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수막종의 악성 진행에 대한 후향적 관찰

Malignant progression of meningioma: A retrospective observational study

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Abstract

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Objective:

High-grade meningiomas have more aggressive behavior and poorer prognosis than benign meningiomas. High-grade meningioma may occur de novo or be transformed from a lower grade tumor rarely. We assessed clinical course, treatment outcome, and the factors affecting disease progression and survival of patients with transformed high-grade meningioma.

Methods:

Total 27 patients who were treated surgically first in our institution and showed a histological progression from a lower grade through follow-up were

selected. We reviewed the patient's medical records including demographic data, clinical histories, radiologic evaluations and pathologic reports. We assessed the timing and course of recurrence and malignant progression, treatment modalities, outpatient follow-up, and survival. Prognostic factor analysis for malignant progression and post-progression survival was performed.

Results:

Thirteen patients were females, and 14 were males. The mean age at the first diagnosis was 46.1 years. The most common presentations were hemiparesis and visual disturbance. The most prevalent locations were parasagittal/falx area and skull base. Twelve patients received gross total resection and 15 patients received subtotal resection. Sixteen patients were with atypical meningioma transformed from benign. Six patients were with anaplastic meningioma transformed from benign. Four patients were with anaplastic meningioma transformed from atypical. One patient was diagnosed with anaplastic meningioma transformed from benign through atypical. Twelve patients underwent adjuvant treatment in between the first operation and malignant progression. Seventeen patients got adjuvant treatment after malignant progression.

Initial tumor pathology (benign vs. atypical), age (under vs. over 50 years), and tumor location (convexity vs. non-convexity) were predictive for

progression-free survival. Tumor pathology (atypical vs. anaplastic) and age (under vs. over 50 years) were prognostic for post-progression survival.

Conclusion:

Higher-grade tumor, old age and non-convexity location were related to shorter progression-free survival. Anaplastic pathology and old age might predict unfavorable outcome after progression. The prognosis of transformed meningioma might be poorer than that of de novo meningioma.

Keywords:

Meningioma; Malignant progression; Atypical meningioma; Anaplastic meningioma

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Introduction

Meningioma, the most common primary intracranial tumor, occupied 13-30% of all primary brain tumor [1,2]. More than 90% of these tumors are classified as WHO grade I with favorable outcome. High-grade meningiomas belonging to WHO grade II and III have more aggressive behavior and poorer prognosis than benign meningioma. High-grade meningioma may occur de novo or be transformed from a lower grade tumor rarely [3].

The curative treatment of meningioma is complete surgical resection. If the tumor cannot be completely removed due to the tumor size, location, and the degree of involvement of surrounding brain tissue and vital neurovascular structures, radiotherapy or stereotactic radiosurgery are used as adjunctive therapy. The accumulation of genetic alterations in the residual tumor will change the nature of subpopulation of tumor cells gradually. As observed in glioma, well-differentiated and indolent-growing tumors may dedifferentiate to more malignant form over a long period of time [2].

We focused on patients with malignant progression of meningioma. Clinical course and treatment outcome of these patients were reviewed and the factors affecting disease progression and survival were assessed. The aim of this study is to find distinguishing characteristics of transformed meningioma compared with de novo high-grade meningioma and to help establishing the policy of treatment and follow-up.

Materials and Methods

Patient selection

Total 2035 patients underwent craniotomy and were diagnosed with intracranial meningioma between January 1986 and December 2013 in our institution (Seoul National University Hospital). Of those patients, 203 patients had atypical meningioma, and 59 patients had anaplastic meningiomas. The patients with other histological variants of high-grade meningioma such as chordoid, clear cell, rhabdoid, and papillary subtype were excluded. We reviewed the medical records with patients with recurrent high-grade meningioma, and sought cases showed a histological progression from a lower grade. The patients treated surgically and were diagnosed with meningioma initially in other hospital before visiting our hospital and the patients with neurofibromatosis type 1 or 2 were excluded. Finally, 27 patients were selected.

Data collection

We reviewed the patient's medical records to obtain demographic data, clinical histories and chief complaints. We assessed the timing and course of recurrence and malignant progression, outpatient follow-up, and survival. Neuroimaging was used to track the location, shape and change after treatment. The extent of removal of the tumor and the presence of skull involvement were identified. If the information on the surgical record is

insufficient, we identified Simpson's grade and skull involvement with reference to the immediate post-operative MR imaging. Pathologic reports were used to confirm pathological diagnosis and specific findings and immunohistochemistry. Seoul National University Hospital Institutional Review Board approved this study.

Statistical analysis

Progression-free survival (PFS) was defined as the period from the first operation date until the malignant progression. Post-progression survival (PPS) was defined as the period from the malignant progression to death or end date of this study. Kaplan-Meier curves with log-rank test were used to calculate PFS and PPS rates. Cox regression test was conducted to analyze prognostic factors. Statistical analyses were performed using SPSS statistics, version 24.0 (IBM Corporation, Armonk, NY, USA). $P<0.05$ were used to determine statistical significance.

Results

Among 27 patients, 13 (48.1%) were females, and 14 (51.9%) were males. The mean age at the first diagnosis was 46.1 years and ranges from 12.1 to 70.0 years. The most common presentations were hemiparesis and visual disturbance. The patients with parasagittal/falx meningioma complained hemiparesis, the patients with tuberculum sella meningioma presented with visual disturbance. If the tumor involved cavernous sinus or posterior fossa, the patients revealed cranial nerve dysfunction. The patients were divided into 3 groups as the pattern of malignant progression. The first group contained 16 patients with atypical meningioma transformed from benign meningioma, the second group included 6 patients with anaplastic meningioma transformed from benign meningioma, and the third group consisted of 4 patients with anaplastic meningioma transformed from atypical meningioma. One patient was diagnosed with benign meningioma initially. The tumor recurred 2 years after the first operation, the patient was diagnosed with atypical meningioma through the second operation. Five years after the second operation, the tumor was recurred again and the final diagnosis was anaplastic meningioma (Table 1).

Table 1. Patient Characteristics

Variable	Value (percentage)
Total number of patients	27
Mean age at diagnosis	46.1 yrs (range: 12.1 – 70.0)
Gender	
Female	13 (48.1)
Male	14 (51.9)
Clinical symptoms	
Hemiparesis	7 (25.9)
Visual disturbance	7 (25.9)
Headache	5 (18.5)
Cranial nerve dysfunction	3 (11.1)
Dizziness	2 (7.4)
Seizure	1 (3.7)
Dysphasia	1 (3.7)
Hemiparesthesia	1 (3.7)
Type of progression	
Benign → Atypical	16 (59.3)
Benign → Anaplastic	6 (22.2)
Atypical → Anaplastic	4 (14.8)
Benign→ Atypical → Anaplastic	1 (3.7)

Six (22.2%) of tumors were located at the cerebral convexity, 8 (29.6%) were located in the parasagittal or falcine area, 8 (29.6%) were in the skull base, 4 (14.8%) were in the posterior fossa, and 1 (3.7%) was in the trigone of the lateral ventricle. Skull invasion was observed in 6. Twelve patients received gross total resection and 15 patients received subtotal resection. Twelve patients underwent adjuvant treatment in between the first operation and malignant progression and 15 patients did not any intermediate treatment until progression (Table 2).

Table 2. Tumor location, skull invasion, the extent of resection (Simpson's grading) of the first surgery, and adjuvant treatment before malignant progression

Variable	Value (percentage)	
	Benign	Atypical
Tumor location		
Convexity	4 (17.4)	2 (50.0)
Parasagittal/Falx	7 (30.4)	1 (25.0)
Skull base	7 (30.4)	1 (25.0)
Posterior fossa	4 (17.4)	
Intraventricular	1 (4.3)	
Skull invasion		
No	18 (78.3)	3 (75.0)
Yes	5 (21.7)	1 (25.0)
Simpson's grade of the first surgery		
GTR (I – III)		
I	2 (8.7)	2 (50.0)
II	3 (13.0)	1 (25.0)
III	3 (13.0)	1 (25.0)
STR (IV – V)		
IV	12 (52.2)	
V	3 (13.0)	
Pre-progression treatment		
Adjuvant treatment before progression	9 (39.1)	3 (75.0)
No treatment	14 (60.9)	1 (25.0)

Progression-free survival

Initial diagnosis at the first operation, gender, age, tumor location, extent of tumor resection, skull invasion, and adjuvant treatment before malignant progression were analyzed as possible prognostic factors for progression-free survival.

Twenty-three patients were diagnosed with benign meningioma at the first operation and 4 patients were with atypical meningioma. The median progression-free survival (PFS) were 79.3 (range: 10.7 – 284.9) months and 39.6 (range: 13.5 - 62.5) months, respectively. 3-year PFS rate of patients with benign meningioma was 65.2%, 5-year PFS rate was 60.9% and 10-year PFS rate was 26.1%. 3-year PFS rate of patients with atypical meningioma was 50%, 5-year PFS rate was 25%, and 10-year PFS rate was 0%. The difference of PFS between two groups did not reach statistical significance (p=0.068) (Fig 1).

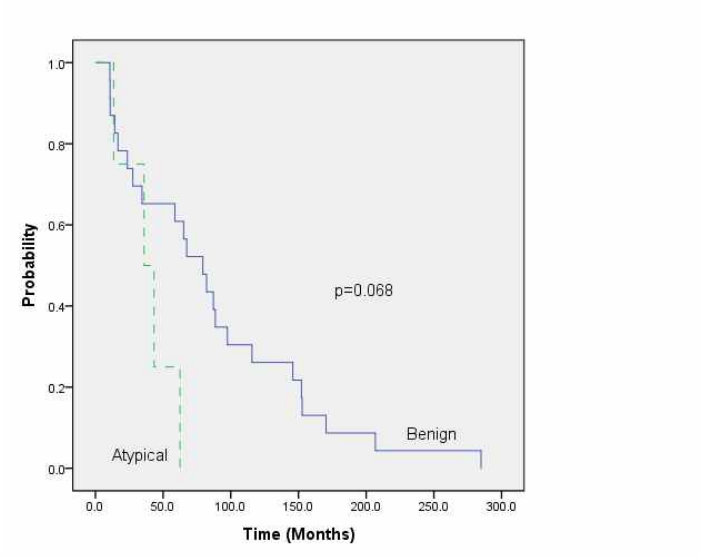

Figure 1. Kaplan-Meier progression-free survival curves for patients with benign meningioma versus patients with atypical meningioma.

The median PFS were 82.1 months for females and 62.5 months for males. The difference of PFS did not achieve statistical significance (p=0.295)

The mean age at the first diagnosis was 46.1 (range: 12.1 – 70.0) months. The median PFS were 87.1 months for patients under 50 years of age and 23.6 months for patients over 50 years of age. There was significant difference (p=0.013) in age groups (Fig 2).

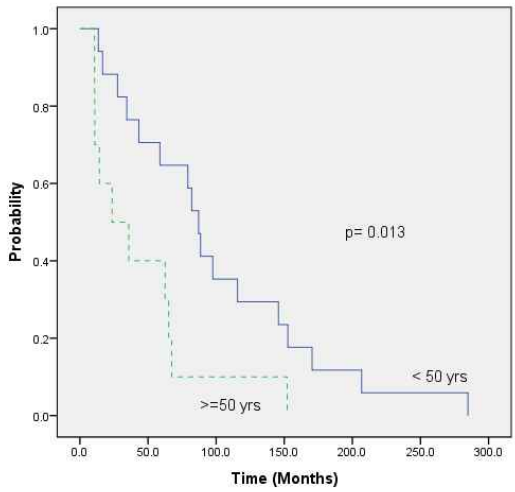

Figure 2. Kaplan-Meier progression-free survival curves for younger patients (< 50 years of age) versus elder patients (≥ 50 years of age)

Tumor location was categorized as convexity and non-convexity. Non-convexity included parasagittal/falx, skull base, posterior fossa and intraventricular. The median PFS was 145.8 (range: 35.9 – 284.9) months for convexity group and 62.5 (range: 10.7 – 152.7) months for non-convexity group. Clear difference (p=0.011) was showed in tumor location (Fig 3).

The median PFS was 62.5 months for patients with no skull invasion and 88.6 months for patients with skull invasion. The difference did not reach statistical significance (p=0.581).

Extent of resection was classified as gross total resection (GTR); Simpson grade I-III and subtotal resection (STR); Simpson grade IV-V. The median PFS was 67.4 months for GTR group and 58.7 months for STR group. The difference was not significant (p=0.132).

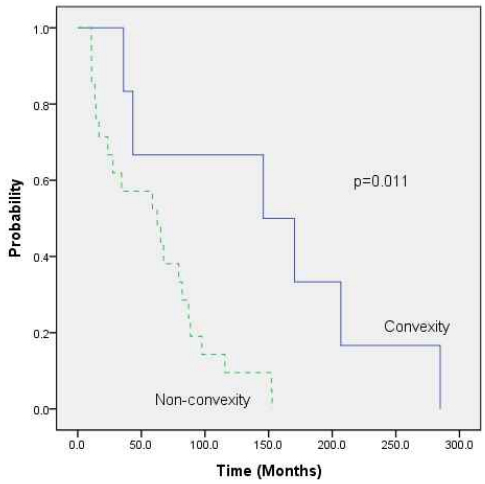

Figure 3. Kaplan-Meier progression-free survival curves for convexity tumors versus non-convexity tumors.

The median PFS was 58.7 months for patients who did not undergo adjuvant treatment before progression and 79.3 months for patients who underwent adjuvant treatment before progression. The difference between two groups was not statistically significant (p=0.397).

Age under 50 years-old and convexity location were significant prognostic factors for progression-free survival (Table 3).

Table 3. Univariate analysis of the prognostic factors for progression-free survival

Factor	N	Median PFS	HR (95% CI)	p
First diagnosis				
Benign	23	79.3	2.88 (0.88-9.47)	0.068
Atypical	4	39.6		
Age at the first diagnosis				
<50 yrs	17	87.1	2.84 (1.21-6.65)	**0.013**
≥50 yrs	10	23.6		
Tumor location				
Convexity	6	145.8	4.55 (1.30-15.92)	**0.011**
Non-convexity	21	62.5		
Skull invasion				
No	21	62.5	0.77 (0.30-1.95)	0.581
Yes	6	88.6		
Extent of resection				
GTR (Simpson I-III)	12	67.4	1.88 (0.82-4.34)	0.132
STR (Simpson IV,V)	15	58.7		
Adjuvant treatment before progression				
Yes	12	79.3	1.42 (0.63-3.18)	0.397
No	15	58.7		

Post-progression survival

The second diagnosis at progression, the age at the first diagnosis, the age at progression, tumor location, extent of resection at progression, brain invasion, Ki-67, and post-progression adjuvant treatment were included as the possible prognostic factors for post-progression survival (PPS).

Seventeen patients were diagnosed with atypical meningioma and 10 patients were diagnosed with anaplastic meningioma at progression. The median PPS was 64.4 (range: 0.6 – 140.1) months for patients with atypical meningioma and 19.3 (range: 0.3 – 132.6) months for patients with anaplastic meningioma. There was significant difference (p=0.034) of PPS between two groups (Fig 4). 3-year PPS rate was 64.7%, 5-year PPS rate was 58.2%, and 10-year PPS rate was 49.9% for patients with atypical meningioma. 3-year PPS rate was 40.0%, 5-year PPS rate was 30.0%, and 10-year PPS rate was 10.0% for patients with anaplastic meningioma.

The median PPS was 88.5 months for patients under 50 years of age and 7.0 months for patients over 50 years of age at the first diagnosis. The difference of PPS was significant (p=0.028) (Fig 5).

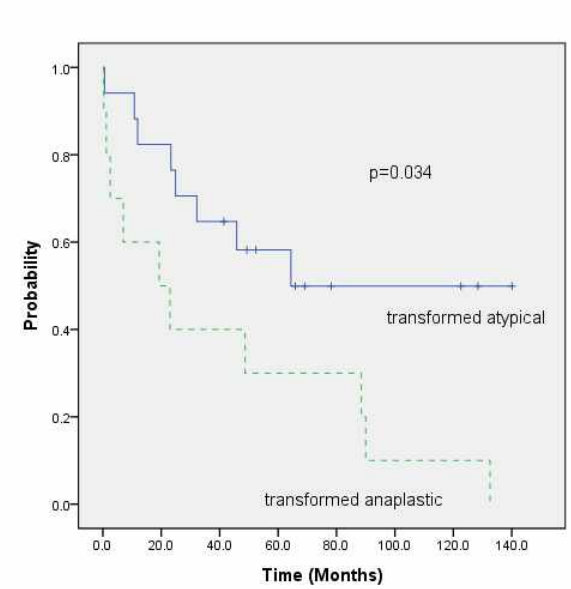

Figure 4. Kaplan-Meier post-progression survival curves for patients with atypical meningioma versus anaplastic meningioma after progression.

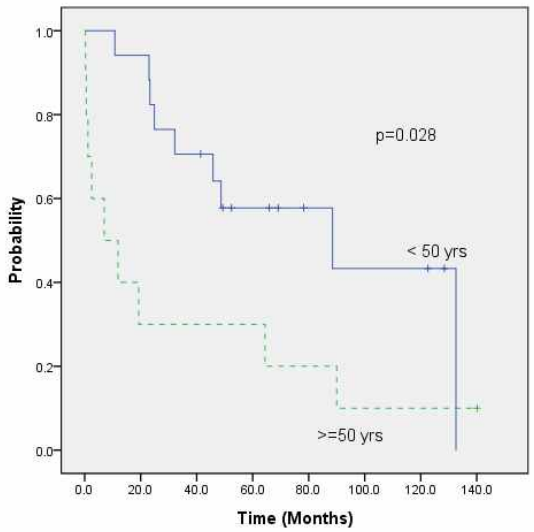

Figure 5. Kaplan-Meier post-progression survival curves for patients under 50 years versus over 50 years at the first diagnosis.

The median PPS was 88.5 months for patients under 50 years of age and 19.3 months for patients over 50 years of age at progression (Fig 6).

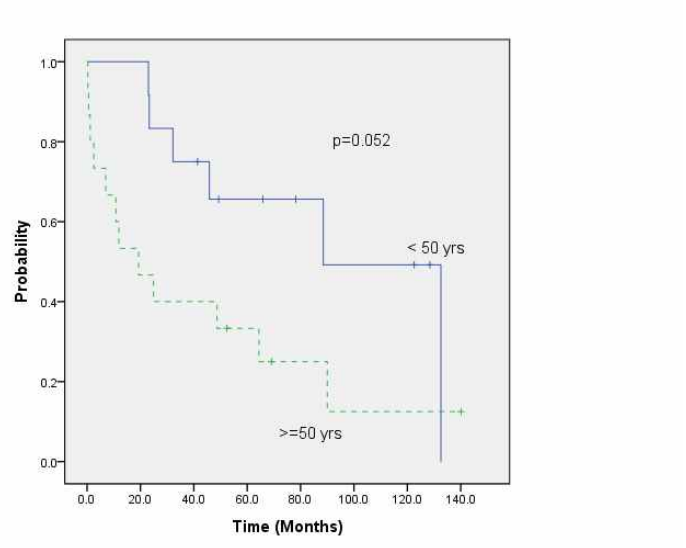

Figure 6. Kaplan-Meier post-progression survival curves for patients under 50 years versus over 50 years at progression

The difference of PPS in tumor location (Convexity vs. Non-convexity), extent of resection at progression (GTR vs. STR), Ki-67 (<5% vs. ≥5%), brain invasion and post-progression adjuvant treatment did not achieve statistical significance (Table 4).

We chased the course of salvage treatment when recurred after malignant progression. Salvage treatment modalities included adjuvant radiotherapy, stereotactic radiosurgery and surgery. 64.7% (11/17) of patients with transformed atypical meningioma and 60% (6/10) of patients with transformed anaplastic meningioma were treated additionally (Table 5).

Table 4. Univariate analysis of possible prognostic factors for post-progression survival

Factor	N	Median PPS	HR (95% CI)	p
Diagnosis at progression				
Atypical	17	64.4	2.68 (1.04 – 6.87)	**0.034**
Anaplastic	10	19.3		
Age at the first diagnosis				
< 50 yrs	17	88.5	2.78 (1.08 – 7.17)	**0.028**
≥ 50 yrs	10	7.0		
Age at progression				
< 50 yrs	12	88.5	2.57 (0.96 – 6.89)	0.052
≥ 50 yrs	15	19.3		
Tumor location				
Convexity	6	88.5	1.38 (0.45 – 4.24)	0.570
Non-convexity	21	45.8		
Extent of resection				
GTR (Simpson I–III)	11	88.5	1.16 (0.45 – 3.00)	0.761
STR (Simpson IV, V)	16	32.2		
Ki-67				
<5%	9	90.0	1.32 (0.45 – 3.87)	0.612
≥5%	16	24.9		
Brain invasion				
No	12	-	2.26 (0.78 – 6.51)	0.123
Yes	15	23.3		

Adjuvant treatment after progression				
Yes	17	64.4	1.55 (0.58 – 4.10)	0.377
No	10	32.2		

Table 5. Salvage treatment after malignant progression

Treatment modality	Atypical	Anaplastic
No treatment	6	4
RT† only	2	2
SRS‡ only	5	2
RT + surgery	0	1
SRS + surgery	2	0
RT + SRS + surgery	2	1
Total	17	10

†: radiotherapy

‡: stereotactic radiosurgery

Discussion

In our institution, the rate of progression from benign to high-grade tumor was 1.3%. The previous series reported the rate from 0.16 to 2% [2,3]. Malignant progression represented 7.9% in the group with atypical meningioma and 18.6% in the group with anaplastic meningioma during the investigation period in our study. The rate of malignant progression in the group with atypical meningioma was lower than the rate 14 to 29% reported in the literature [2,3]. Yang *et al.* reported atypical and anaplastic meningioma series during earlier period in our institution. The rate of progression was 17.5% in the atypical group and 54.2% in the anaplastic group [4]. After the application of 2007 WHO classification, many benign meningiomas were reclassified to atypical meningiomas and the proportion of atypical meningioma increased significantly [5]. Therefore, the rate of progression might decrease as the denominator of the rate increased. On the other hand, it may mean that developed surgical techniques and fine-tuned follow-up have improved tumor control and reduced the incidence of recurrence. We did not count recurrent but not progressed cases seperately. 14 to 28.5% of recurrent benign meningiomas and 26 to 33% of recurrent atypical meningiomas were transformed into higher-grade tumors in the literature [2,3].

There were 6 patients with over 10 years of interval from the first diagnosis to malignant progression. The maximum was 284.9 months, about 23.7 years. Among 6 patients, 4 patients were with benign meningioma initially and 4

patients didn't any treatment between the first operation and the second operation.

The preponderance of females with benign meningioma is well known [6]. F:M ratio was 11:12 in the patients with benign meningioma in our study. Male is predominant in the high-grade meningioma. Similarly, the predominance of males may present in the group with tumor progressed from benign to malignant.

The mean age at diagnosis ranged from 51 to 58 years in the benign meningioma series [7-9] and from 49 to 58 years in the atypical meningioma series [1,10,11]. The mean age of patients was 46.2 years for the patients with benign meningioma and 45.2 years for the patients with atypical meningioma in our study. In one study of malignant progressed cases, the mean age at diagnosis was 48.65 years for the group who first had benign tumors and 53.3 years for the group with atypical tumors [2]. The age at diagnosis of patients who experienced malignant progression is younger. In addition, when the patients were divided into young group and old group based on 50 years of age at diagnosis, young group had longer PFS than old group and the difference achieved significance.

Parasagittal/falx and skull base were most prevalent locations of tumors in this study. If the tumor invades superior sagittal sinus, some tumor tissues remain in the sinus after removing parasagittal meningioma. It is difficult to access tumor and to remove origin dura in the surgery of skull base meningioma. Convexity meningiomas are expected to have a low recurrence

rate given their easy resectability [12]. In our study, convexity tumors had long PFS over 10 years and the difference of PFS with non-convexity was statistically significant. All our cases experienced progression. Recurrence and progression will occur in a location that is likely to leave residual tumor relatively.

The extent of resection has been considered as the most important factor related to the recurrence of meningioma. Simpson's grade is categorized into five grades [13]. It was difficult to analyze the relation between each grade and PFS because the total number of patients of our study was small. Therefore we reclassified into two groups, GTR (Simpson grade I-III) group and STR (Simpson grade IV-V) group. However, more radical resection did not contribute to significant lengthening of PFS in our study. When only benign cases were analyzed except atypical cases, the difference of PFS between GTR group and STR group was significant.

Under the assumption that skull invasion is one of the biologic features of aggressive meningioma, we expected that skull invasion be related to shorter PFS. PFS for the group with skull invasion was rather longer than for the group without skull invasion and the difference was not significant. If there was skull invasion, the resection of tumor would be more radical and less residual tumor would be left. However, the extent of resection in the presence of skull involvement did not reflect aggressive resection in our results. Among 6 patients with skull invasion, 3 patients underwent GTR and 3 patients underwent STR.

After the first operation, three-quarters of the patients with atypical meningioma underwent postoperative adjuvant radiotherapy (ART). If the tumor was removed subtotally, the patients underwent postoperative ART or stereotactic radiosurgery (SRS). If the patients had a history of radiotherapy, they were not able to receive radiotherapy again at the time of recurrence and they had to undergo stereotactic radiosurgery or re-operation. After progression to high-grade, most patients with anaplastic meningioma were performed ART even though the extent of resection was GTR. Some patients had no time to receive ART because the disease deteriorated quickly after progression and they were expired. ART of anaplastic meningioma regardless of the extent of surgery has been standard of treatment. However, the adjuvant treatment after surgical resection of atypical meningioma is controversial. Many advocate ART after STR of atypical meningioma, but there is a debate about whether to observe or carry out ART after GTR [14].

PPS in our study can be compared with overall survival (OS) in the literature. The median PPS was 64.4 months for patients with transformed atypical meningioma. 3-year PPS rate was 64.7%, 5-year PPS rate was 58.2%, and 10-year PPS rate was 49.9%. The median OS ranged from 128 to 146.4 months in other atypical meningioma series [1,4,11]. 5-year OS rate was 81% in one study [11]. Another study showed 89.6% of 10-year OS rate [4]. The median PPS was 19.3 months for patients with transformed anaplastic meningioma. 3-year PPS rate was 40.0%, 5-year PPS rate was 30.0%, and 10-year PPS rate was 10.0%. The median OS ranged from 18.2 to 59 months in other anaplastic

meningioma series. 3-year OS rate ranged from 55 to 68% and 5-year OS rate ranged from 35 to 49.2% [4,6,15]. The prognosis of our patients was poorer than of the patients in other series including de novo cases. Krayenbuhl *et al.* compared clinical course and outcome of transformed meningioma with de novo high-grade meningioma [3]. The survival of patients with transformed meningioma from a lower grade was shorter than those with de novo high-grade meningioma in that study.

Ki-67 proliferative index is used as the prognostic factor for recurrence of tumor [7]. We wanted to look over the change of Ki-67 before and after progression. However, specific findings were often missed in the past pathologic reports, making it difficult to see changes. Only 10 patients had both the record of Ki-67 at the first operation and the record at the second operation. The values increased through progression except 2 cases. For PPS, Ki-67 was not predictive in this study.

The current study has some limitations. The data collection of our study was retrospective, and the number of cohort was small. Thus, there is potential bias. It may be needed to compare our results with outcome of recurrent but not progressed cases during the same period in our institution to find out the difference of affecting factors between recurrence and malignant progression.

Conclusion

Higher-grade tumor at the first diagnosis, old age and non-convexity location were related to shorter progression-free survival of malignant transformed meningioma. Anaplastic pathology and old age might predict unfavorable outcome after progression. The prognosis of transformed meningioma might be poorer than that of de novo meningioma.

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국문초록

수막종의 악성 진행에 대한 후향적 관찰

목적

WHO 등급 2 와 3 에 해당하는 악성 수막종은 양성 수막종보다 공격적인 양상을 보이며 예후가 나쁘다. 악성 수막종은 처음부터 악성으로 나타나거나 드물게 저등급 수막종에서 형질변환되어 발생하기도 한다. 이 연구에서는 악성으로 진행한 수막종 환자들의 치료 과정 및 결과를 살펴보고 악성 진행 및 이후의 생존에 영향을 미치는 인자들에 대해 분석하고자 한다.

방법

우리 병원에서 처음 수술을 받았으며, 이후 악성으로의 진행이 수술 및 병리검사로 확인된 환자 27 명을 연구대상으로 선정하였다. 의무기록을 통해 인구학적 정보, 병력, 영상검사 및 병리검사 결과를 검토하였으며 악성진행으로의 과정 및 시기, 치료방법, 추적관찰 및 생존여부를 파악하였다. 악성 진행 기간 및 생존기간에 영향을 미칠 수 있는 요소에 대한 분석을 시행하였다.

결과

여성이 13 명, 남성이 14 명이었으며 첫 진단 시 평균 연령은 46.1 세였다. 가장 흔한 주소는 편마비 및 시력/시야 장애였다. 종양의 위치로는 시상동인접수막종 및 겸상수막종, 뇌기저부수막종이 가장 많이 발생하였다. 12 명이 종양의 완전 절제술을 받았고, 15 명에서는 수술 후 일부 종양이 남았다. 양성에서 비정형으로 진행한 경우는 16 명, 양성에서 역형성으로 진행한 경우는 6 명, 비정형에서 역형성으로 진행한 경우는 4 명, 그리고 1 명은 양성에서 진행하여 비정형을 진단받은 후 최종적으로 역형성을 진단받았다. 악성 진행 전 중간 치료를 시행한 환자는 12 명이었다. 악성 진행 후 보조치료를 받은 환자는 17 명이었다.

종양의 악성도, 50 세를 기준으로 한 진단 시 연령, 종양위치가 대뇌궁륭부인지의 여부가 악성으로의 진행기간을 예측할 수 있는 인자로 분석되었다. 악성진행 이후의 생존기간을 예측할 수 있는 인자로는 종양의 악성도 및 50 세 기준의 진행 시 연령을 들 수 있다.

결론

첫 진단 시 고등급의 종양, 50 세 이상의 고령, 대뇌궁륭 이외의 위치가 빠른 악성진행과 관련이 있을 수 있다. 악성 진행을

진단받았을 때 고등급의 종양, 50 세 이상의 고령이 악성진행 이후의 생존기간의 단축에 영향을 줄 수 있다. 형질변환을 거쳐 진행된 악성 수막종의 예후는 처음부터 악성으로 발생한 경우보다 나쁠 수 있다.

주요어: 수막종, 악성 진행, 비정형 수막종, 역형성 수막종

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