의학석사 학위논문

성인 털모양별아교세포종의 임상양상 및 예후인자에 대한 후향적 분석 연구

A Retrospective Analysis of Surgical outcome in 71 adult patients with pilocytic astrocytoma

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의 학 과
서 정 한

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2018 년 12 월

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Abstract

Background

Pilocytic astrocytomas (PAs) frequently affect the pediatric population. On the contrary, only rare case series in adults were reported. Some reported adult PA represented more aggressive behavior than pediatric patients but it is a relatively unknown entity about their prognosis and management. The goal of this study is to evaluate prognostic factors and treatment outcomes in adult PA patients to assess overall prognosis after surgery.

Methods

We reviewed 71 adult patients diagnosed of PA in single institution between 1999 and 2017. We investigated OS (overall survival) and PFS (progression-free survival) of our patients along with prognostic factors. PFS and OS were calculated using the Kaplan-Meier method. Prognostic factors were analyzed using Cox-Proportional Hazard model.

Results

A total of 71 adult patients were diagnosed with PA at our institution between 1999 and 2017 (40 men and 31 women). During the median follow-up of 75.6 months, progression or recurrence of tumor occurred in 19 patients (26.8%). The extent of resection was strongly correlated to both PFS and OS (Kaplan Meier estimates, log-rank test, $p<0.001$) The overall survival rates at 5 year with APAs who achieved CR, PR and biopsy were 97%, 94% and 56%, respectively. And progression free survival rates at 5 year in CR, PR and biopsy patients were 91%, 63% and 32%, respectively.

Conclusion

Adult PAs have more aggressive clinical behavior than pediatric PAs. Our study showed extent of resection (EOR); STR and biopsy, age of 40 or over and deep location were associated with poor prognostic factors for OS and PFS.

차 례

Tables and figures

Introduction

Pilocytic astrocytoma (PA) is a primary brain tumor classified as World Health Organization (WHO) grade I. PAs are most often diagnosed in children that accounts for approximately 25% of pediatric brain tumors.[1, 2] Adult pilocytic astrocytomas are less studied because of its lower incidence of 4.8 per 1million.[3] Some recent studies suggested that APAs have a more aggressive behavior when compared with Juvenile PAs, with a higher incidence of tumor recurrence and progression. [4]

As for their management, complete surgical resection may provide a chance of cure with excellent long-term survival.[3] But in some cases, it is hard to achieve complete resection due to its location such as thalamus or brainstem. Residual tumors after incomplete resection or biopsy often remain stable, although they may progress.[3, 4] Radiotherapy, chemotherapy or observation with clinical follow-up have been used for residual or recurrent tumors according to institutional treatment protocol.

We reviewed 71 adult patients diagnosed of PA in single institution between 1999 and 2017. The goal of this study is to evaluate prognostic factors and treatment outcomes in adult PA patients to assess overall prognosis after surgery. We specifically analyzed the relationship between extent of tumor resection and recurrence.

Methods

Our institutional database was searched for patients of an age 18 years or older who underwent surgery and were diagnosed with PA between 1999 and 2017. Only newly diagnosed cases were enrolled into the study and those of recurrent tumors with unavailable information on primary tumors were excluded.

Our institution used following treatment strategy for suspected PA patients. If possible, complete resection (CR) was firstly considered for having chance of cure the disease. After CR, patients were observed and followed up. When partial resection (PR) was done, the residual lesion was observed primarily. However, in case of patients who had deep seated lesion which complex redo surgery was anticipated and who had severe fear of progression of disease, we considered adjuvant radiotherapy.

A retrospective chart review was performed and the following data were recorded: gender, age at the diagnosis, location of the tumor, extent of surgical resection (complete or partial or biopsy), total follow-up period, episodes of radiological tumor recurrence, progression free survival and overall survival.

We investigated OS (overall survival) and PFS (progression-free survival) of our patients along with prognostic factors. The period of OS was defined as the time interval between the date of the initial diagnosis and the date of death. The period of PFS was defined as the time interval between the date of initial treatment and the date of tumor recurrence or progression based on radiologic findings. PFS and OS were calculated using the Kaplan-Meier method.

Prognostic factors for the OS and the PFS were analyzed including the age, gender, the location of tumor, the extent of resection (complete resection, partial resection and biopsy), and adjuvant radiotherapy. Prognostic factors were analyzed using Cox-Proportional Hazard model.

All statistical analyses were conducted using SPSS ver. 21.0 (SPSS Inc, Chicago, IL). Result of p value ≤ 0.05 was considered statistically significant.

Institutional review board approval was granted for this study.

Results

Patient characteristics

A total of 71 patients were diagnosed with APA at our institution between 1999 and 2017 (40 men and 31 women). The mean follow-up duration was 73.3 (range, 5-247) months.

MRI studies were performed in all patients before surgery. MRI showed the primary tumor located in the cerebrum (n=17, 23.9%), cerebellum (n=25, 35.2%), intra-ventricle (n=11, 15.5%), diencephalon (n=12, 16.9%), basal ganglia (n=3, 4.2%) and brainstem (n=3, 4.2%) (Table 1)

Treatment modalities

All the patients underwent surgery. Complete resection (CR) was achieved in 40 patients (56.3%). Partial resection (PR) and biopsy was done in 17 (23.9%) and 14 patients (19.7%), respectively.

Most of the patients (55 of 71 77.5%) did not receive any form of adjuvant therapy. 11 patients (15.5%) received adjuvant RT with the median dose of 52.1 Gy. (Table 1)

Patient outcome

During the median follow-up of 75.6 months, progression or recurrence of tumor occurred in 19 patients (26.8%) with the median time to event of 21 months after initial surgery (range, 3-112 months). Death was observed in 10 patients (14.1%). The cause of death was progression of disease in all patients. The median time to death was 30 months (range, 5-158 months). The overall survival rates at 3, 5, and 10 years were 89%, 82%, and 80%, whereas the PFS rates at 3, 5, and 10 years were 75%, 73% and 66%. (Table 1)

Impact of the Extent of resection on OS and PFS

Kaplan Meier curves of overall survival (OS) and progression free survival (PFS) for patients with pilocytic astrocytoma by extent of resection (EOR) are illustrated in Fig. 1. The extent of resection was strongly correlated to both PFS and OS (Kaplan Meier estimates, log-

rank test, $p<0.001$) The overall survival rates at 5 year with APAs who achieved CR, PR and biopsy were 97%, 94% and 56%, respectively. Progression free survival rates at 5 year in CR, PR and biopsy patients were 91%, 63% and 32%, respectively.

Prognostic Factor

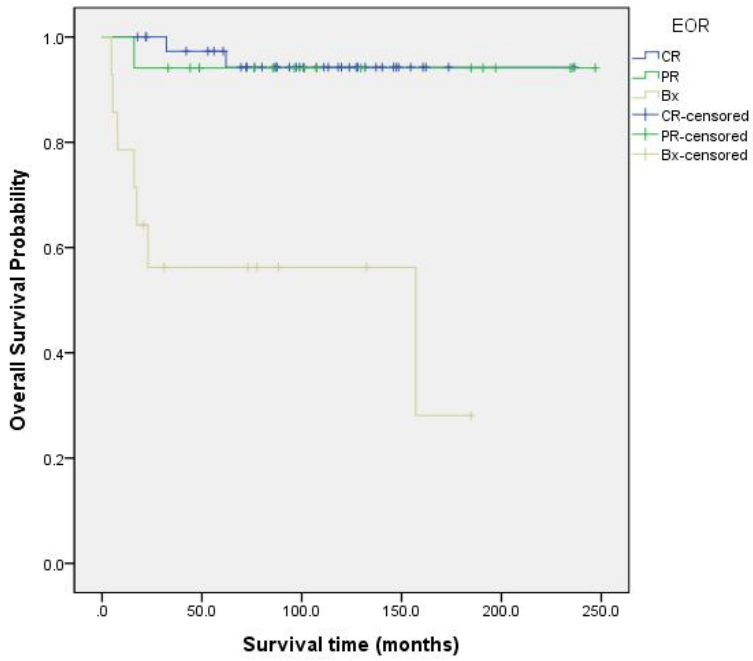
Univariate analysis and multivariate analysis using Cox proportional hazard models of each factors for OS and PFS were performed. In univariate analysis for OS, adverse prognostic factors included old age (>40yr), deep location (Diencephalon+Basal ganglia+Brain stem), incomplete resection (biopsy) and adjuvant RT. Adverse prognostic factors for PFS included old age (>40yr), deep location, incomplete resection (PR/biopsy) and adjuvant RT (Table 2). In multivariate analysis, adverse prognostic factors for PFS and OS included old age (>40yr) and incomplete resection (biopsy) (Table 3).

Table 1. Patient characteristics

Patient characteristics	No. (%)
Age at diagnosis	
18-29	36 (50.7%)
30-49	24 (33.8%)
>50	11 (15.5%)
Sex	
Male	40 (56.3%)
Female	31 (43.7%)
Tumor location	
Cerebrum	17 (23.9%)
Cerebellum	25 (35.2%)
Diencephalon +BG† +BS‡	18 (25.4%)
Intra-ventricle	11 (15.5%)
Extent of resection	
Complete resection	40 (56.3%)
Partial resection	17 (23.9%)
Biopsy	14 (19.7%)
Adjuvant treatment	
None	55 (77.5%)
Radiotherapy	11 (15.5%)
Others	5 (7.0%)
Length of follow up	75.6 months
Progression	
No	52 (73.2%)
Yes	19 (26.8%)
Survival	
Alive	61 (85.9%)
Death	10 (14.1%)

†Basal ganglia, ‡ Brainstem

Figure 1. PFS and OS (GTR vs STR vs Bx.)



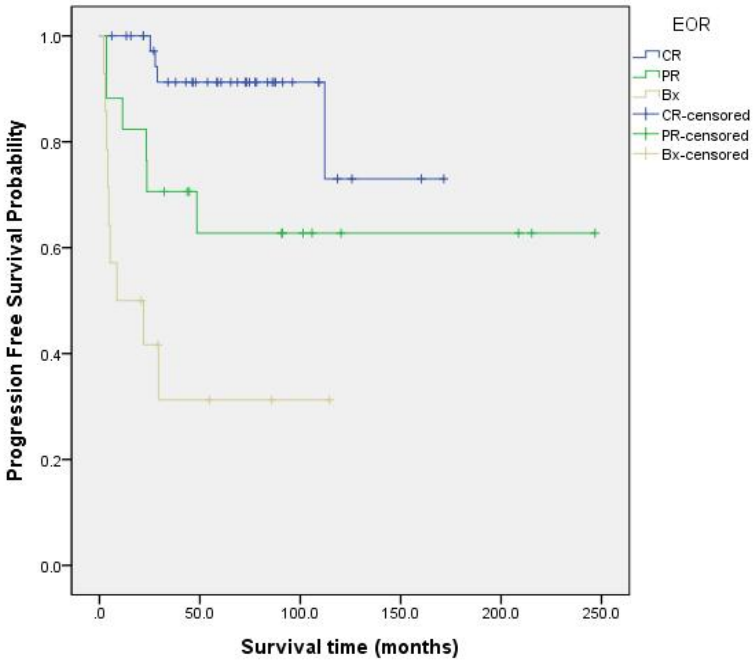


Table 2. Cox proportional hazards Univariate Regression for Overall survival and Progression-free survival in adult patients with pilocytic astrocytoma

Parameter	Overall survival			Progression-free survival		
	HR	95% CI	P value	HR	95% CI	P value
Age >40	6.192	1.713-22.385	0.005	3.575	1.441-8.872	0.006
Male sex	2.983	0.632-14.072	0.167	1.457	0.573-3.704	0.429
Deep Location	5.013	1.413-17.789	0.013	3.820	1.537-9.49	0.004
EOR						
CR	1	-	-	1	-	-
PR	1.050	0.094-11.725	0.968	3.747	1.054-13.316	0.041
Bx	13.274	2.729-64.564	0.001	11.168	3.405-36.627	<0.001
Size (>5cm)	0.314	0.040-2.481	0.272	0.686	0.227-2.073	0.504
Adjuvant RT	4.449	1.249-15.850	0.021	4.385	1.693-11.361	0.002

Table 3. Cox proportional hazards Multivariate Regression for Overall survival and Progression-free survival in adult patients with pilocytic astrocytoma

Parameter	Overall survival			Progression-free survival		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age >40	7.874	2.033-30.505	0.003	2.911	1.169-7.245	0.022
EOR						
CR	1	-	-	1	-	-
PR	0.783	0.068-9.056	0.783	3.527	0.992-12.538	0.051
Bx	13.992	2.850-68.690	0.001	9.926	2.997-32.876	<0.001

Discussion

Pilocytic astrocytomas (PA) are more common in pediatric patients than adult. Most pediatric pilocytic astrocytomas occur in the cerebellum and known for well circumscribed lesions and indolent nature with high survival rate at long term follow-up.[3, 5] In contrast, adult PAs are rare and often reported to not be benign. Recurrence rates are high and tumor-related deaths are frequent.[4, 6] Stuer et al., reported 10-year (1995-2005) experience of adult PAs, recurrence and malignant transformation rates of adult PA were 30 and 50%, respectively and 18% of patients were died.[4] Also, Theeler et al. and Joshua et al. reported 22-year and 10-year experiences of adult PA series, from these report, recurrence rate of adult PA was 42% and 30%, respectively, death rate was 13% and 10% respectively.[7, 8] In our cohort, 27% of patients experienced disease progression or recurrence and 14% of patients were died.

Complete resection is known for curative treatment of PAs. Generally, extent of resection is major prognostic factor in the clinical course of pediatric PAs.[9] In adult PA, complete resection and extent of resection have also been shown to be associated with favorable prognosis.[4, 10] Johnson et al. analyzed 865 adult pilocytic astrocytoma patients from the USA National Cancer Institute (NCI) database and revealed a significantly low hazard ratio of death of 0.3 for gross total resection compared with subtotal resection or biopsy.[10] Likewise, Stuer et al. reported 4 times higher recurrence rates of partially resected APA tumors than completely resected tumors.[4]

In our study, patients who underwent CR showed better prognosis than those who underwent PR or biopsy. This result is consistent with previously reported data, complete surgical resection of PA is still remained important goal of surgery and it provides chance for excellent outcome.

However, there are circumstances in which incomplete removal is inevitable. Attempting complete resection for PAs in deep location such as diencephalon or brain stem are great challenges because it harbors higher surgical complication risk. Surgery for tumors in these regions was typically PR or biopsy for tissue confirmation in order to avoid complications. In our case series, deep location (diencephalon, basal ganglia, brain stem) of tumor was found in 18 patients (25%). Among them, 6 patients (33%) underwent partial resection, 12 patients (67%) underwent only biopsy and complete resection wasn't achieved among these patients. The clinical course after incomplete resection is unpredictable, residual tumor may stay stable or progress.[3, 11] In our case series, 15 out of 21 residual tumors progressed and 8 patients were dead.

There is a controversy with the use of adjuvant radiotherapy after incomplete resection. Theeler et al. reported that patients treated with RT and subgroup of patients treated with surgical resection plus adjuvant RT had significantly reduced PFS compared with patients who were not irradiated.[7] In contrast, Ishkanian et al. recently reported a retrospective study comparing upfront observation versus post-operative radiation therapy for surgically treated 30 adult PA patients.[12] In this study, 5-year PFS was 91% progression-free survival in patients who underwent post-operative radiation while 5 year PFS was 42% in patients who underwent surgery with upfront observation.[12] In our case series, we found significant association between adjuvant radiation and reduced PFS in univariate analysis but not in multivariate analysis. In our institution, adjuvant radiation was applied mainly to incompletely resected tumors. Adjuvant radiotherapy was performed in 11 patients, only 1 patient underwent complete resection. As we reviewed, complete resection is strongly associated to better prognosis. Radiotherapy is still remaining controversy for adjuvant therapy after surgery.

There are some limitations of our study. Considering the rare incidence of adult PAs, it is not possible to collect large number of cases in a short period. Our study spans about 20 years, surgical technique and equipment which could affect the outcome had changed during the period. Despite the limitation, considering its rare incidence our study included large amount of adult PA cases (71 patients). In the future, we need well designed, multi-institutional prospective study for adult PA to set up treatment consensus and strategy.

Conclusion

Adult PA has more aggressive clinical behavior than pediatric PAs. Our study showed incomplete resection and old age (over 40) were associated with poor prognostic factor for OS and PFS.

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국문요약

연구배경: 털모양별아교세포종은 소아에서 호발하는 저등급의 교종이다. 반면에 성인에서 발생하는 경우는 드물다. 몇몇 보고에 따르면 성인 털모양별아교세포종의 예후는 소아의 경우보다 안 좋은 것으로 확인되었지만, 낮은 발병률 때문에 정확한 예후와 치료에 대해서는 상대적으로 잘 알려지지 않았다. 이 연구의 목적은 성인 털모양아교세포종 환자의 예후 인자와 치료 결과를 평가하여 수술 후 전반적인 예후를 평가하는 데 있다.

연구방법: 우리는 1999 년과 2017 년 사이에 단일기관에서 털모양별아교세포종으로 진단된 71 명의 성인 환자를 살펴보았다. 우리는 환자들의 예후 인자와 함께 전체생존율, 무진행 생존율을 조사하였다. 전체생존율과 무진행생존율은 카플란-마이어 방법으로 계산하였고 예후인자는 콕스 비례 위험 모델을 이용하여 분석하였다.

연구결과: 1999 년과 2017 년 사이에 우리 기관에서 털모양별아교세포종으로 총 71 명의 환자가 진단되었다. (남자 40 명, 여자 31 명) 75.6 개월의 추적 관찰 기간 동안 종양의 진행 또는 재발은 19 명 (26.8 %)에서 발생하였고 10 명 (14.1%)의 환자가 사망하였다. 종양절제 정도는 전체생존율과 무진행생존율과 유의미한 상관관계가 있었다. (Kaplan Meier 추정, log-rank test, $p < 0.001$). 종양완전절제, 부분절제 및 조직생검을 시행하였던 환자의 5 년 생존율은 각각 97%, 94%, 56%였으며 그들의 5 년 무진행생존율은 각각 91%, 63% 및 32%였다.

결론: 우리의 연구를 통해 불완전 종양절제, 40세 이상의 나이 그리고 깊은 위치가 성인 털모양별아교세포종의 불량한 예후인자임을 밝혔다.

중심단어: 성인 털모양별아교세포종, 종양 절제 정도, 예후인자