conditions before and after operation were expressed via Karnofsky Performance Scale(KPS). The Glasgow Outcome Scale(GOS) was also used to evaluate postoperative clinical outcome. Detailed information of the 70 cases was listed in **Table 1**.

Immunohistochemical examination

Sections were routinely stained with hematoxylin and eosin (H&E), PAS with or without diastase. Targets for immunohistochemical staining included: epithelial membrane antigen (EMA, monoclonal, DAKO, Hamburg, Germany), vimentin (Vim, monoclonal, DAKO, Hamburg, Germany), CEA (monoclonal, DAKO, Hamburg, Germany), broad-spectrum CK (monoclonal, DAKO, Hamburg, Germany), PR (monoclonal, DAKO, Hamburg, Germany). Ki-67 antigen (MIB-1, monoclonal, DAKO, Hamburg, Germany) expression was also investigated. Immunohistochemical examination was performed previously by the diagnosing pathologists, right after each tumor was resected. Recheck of sections was carried out by the two pathologists in this research team. As mentioned above, the positive immumohistochemical staining of CEA, CK and PR to the secretory inclusions and/ or tumor cells was highly concordant in abundant previous cases studies, the majority of which showing 100% positivity. So we did not supplement undone staining process for those antigens and checked only the sections prepared previously in our routine histopathological practice.

Table 1. Summary of clinical, radiological and immunohistochemical findings in 70 secretory meningiomas (The cases were arrayed by date of admission)[1, 2, 3, 4, 5, 6, 7]

Patient	Gender	Age	Locations	Tumor Margin	Peritumoral Interface	T2 Weighted	Gd-DPTA Enhancement	Size	PTBE	Resection Grade	PAS	CEA	CK	PR	ER	MIB-1 %
1	F	45	Medial sphenoid wing	NA	NA	NA	NA	5×4×4	NA	4	+					0
2	F	48	Fronto-temporal convexity	IR	Y	2	4	4.5×2.5×4	1	1	+		+			3
3	F	62	Frontal convexity	R	Y	3	4	2×1.5×2	1	1	+					0.1
4	M	58	Petroclival	IR	Y	3	4	5.5×4×4	1	2	+	+	+			<1
5	F	42	Cavernous sinus	R	Y	3	4	4×2.5×3	1	4	+		+			<1
6	F	56	Temporal convexity	NA	NA	NA	NA	2×2×2	NA	1	+		+			<1
7	F	35	Olfactory groove	R	Y	3	4	2.5×3×3	2	1	+		+			<1
8	M	73	Foramen magnum	NA	NA	NA	NA	NA	NA	2	+					<1
9	M	56	Cerebellopontine	R	Y	3	4	4×4.5×3.5	0	2	+		+			<1
10	M	49	Medial sphenoid wing	R	NA	NA	NA	3×3×3	2	2	+		+			0
11	F	40	Lateral sphenoid wing	R	Y	3	4	3.5×3.5×3.5	0	1	+		+/-			<1
12	M	55	Petroclival	NA	NA	NA	NA	NA	NA	4	+					<1
13	M	50	Middle sphenoid wing	R	N	3	4	2×2.5×2.5	2	2	+					1
14	M	52	Petroclival	NA	NA	NA	NA	NA	NA	3	+					<1
15	F	41	Petroclival	NA	NA	NA	NA	4×5×6	NA	2	+					<1
16	F	61	Frontal falx	NA	NA	NA	4	NA	NA	2	+					1
17	M	47	Frontal convexity	IR	Y	3	NA	5×4.5×4.5	3	1	+					1
18	F	63	Petroclival	R	Y	3	NA	1.5×1.5×1.5	0	2	+					<1
19	M	33	Medial sphenoid wing	R	Y	3	NA	3.5×2.5×2.5	1	2	+					<1
20	F	44	Middle fossa floor	R	Y	3	4	4×3.5×3.5	2	2	+					0
21	M	59	Frontal convexity	IR	N	3	4	3×3×3	3	1	+					<1
22	F	59	Jugular foramen	R	NA	NA	NA	4×5×4	0	2	+					1
23	F	44	Medial sphenoid wing	R	Y	3	4	1.5×3×2	1	2	+					1
24	F	56	Petroclival	NA	NA	NA	NA	4×5×3	1	4	+					<1
25	F	78	Frontal parasagittal	IR	N	3	4	3.5×3.5×3.5	3	2	+					3
26	F	67	Frontal convexity	NA	NA	NA	NA	NA	NA	1	+		+			1
27	F	57	Medial sphenoid wing	R	NA	NA	NA	3×3×3	0	2	+					1
28	F	58	Cerebellopontine	NA	NA	NA	NA	3×4×3	NA	2	+					1
29	F	42	Spheno-orbital	R	Y	3	4	3×2×1	1	4	+					<1
30	F	38	Foramen magnum	R	Y	3	NA	2.5×2.7×2.8	0	4	+					1
31	F	50	Spheno-orbital	R	Y	3	4	2.5×2.5×2	0	1	+	+				1
32	F	48	Spheno-orbital	NA	NA	NA	NA	NA	NA	1	+	+				1
33	F	55	Frontal convexity	R	Y	3	4	1.2×1.3×1	2	1	+					<1
34	F	46	Petroclival	R	Y	3	4	5×4×3	0	3	+					<1
35	M	51	Foramen magnum	R	Y	3	4	3.3×4.2×4.6	0	2	+		+/-			<1

36	F	52	Middle sphenoid wing	R	Y	3	4	2×3×3	2	2	+					<1
37	F	35	Lateral sphenoid wing	NA	NA	NA	NA	4×4×4	NA	2	+		+/-			<1
38	F	59	Petroclival	R	Y	3	3	4×3×4	1	2	+					<1
39	F	55	Frontal parasagittal	NA	NA	NA	NA	NA	NA	2	+					<1
40	F	52	Medial sphenoid wing	R	N	3	4	4×4×4	2	2	+					<1
41	F	51	Petroclival	NA	NA	NA	NA	4.5×4.5×3.0	NA	4	+					<1
42	F	51	Cerebellopontine	R	Y	3	4	3.5×3×2	0	2	+					<1
43	F	45	1. Tuberculum sellae (secretory)	R	Y	3	NA	2.5×2.5×2	0	2	+					<1
			2. Frontal convexity (fibroblastic)				NA									
44	M	55	Petroclival	R	Y	3	4	4×4×3	0	2	+					1
45	F	49	Petroclival	R	Y	3	NA	5×4×4	0	3	+	+/-	+/-			1
46	F	54	Petroclival	R	Y	3	4	4×3×2.5	0	2	+	+	+			2
47	F	49	Frontal convexity	R	Y	3	NA	2×3×3	3	1	+	+/-	+/-			2
48	M	56	Petroclival	R	Y	3	4	4×4×3	0	2	+					1
49	F	46	Medial sphenoid wing	R	Y	NA	NA	4×3.5×3.5	2	2	+					2
50	F	42	Frontal falx	IR	N	3	3	6.5×3.5×4	2	1	+					4
51	F	43	Petroclival	R	NA	NA	NA	NA	1	4	+					2
52	F	60	Petroclival	R	Y	3	4	3×2.4×2.5	0	2	+			+	-	1
53	F	46	Petroclival	R	Y	2	4	2.5×2×2.6	0	2	+			+	-	1
54	F	64	Frontal convexity	IR	N	3	NA	5×4.5×4	3	1	+			+	-	<1
55	M	56	Petroclival	R	Y	3	4	3.2×3.5×3	0	4	+			+	-	<1
56	F	64	Cerebellopontine	R	N	3	4	3.5×4×2.7	1	2	+			+	-	2
57	F	60	Lateral sphenoid wing	R	Y	3	4	2×2.5×2.5	0	2	+			+	-	3
58	F	60	1. Frontal convexity (secretory)	R	Y	3	4	2×1.5×2	0	1	+			+	-	<1
			2. Tuberculum sellae (γ-knife)				NA									
			3. Petroclival (γ-knife)				NA									
59	F	59	Foramen magnum	R	Y	2	NA	1.6×0.8×1.3	0	2	+			-/+	-	<1
60	M	62	Cerebellopontine	R	NA	NA	NA	4×4×3	1	2	+	+/-	-/+	+	-	<1
61	F	57	Frontal convexity	R	Y	3	2	4.5×4×4	3	1	+			+		1
62	M	64	Cerebellopontine	R	N	3	4	4×3.5×3.5	0	2	+	+/-	+/-	+		1
63	F	44	Petroclival (recurrent)	NA	NA	NA	NA	4×4×4	NA	4	+			+		1
64	F	55	Temporal convexity	R	Y	3	4	1.5×2×2	1	1	+			+	-	<1
65	M	38	Foramen magnum	NA	NA	NA	NA	NA	NA	4	+	+	+	+		<1
66	M	38	Cerebellopontine	NA	NA	NA	NA	5×5×3	NA	2	+	+/-	+	+		1
67	F	56	Middle fossa floor	R	NA	NA	NA	2×3×2	2	2	+	+	+	+		<1
68	F	73	Middle sphenoid wing	R	NA	NA	NA	2.5×2×2	2	2	+	+/-	+	+		1
69	F	55	Frontal convexity	R	N	3	4	3×2×2.5	2	1	+	+/-	+/-	+		<1
70	M	62	Lateral sphenoid wing	IR	Y	3	4	4×3×2.8	3	1	+	+	+	+		1

[1]F, female; [2]M, male; [3]IR, irregular; [4]R, regular; [5]Y, yes; [6]N, no; [7]NA, not available.

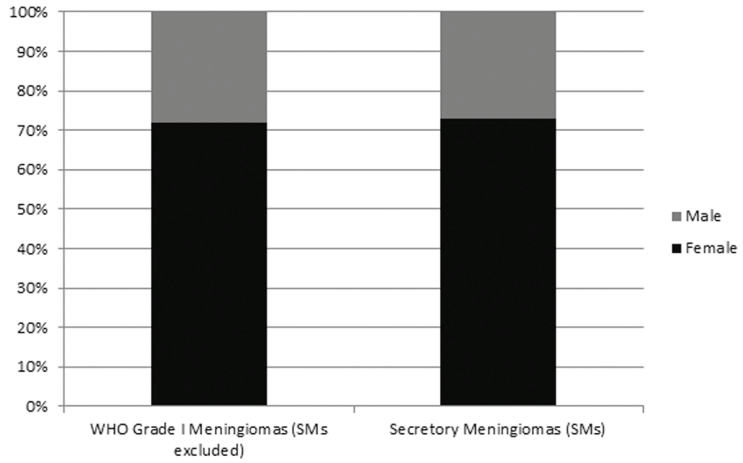

Figure 1. Female: male ratios of the 70 SMs and all other WHO grade I meningiomas operated during the same period (P>0.05).

Statistical analysis

Statistical analysis was performed using a commercially available computer software (SPSS 16.0 for Windows; SPSS, Chicago, Ill). Categorical variables were compared with the Pearsonχ^2-test, and continuous variables with the Student t test. Comparison for mean value of continuous variables was performed with ANOVA. Spearman rank correlation coefficients was used in univariate analysis of the correlations between PTBE and gender, age, tumor volume, peritumoral rim, tumor margin and locations (**Table 1**). Furthermore, ordinal logistic regression was applied for multivariate analysis of those factors. Probability values of less than 0.05 were accepted as statistically significant.

Results

Gender and age

51 of the 70 SM cases were female (ratio of female to male, 2.68: 1). During the same time span, there were 3451 female patients in the total of 4789 WHO grade I meningioma cases operated in the institute. With the 70 SM patients excluded, the female: male ratio for all other WHO grade I meningiomas was 2.58: 1. No significant difference (P=0.88) was found between the female: male ratios of SMs and other WHO grade I meningiomas as a whole (**Figure 1**). The mean age for the 70 cases was 52.64 (female, 52.37, male, 53.37; range, 33 to 78) years (**Table 1**).

Tumor locations

The 70 SMs were located at the petroclival (n=18), sphenoid wing (n=17), including 4 lateral sphenoid wing, 3 middle sphenoid wing, 7 medial sphenoid wing and 3 sphenoorbital meningiomas), middle fossa floor (n=2), cerebellopontine (n=7), foramen magnum (n=5), jugular foramen (n=1), olfactory groove (n=1), tuberculum sellae (n=1), cavernous sinus (n=1), convexity (n=13, including 10 frontal convexity, 1 fronto-temporal convexity and 2 temporal convexity meningiomas), falx (2 cases) and parasagital region(2 cases). The locations were summarized in **Figure 2** and **Table 1**.

To sum up, 53 of the 70 SMs were located at the cranial base. Petroclival (18 cases) and the sphenoid wing (17 cases) were the most common locations.

Preoperative symptoms

Accidental tumor discovery was seen in 7 patients, 3 of who was diagnosed by CT scan performed after intra-cerebral hemorrhage or mild head trauma. Non-specific chief complaints, such as dizziness and headache, was presented by 23 patients. Gait instability was noted in 8 cases with posterior cranial fossa meningiomas. Generalized or partial seizure attack was presented by 7 supra-tentorial meningiomas and 1 petroclival meningioma that had middle fossa floor extension. Apparent exophthalmos was seen in all of the 3 sphenoorbital meningiomas. Cranial nerve involvement was commonly seen in cases located at medial sphenoid wing, tuberculum sellae, cavernous sinus and posterior fossa (58.3%, 21 of 36 patients). The duration of tumor related symptoms before admission ranged from 2 days to 5 years.

History and comorbidities

2 patients reported history of mild head trauma, though both of which happened less than a month before admission. Only 1 60-year-old

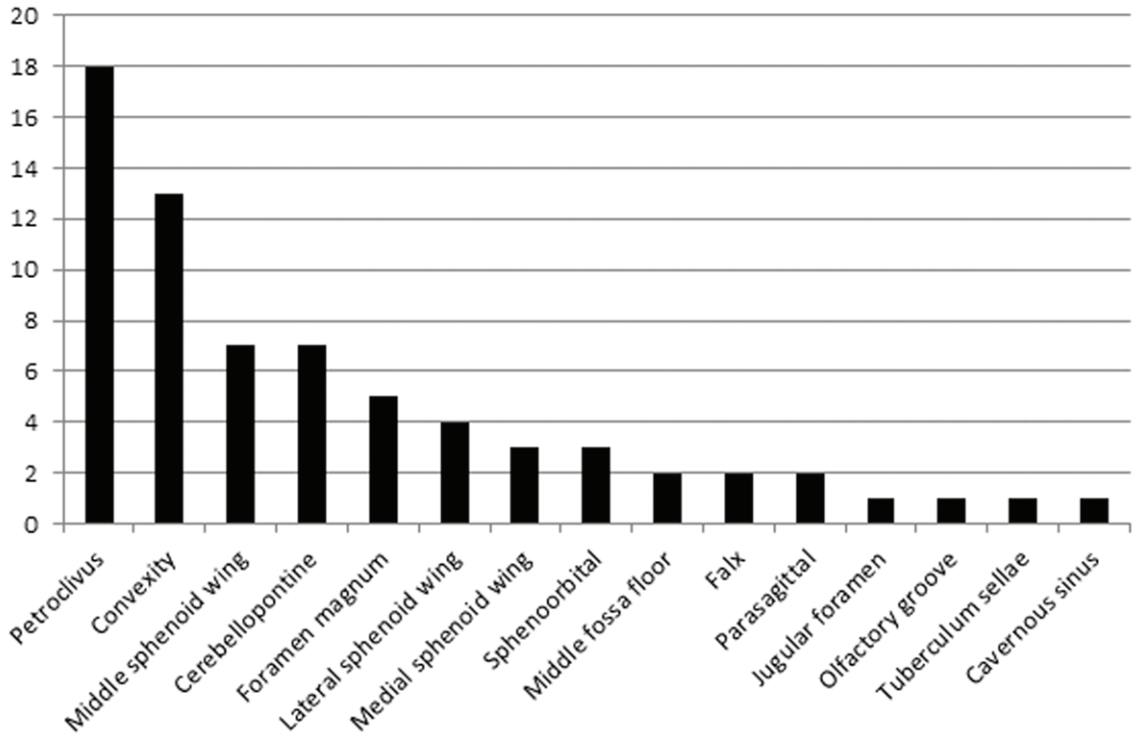

Figure 2. Locations of the 70 secretory meningiomas.

female patient reported history of hysteromyomectomy. A 46-year-old female patient suffered SLE and had been in continuous low dose prednisone use (5mg tid. p.o.) for 6 years before meningioma discovery. 4 patients reported past history of Schistosomiasis, a common parasitic disease in rural China. 17 patients had a history of hypertension 6 to 20 years before admission.

A 45-year-old female patient who harbored a tuberculum sellae SM did a serum CEA test preoperatively, the result of which was 1.34 ug/L (normal, <10 ug/L).

A recurrent meningioma was presented, who received subtotal petroclival meningioma (SM) removal in some other hospital 2 years before our operation. 3 patients were found with multiple intracranial lesions. There was a 56-year-old male patient who was diagnosed as petroclival meningioma with head CT following acute hemorrhage of left parieto-occipital cavernous heamangioma (CM). Hospitalized observation was given to him, followed with meningioma resection and no aggressive treatment for the CM. Another patient had a tuberculum sellae meningioma (secretory) and a right frontal convexity meningioma (fibroblastic), both of which resected in only 1 surgical procedure via modified pterional approach. The other patient had 3 concurrent meningiomas (right frontal convexity, tuberculum sellae and left petroclival), who was given removal of the right frontal tumor, and gamma-knife therapy for the other two.

Radiological findings

In total, 24 preoperative CT and 46 preoperative MR images were collected after last follow-up. Important radiological features of the cases were listed in **Table 1**. Preoperative diagnosis of the 70 cases was all recorded as meningioma, with basic typical meningioma radiological features, such as extracerebral location, dura-tail enhancement#, etc. Smooth, regular tumor margin was observed in 83.3% (45/54) cases on CT or MR images. Recognizable peritumoral rim, as shown on MR images, existed in 80.4% (37/46) cases. Cystic changes were found in only 2 cases: one of them was a cerebellopontine meningioma with a sole cyst, the other one was a frontal convexity meningioma with multilocular cysts (**Figure 3**). In both cases, no cyst wall enhancement was witnessed. Only 8.3%

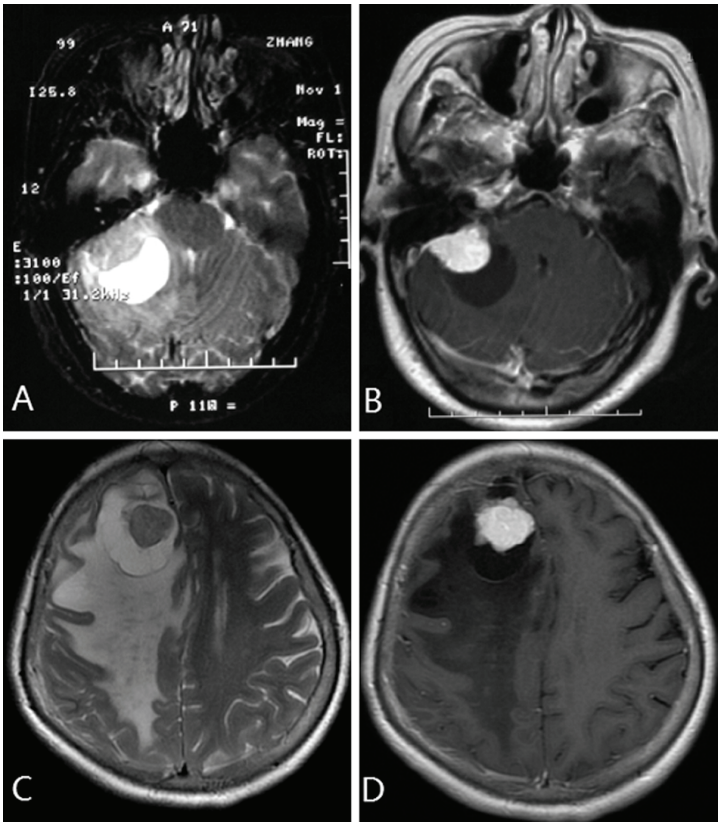

Figure 3. Axial T2 weighted and Gd-DTPA enhanced MR images of 2 SMs with cystic changes. A & B: case 56; C & D: case 54.

(2/24) cases showed possible intra-tumoral calcification on CT scan. Combined with intra-operative findings, we noted that 12.9% (9/70) SMs caused hyperostosis of the nearby bone tissue, including 3 sphenoorbital meningiomas and other 6 meningiomas of supra-tentorial locations.

Interestingly, all cases (43/43) with available data showed hypo- or iso- signal in T1 weighted image, while 95.6% (43/45) cases showed hyper-signal in T2 weighted or T2 flair images. Except for 2 cases that might had intratumoral hemorrhage/necrosis (**Figure 4**), all other cases with available preoperative Gd-DTPA enhanced MR images (95%, 38/40) showed homogeneous strong enhancement of the tumor, which we called specifically "xenon light"-like enhancement (**Figure 5** and **Figure 6**).

As for the extent of PTBE, we observed 40.7% (22/54 cases) grade 0, 24.1% (13/54 cases) grade 1, 22.2% (12/54 cases) grade 2 and 13.0% (7/54 cases) grade 3. Only grade 0 or 1 PTBE was found for tumors with the following locations, tuberculum sellae, cerebellopontine, the petroclival region, jugular foramen and foramen magnum. Grade 2 PTBE was present in 12 cases, located at middle or medial sphenoid wing (n=6), frontal convexity (n=2), middle fossa floor (n=2), olfactory groove (n=1) and frontal falx (n=1). Grade 3 PTBE was present in 5 frontal convexity, 1 frontal parasagittal and 1 lateral sphenoid wing meningiomas. All cases with grade 3 PTBE manifested midline shift to the contra-lateral cerebrum more than 10 mm. Illustrating cases with typical grade 0 to 3 PTBE, which had a similar right frontal location were illustrated in **Figure 7**.

PTBE was not correlated with gender (correlation coefficient [r]=0.02, P=0.886) or age (correlation coefficient [r]=0.001, P=0.992) of patients. The 70 cases were divided into two groups, group 1 for cranial base and group 2 for non-cranial base meningiomas. Non-cranial base tumors tended to cause more severe PTBE (**Figure 8**). Tumor volume was stratified into 4 levels, divided by 25%, 50% and 75% volume quantile. No significant correlation was discovered between tumor volume and PTBE in our series (correlation coefficient [r]=0.070, P=0.620). Furthermore, mean volume of cases with grade 0 to 3 PTBE was not significantly different with each other (P=0.239, ANOVA). Details of the patients' radiological features were listed in **Table 1**. However, absence of peritumoral rim (correlation coefficient [r]=0.408, P<0.01), irregular tumor margin (correlation coefficient [r]=0.477, P<0.001) and non-cranial base location (correlation coefficient [r]=0.501, P<0.001) were significantly correlated with higher grade of PTBE, in univariate analysis. Multivariate analysis showed non-cranial base location was the only factor that correlated with more severe PTBE (P<0.001).

Operation

Simpson grade 1 resection was achieved in 19 secretory meningiomas and 1 fibroblastic

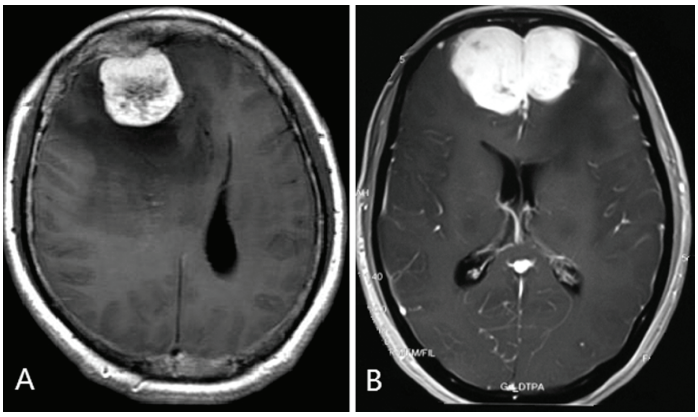

Figure 4. The tumor with heterogeneous strong enhancement (A. case 61) and the tumor with homogeneous strong enhancement with small focal defects (B. case 50).

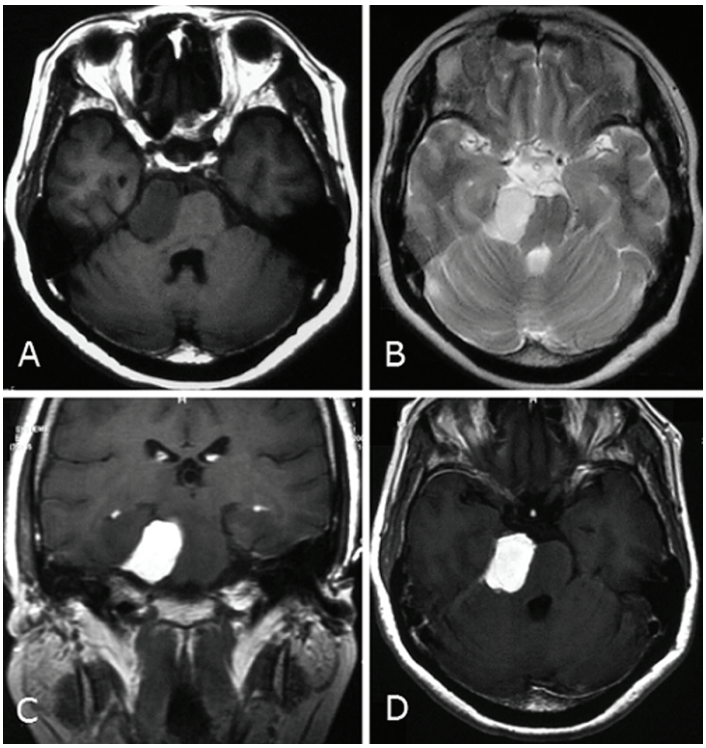

Figure 5. Axial T1 weighted (A), T2 weighted (B), typical "xenon light-like coronal and axial Gd-DTPA enhanced (C and D) MR images of a secretory meningioma with grade 0 PTBE (case 52).

meningioma concomitant with a tuberculum sellae SM (**Table 1**). Tumor locations of the 19 cases were convexity (n=14), lateral sphenoid wing (n=2), sphenoorbital (n=2), olfactory groove (n=1) and falx (n=1). Simpson grade 2 resection was observed in 37 operations, most of which were located at the cranial base (n=34). Simpson grade 3 resection was noted in 3 petroclival meningiomas. The remaining 11 cases reported a Simpson grade 4 resection, locating at the petroclival region (n=6), foramen magnum (n=2), medial sphenoid wing (n=1), sphenoorbital region(n=1) and cavernous sinus (n=1). Cases with Simpson grade 3 to 4 tumor resection was thought to have residual tumor (**Table 1**).

Intra-operative evaluation of Simpson resection grade were confirmed by postoperative CT and/or MRI scan in 57 cases. Simpson grade 1 resection was more often achieved in non-cranial base tumors than cranial base tumors ($P<0.01$, X^2 test). In contrary, Simpson grade 2 resection was mostly seen in cranial base tumors ($P<0.001$, X^2 test). Moreover, Simpson grade 3 to 4 tumor resection were only seen in cranial base tumors, especially petroclival meningiomas. Lower Simpson resection grade was achieved for non-cranial base SMs($P<0.001$, χ^2 test) (**Figure 9**). Operations for non-cranial base SMs were more radical.

Intraoperative frozen section pathological diagnosis was performed for 4 operations. With all diagnosed to be meningiomas, only 1 of them was further classified into the secretory subtype.

Postoperative complications

Complications following operations usually were related to the tumor locations (**Table 2**). Except for 2 cases who had short-term postoperative fever (1 frontal convexity meningioma and 1 sphenoorbital meningioma) cured by intravenous antibiotics administration. All cases with the following tumor locations had uneventful postoperative course: frontal convexity (n=12), frontal parasagittal regions (n=2), middle fossa floor (n=2), sphenoorbital region (n=2) and middle sphenoid wing (n=3). Uneventful hospital stay was also achieved in 1 falx, 2 lateral sphenoid wing, 2 medial sphenoid wing, 1 cavernous sinus, 1

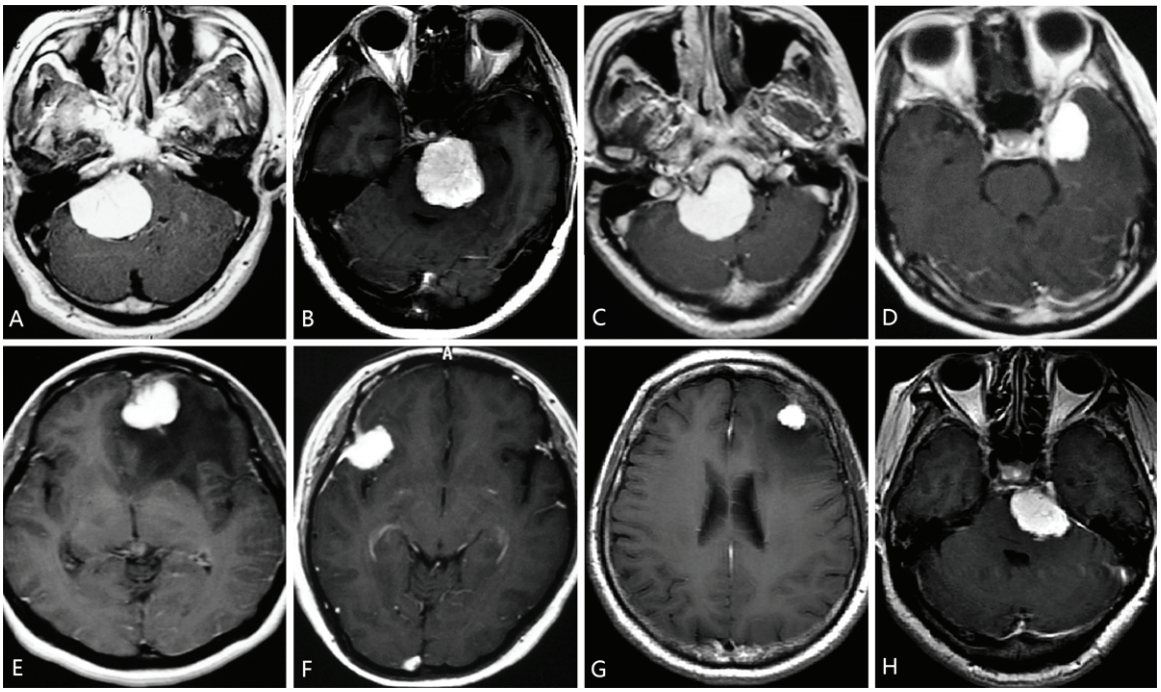

Figure 6. 8 cases with typical "xenon light"-like gadolinium enhanced MR images, manifested in coronal view. A: case 9; B: case 21; C: case 35; D: case 39; E: case 7; F: case 11; G: case 22; H: case 23.

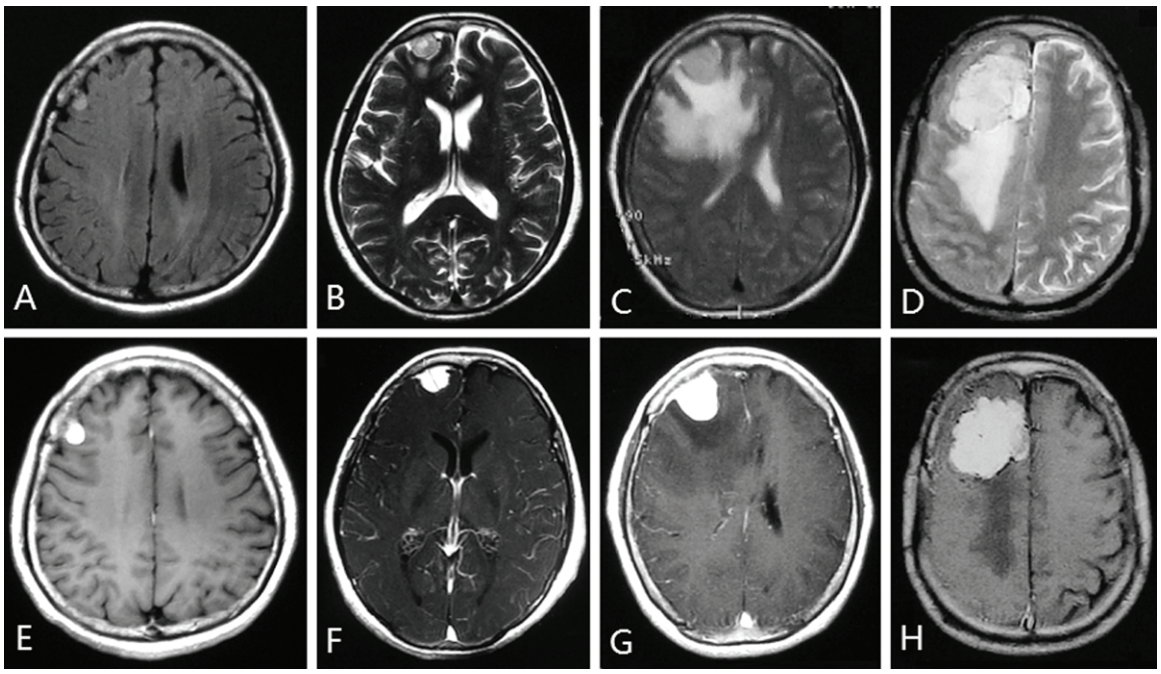

Figure 7. 4 cases with respective grade 0 to 3 PTBE, manifested by axial T2 weighted (flair) and Gd-DTPA enhanced images. A and E: grade 0 PTBE (case 58); B and F: grade 1 PTBE (case 3); C and G: grade 2 PTBE, (case 69); D and H: grade 3 PTBE (case 17).

cerebellopontine and 1 foramen magnum meningiomas. Non-cranial base tumors were more often observed with an uneventful hospital stay ($p<0.01$, χ^2test).

Wound infection and delayed wound healing was observed in a 49-year-old male patient with left medial sphenoid wing meningioma, who had 6 years uncontrolled history of Type 2

Table 2. Comparison of post-operative and long-term outcome between cranial base and non-cranial base secretory meningiomas[1, 2, 3]

	Cranial base tumors	Non-cranial base tumors	Total
Post-operative complications			
Wound infection	1/53	0/17	1/70
Intracranial infection or FUO	12/53	1/17	13/70
Pneumonia	5/53	0/17	5/70
Subcutaneous hydrops	4/53	0/17	4/70
CSF leakage	1/53	0/17	1/70
Hydrocephalus	1/53	0/17	1/70
Post-operative hematoma	4/53	0/17	4/70
Brain infection	2/53	0/17	2/70
Acute renal failure	2/53	0/17	2/70
Liver function disorders	2/53	0/17	2/70
New neurological deficits			
Cranial nerve impairment	24/53	0/17	24/70
Gait instability	2/53	0/17	2/70
Frontal syndrome	2/53	1/17	3/70
Tracheotomy	3/53	0/17	3/70
Tumor Remnant	14/53	0/17	14/70
GOS at discharge			
Dead	0/53	0/17	0/70
Vegetative state	2/53	0/17	2/70
Severe disability	4/53	0/17	4/70
Moderate disability	2/53	0/17	2/70
Good recovery	45/53	17/17	62/70
At last follow-up			
Epilepsy	2/44	1/17	3/61
Tumor progression	1/44	0/17	1/61
GOS at last follow-up			
Dead	3/53	0/17	3/70
Vegetative state	0/53	0/17	0/70
Severe disability	0/53	0/17	0/70
Moderate disability	0/53	0/17	0/70
Good recovery	41/53	17/17	58/70
Lost to follow-up	9/53	0/17	9/70

[1]CSF, cerebral spinal fluid; [2]FUO, fever with unknown origin; [3]GOS, Glasgow Outcome score.

Diabetes. In total, short-term body temperature elevation was observed in 18 cases, postoperatively. 5 of them were due to pneumonia, as proved on lung CT scan. Among the other 13 cases, lumber drainage was performed in 5 (3 foramen magnum and 2 petroclival meningiomas), of whom elevated white blood cell count and decreased glucose content were present in the cerebrospinal fluid samples. Due to lack of microbiologic culture/assay, intracranial infection was not excluded from those 5 cases.

A petroclival meningioma patient suffered 4 weeks of cerebrospinal fluid rhinorrhea, which was cured by 2 weeks of combined dehydration, cerebrospinal fluid secretion inhibition, contralateral side decubitus and 2 weeks of continuous lumber drainage. Reoperation for operation site hematoma was performed in 2 sphenoid wing meningiomas and for remote frontal epidural hematoma in a petroclival meningioma. Another case that had operation site hematoma was given only observation and

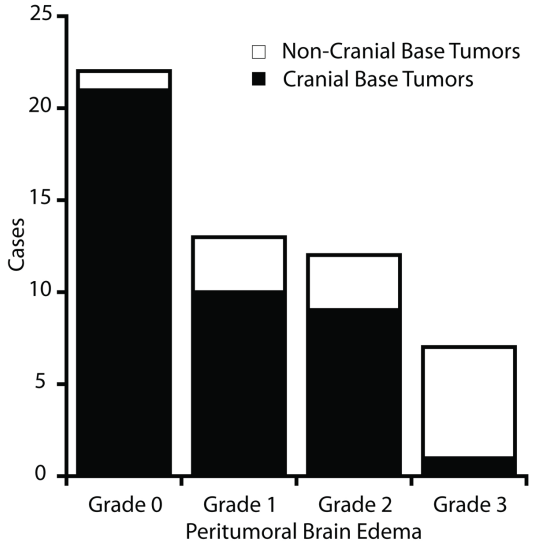

Figure 8. Comparison of PTBE for cranial base and non-cranial base tumors.

was in vegetative state at discharge (dead at follow-up). Doubtful brain stem infarction, manifested as lower intensity on CT scan, was present in 2 petroclival meningiomas, both of which died during follow-up. 2 petroclival meningioma patients experienced acute renal function failure, mainly due to use of high dose mannitol. Hemodialysis was given to one of them, who recovered days later. The other case refused aggressive treatment and died soon after discharge.

Recognizable new postoperative cranial nerve impairment was recorded in 15 petroclival, 5 cerebellopontine, 2 medial sphenoid wing, 1 foramen magnum and 1 jugular foramen meningiomas. 16 of the 31 posterior fossa meningioma patients reported mild to overt facial paralysis. Among the 16 patients with facial paralysis, 5 patients reported partial to complete recovery at last follow-up. Frontal syndrome was observed in 3 cases (1 frontal falx, 1 medial sphenoid wing and 1 olfactory groove meningiomas). The patient who was given resection of olfactory groove meningioma had been suffering from unrecovered fear of confined space before last follow-up and insisted on receiving fast CT scan instead of MR.

Other postoperative complications or new neurological deficits included subcutaneous hydrops (n=4), hydrocephalus (n=1), liver function disorders (n=2) and gait instability (n=2).

As mentioned above, cranial base SMs were associated with more postoperative complications and new neurological deficits (**Table 2**).

Furthermore, tracheotomy was performed in 3 patients with tumor locations of jugular foramen, foramen magnum and the petroclival region, the latter 2 of who died in follow-up.

At discharge, all the 17 patients with non-cranial base tumors were in good recovery, as evaluated with Glasgow Outcome Score. Among the 53 cranial base cases, 45 was good, 2 patients showed moderate disability, 4 patients showed severe disability, 2 patients were in vegetative state at discharge (**Table 2**). Skull base tumors showed worse short-term prognosis.

Histological findings

Immunohistochemical staining of EMA, Vim, and PAS were positive in all 70 cases. Available data revealed 100% CEA, CK and PR positive rates in our series (**Table 1**). MIB-1 proliferation index ranged from 0 to 4% (**Table 1**). 87.1% (61/70) cases were observed with MIB-1≤1%, with the median MIB-1 as also <1%. Typical microscopic immunohistochemical staining features were shown in **Figure 10**.

Follow-up

Follow-up time ranged from 16 to 85 months, with a median of 48 months. 9 cases were lost to follow-up (12.9%), all due to contact information unavailability. However, among those 9 cases, 3 preoperative and 2 follow-up MR images were obtained by searching the archives of the radiological department. In total, 54 preoperative CT/MR and 50 follow-up images were finally gathered for analysis.

The patient with 3 concurrent meningiomas (right frontal convexity, tuberculum sellae and left petroclival) was given removal of the first (secretory subtype) and gamma-knife therapy for the latter two. Follow-up MRI revealed no progression of the unresected tumors.

Cases who received Simpson grade 1 to 2 tumor resection reported either good outcome (50 cases) or were lost to follow-up (5 cases), except for 1 case that was given gamma-knife therapy 2 years later due to tumor progression. However, it became unclear whether the opera-

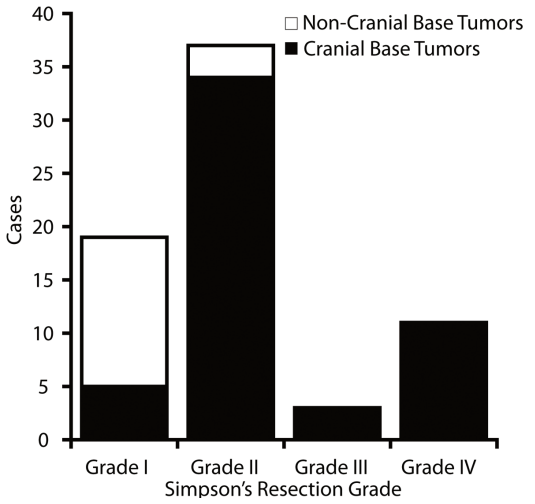

Figure 9. Comparison of Simpson resection grade for cranial base and non-cranial base tumors (*P<0.01; †P<0.001).

tion achieved actually Simpson grade 2 resection because of radiological data unavailability.

Outcome for the 14 cases after Simpson grade 3 or 4 tumor resection were as follows: 4 cases were lost to follow-up; 5 cases received gamma-knife therapy for the residual tumor and showed no tumor progression in follow-up (range, 8 days to 1 year after discharge); 2 cases were given no postoperative radiation therapy, one of whom showed tumor progression (**Figure 11**); 3 cases, located at the petroclival region (n=2) and foramen magnum (n=1), died during follow-up (range, 3 days to 1 year after discharge). The mortality rate was 4.3% in total. The only case who had tumor progression was recommended with gamma-knife therapy, during our follow-up.

In total, 93.4% (57/61) cases reported progression free survival at a medium time of 48 months follow-up (**Table 2**). Except for the 3 patients who died, all the 58 cases who were not lost to follow-up reported to be in good recovery.

Comparison of follow-up for cranial base and non-cranial base SMs was shown in **Table 2**. Cases with cranial base SMs were in worse state at discharge. Tumor progression and mortality were only seen in cranial base SMs cases.

Discussion

Three previous reports described respective series of 44, 31 and 17 SM cases [4, 5, 13]. Other few small series (n≤14) have been published on secretory meningomas [3, 6-10, 14, 15]. Our retrospective investigation of 70 consecutive SMs focusing on the clinical, radiological and pathological features, is the largest series up to now.

Gender of SMs patients

Except for a 11: 0 female: male ratio of SMs reported by Buhl, 2001 [10], other reported ratios were all between 3: 1 to 9.3: 1 [4, 5, 7, 9, 13]. However, our 70 consecutive SMs cases had as low as a 2.68: 1 female: male ratio. Female predominance of SMs was also present in our series, but apparently not as great as the previous ones. Moreover, no significant difference (p=0.88) was found between the female: male ratios of SMs and all other WHO grade I meningiomas operated in our institute during the same period of time.

Serum CEA level

Reviewing the literature, about 57% (4/7) SMs patients were detected with serum CEA elevation [3, 10, 15, 16], with only 7 cases studied in total. Our review of 1 patient also showed normal serum CEA level, which could add to the knowledge of that relationship, to some extent. Research with larger sample size on this specific tumor maker for SMs is still needed.

Tumor locations and radiological findings

SMs were concluded in previous articles as having preference to locate at the sphenoid wing and the frontal convexity [4, 5]. However, due to relatively small sample sizes, those conclusions might not be so convincing. In our series of 70 consecutive SMs, the tumors showed strong preference of cranial base locations (75.7%, 53/70), especially the petroclival (25.7%, 18/70) and, as previously reported, the sphenoid wing (24.3%, 17/70).

We discovered in our series, predominantly typical hypo- to iso-signal T1 weighted and hypersignal T2 weighted (T2 flair) MR images for SMs. Hyper-signal of T2 weighted image in meningiomas was advocated to be correlated with soft tumor consistency [17, 18] and with more severe PTBE [11]. Showed mostly hypersignal on T2 weighted image as in our study, SMs had already been claimed to be accompanied by more severe PTBE in several articles#

[4, 5, 7, 9, 13]. This could be a clue for further research on correlations between PTBE and SMs.

Except for 2 cases, all available Gd-DTPA enhanced MR images in our series revealed strong homogeneous enhancement of the tumor, which we called for the first time in online publications, "xenon light"-like enhancement of SMs. Though could also be witnessed in other subtypes of meningiomas, the high occurrence rate (95%, 38/40) of "xenon light"-like enhancement in our series suggested it might be relatively specific for SMs. Of course, further observations with more SMs cases are needed, to confirm our findings.

Preferred cranial base locations, predominantly hypo- to iso-signal in T1 weighted, hyper-signal in T2 weighted MR images and "xenon light"-like enhancement could make preoperative diagnosis of SMs probable and henceforth promote further research into this meningioma subtype.

SMs and PTBE

SMs were reported to be frequently accompanied with severe PTBE [4, 5, 13, 15, 19, 20], and might lead to life-threatening postoperative situation[4, 13]. Various factors, such as gender, the presence of seizure, tumor size, location, histological differentiation, vascular density, tumor margin, peritumoral rim, and pial-cortical arterial supply to the tumor might be associated with the development of PTBE [11, 21-27].

As analyzed in our series, irregular margin, absence of peritumoral rim, and non-cranial base location were correlated with higher grade of PTBE. Statistically, cranial base meningiomas tended to cause less severe PTBE than non-cranial base meningiomas (**Figure 8**). Presence of arachnoid cisterns and absence of adjacent white matter also pose as factors that prohibited formation of PTBE. White matter in the brain parenchyma has a lower resistance to bulk flow, hence tends to incur more PTBE [28, 29]. The cisternal structures and CSF layer may act as barrier against the development of PTBE [11]. As was in our cases, no grade 2 or grade 3 PTBE was found in tumor locations which were close to the arachnoid cisterns, or where there was less white matter in the adjacent brain, including the tuberculum sellae, cerebellopontine, petroclival region, jugular foramen and foramen magnum. Instead, only 26.1% of these cases showed on preoperative images with grade 1 PTBE, and the rest of them showed no recognizable PTBE at all. As for tumor locations which were far from those buffering structures, however, 83.9% (26/31) were accompanied by PTBE.

To sum up, the extent of PTBE had a lot to do with tumor location. Non-cranial base SMs were usually accompanied by more severe PTBE, than cranial base SMs.

Short-term and long-term outcome

Simpson grade 3 or 4 resection were recorded only in cranial base tumors. Serious postoperative complications or new neurological deficits, such as wound infection, intracranial infection, pneumonia, subcutaneous hydrops, CSF leakage, hydrocephalus, intra-cranial hematoma, brain infarction, acute renal failure, liver function disorder, cranial nerve impairment, gait instability and frontal syndrome were more often observed for cases with cranial base SMs. Procedures such as tracheotomy and reoperation of hematoma evacuation were also only performed in cranial base cases. Surgery for cranial base SMs was more hazardous, making total tumor resection harder for those cases. That also resulted in more serious postoperative complications and new neurological deficits for cranial base SMs.

In follow-up, tumor recurrence or progression were observed merely in those cranial base cases after Simpson grade 3 or 4 resection, the majority of which were given gamma-knife therapy and observed with no further progression. Mortality was also only recorded for 3 cranial base cases. On the other hand, non-cranial base meningiomas, although accompanied with more severe PTBE, had comparatively better outcomes both in peri-operative period and in follow-up (**Table 2**).

As mentioned above, higher Simpson resection grade (subtotal or partial resection) were usually observed in cases with cranial base SMs. In our series, except for 1 case without sufficient clinical and follow-up data, all other cases with Simpson grade 1 or 2 tumor resection were fine at follow-up. No tumor recurrence was found

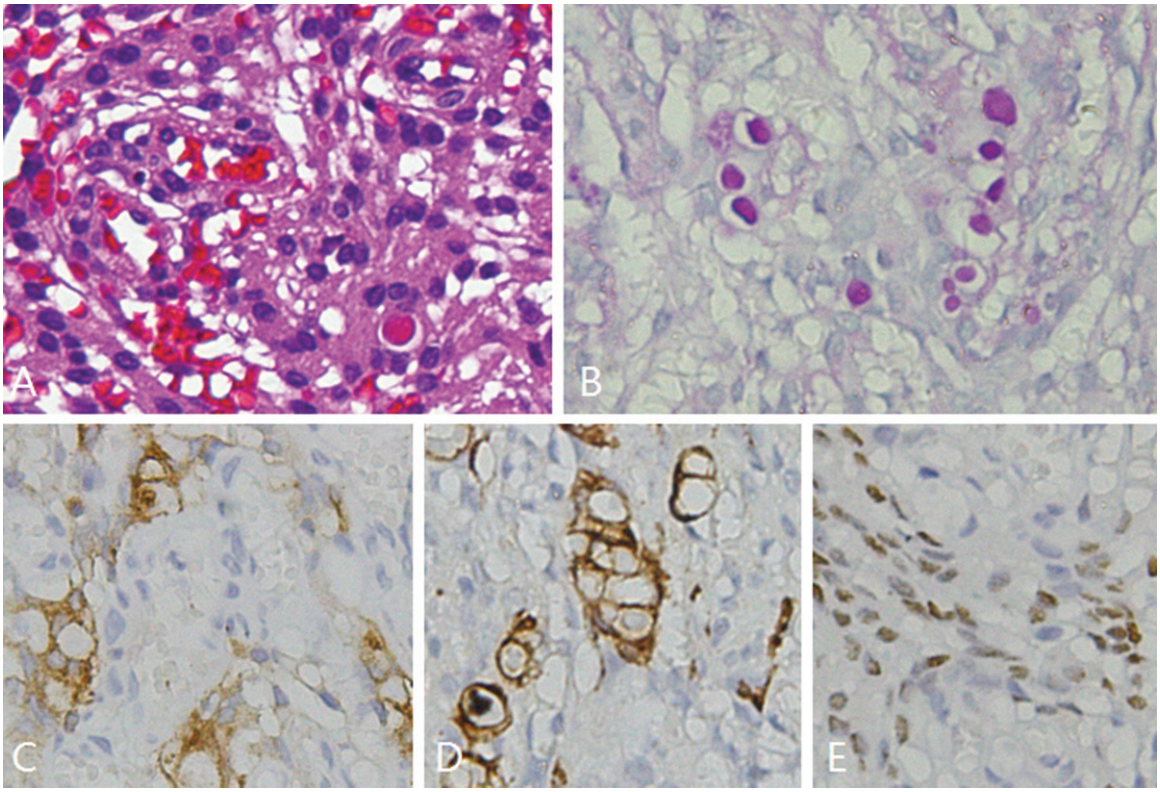

Figure 10. Immunohistochemical features of a secretory meningioma (case 65). A: Abundant pseudopsammoma bodies shown on H&E sections; B: PAS stain; C: Labeling of CEA; D: Labeling of CK; E: Labeling of PR. Original magnification: ×400 for all sections.

among whose cases. As for the cases with subtotal tumor removal, follow-up data showed 3 patients (2 petroclival and 1 foramen magnum SMs) died, at 3 days to 1 year after discharge. All the other 7 cases with subtotal tumor removal were fine at follow-up, given postoperative radiation or not. Only 1 case who received no radiation therapy after subtotal resection showed slight tumor progression. Our observation suggested that residual SMs grew very slowly and reacted quite well to gamma-knife therapy.

With MIB-1 proliferation index below 1% in 87.1% of all cases in our series, secretory meningiomas were featured as a slow growing, benign meningioma subtype. No rapid tumor progression was noted in our follow-up of 7 cases after Simpson grade 3 or 4 tumor resection, even if there was given no postoperative radio-therapy (n=2).

Previous studies had already reported a comparatively good prognosis for SMs, as a benign meningioma subtype. Short-term and long-term prognosis of this unique meningioma subtype was related with locations and resection completeness. As accepted, surgical risks for cranial base meningiomas are comparatively higher than non-cranial base tumors. Tumors in easily approached locations were more often resected completely and had better outcome in follow-up, while deep seated cranial base tumors were more often achieved with subtotal removal and had poorer clinical outcome.

Non-cranial base SMs had fewer postoperative complications and new neurological deficits. A median of 48 months follow-up for the 17 non-cranial base SMs patients showed all of them were in good recovery, with no mortality or tumor recurrence. To make a comparison, all mortality or tumor progression were seen in cases of cranial base SMs (**Table 2**). Although often accompanied by more severe PTBE, non-cranial base SMs had better short-term and long-term prognosis than cranial base SMs.

In conclusion of our findings, the prognosis of SMs cases is highly relevant with surgical risks and operation completeness, rather than the extent of PTBE.

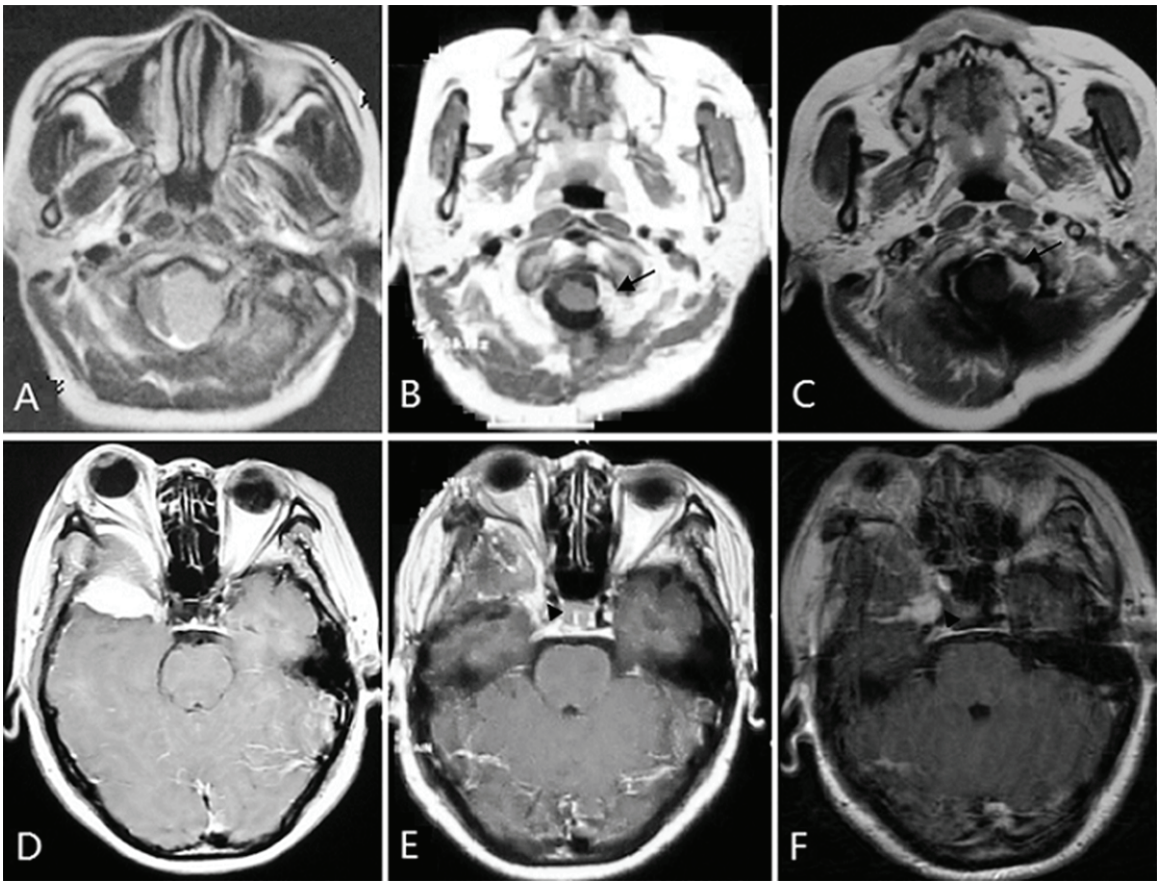

Figure 11. Axial Gd-DTPA enhanced images (A: axial T2 weighted MR image) of 2 untreated postoperative residual SMs. Case 30, A: before operation, B: 9 months, C: 48 months; Case 29, D: before operation, E: 10 months, F: 48 months. The residual tumor was enhanced obviously (arrows in B and C, arrow heads in E and F).

Conclusion

SMs are a benign meningiomas subtype. Intratumoral calcification or cystic changes were scarcely observed in SMs. Preferred cranial base locations, typical hypo- to iso-signal in T1 weighted, hyper-signal in T2 weighted MR images and "xenon light"-like enhancement could make preoperative diagnosis of SMs probable. PTBE in SMs was correlated with irregular margin, absence of peri-tumoral rim and non-cranial base locations. A 100% CEA, CK and PR positivity was seen in our cases that had available data. The prognosis of SMs is comparatively good, as a slow-growing benign tumor. Patients' outcome had a lot to do with surgical risks and extent of tumor resection, rather than the extent of PTBE. Cranial base SMs were more risky for surgical procedure and were often given incomplete tumor resection, hence had worse short-term and long-term prognosis than non-cranial base SMs. Residual operated SMs grew slowly, which reacted quite well to radiation therapy.

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