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Radiation or Chemotherapy rather than Observation may be a Better Modality after Subtotal Resection for Pilocytic Astrocytoma in Children

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Background: Pilocytic astrocytoma (PA) is a low-grade glioma that occurs primarily in children and young adults. The optimal postoperative treatment modality after subtotal resection (STR) of PAs remains to be elucidated. The aim of this study was to compare the efficacies of different post-STR treatment modalities and to examine the risk factors for the progression of PAs.

Methods: We reviewed the medical records of 91 pediatric PA patients in a single institute during a 30-year period. Kaplan-Meier analysis was used to assess overall survival (OS) and progression-free survival (PFS), and Cox proportional hazard models were used to calculate hazard ratios.

Results: The median age of 91 patients was 8.9 years (range, 0.3-17.9). GTR was perfomed, whenever possible. Patients who underwent STR afterwards received either radiotherapy, chemotherapy, or were observed without further treatment, according to clinician preference. In total group, 10-year OS was 97.4% and 10-year PFS was 57.2%. In GTR group (N=33), 10-year OS and PFS was 100%. In STR group (N=49), 10-year OS was 97.7%, while 10-year PFS was 38.6%. STR group underwent following postoperative (PO) modalities; observation (PO-Obs, N=32), radiotherapy (PO-RT, N=10), chemotherapy (PO-CTx, N=7). The 10-year PFS rate was higher in patients who received postoperative treatment (either PO-RT or PO-CTx) than in patients who received PO-Obs (62.5% vs 27.0%, P=0.039). In multivariate analysis for STR group, PO-CTx (Hazard ratio (HR)=0.20, P=0.035) and PO-RTx (HR=0.13, P=0.008) were superior to observation, respectively.

Conclusion: Radiation and chemotherapy are better post-STR treatment modalities than observation for pediatric PA patients.

Key Words: Pilocytic astrocytoma, Postoperative treatment, Subtotal resection

pISSN 2233-5250 / eISSN 2233-4580
http://dx.doi.org/10.15264/cpho.2014.21.2.95
Clin Pediatr Hematol Oncol 2014;21:95～103

Received on September 16, 2014
Revised on October 6, 2014
Accepted on October 17, 2014

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Introduction

Low-grade gliomas (LGGs) are a heterogeneous group of tumors of the central nervous system and include World Health Organization (WHO) grade I and grade II gliomas, such as astrocytomas, oligodendrogliomas, oligoastrocytomas, and mixed neuronal-glial tumors [1]. Low-grade astrocytomas (LGAs) include diffuse astrocytomas, pilomyxoid astrocytomas, and pleomorphic xanthoastrocytomas (WHO grade II), as well as pilocytic astrocytomas (PAs) and subependymal giant cell astrocytomas (WHO grade I). Although their clinical behavior can vary, the majority of LGGs are indolent and do not undergo malignant transformation. Thus, all LGGs were regarded as one entity in many reports.

PA is a slowly growing tumor that occurs primarily in children and young adults. It is the most common brain tumor in children aged 5-14 years and the second most common brain tumor in children aged 0-4 and 15-19 years, accounting for 20% of brain tumors in individuals under the age of 20 years and 30% of all posterior fossa tumors in childhood [2-4]. The cerebellum is the most common site of origin, particularly in children, although the entire neuraxis can be affected, such as the brain stem, optic tract, hypothalamus, spinal cord, and cerebral hemispheres [5,6]. Gross total resection (GTR), whenever possible, is the treatment of choice and yields an excellent 5-year overall survival (OS) rate of 85-100% [6-10]. However, PAs arising in the optic pathway, brain stem, and hypothalamus are not usually amenable to GTR. In these cases, subtotal resection (STR) is typically performed in order to avoid complications such as visual field loss, third nerve palsy, endocrine deficits, and death. However, STR results in less favorable outcomes than does GTR. Fernandez et al., reported that GTR led to 5- and 10-year survival rates of 100% and recurrence rates of 2-5.4%, whereas 42-45% of partially removed have been demonstrated to recur [10]. The behavior of PA underwent STR is unpredictable; recurrence can result in severe neurological deficits or death, while PAs rarely spontaneously regress after STR.

Clinicians dealing with PA patients face several dilemmas: which PAs will progress, whether postoperative first-line treatment is necessary, and whether the benefits of first-line treatment outweigh its side effects. There are no definite clinico-pathologic risk factors that predict outcome after STR and no consensus regarding optimal treatments after STR. Many authors recommend the "wait-and-see" policy, which is based on the premise that the residual tumor will remain silent for many years [4,11]. In previous reports, postoperative treatment after surgery improved progression-free survival (PFS) but not OS; however, most of these studies grouped pathologically heterogeneous LGGs and LGAs altogether, and various treatment strategies [12,13]. Therefore, the most effective treatment modality after STR remains to be elucidated [4]. Reoperation at the time of recurrence or progression is one treatment option; however, surgical morbidity and neurological complications due to surgery or tumor progression per se are risk factors that must be considered [14]. Furthermore, the low success rate of GTR as the second operation can result in subsequent operations or multimodality treatment approaches [4].

Our goals were to determine the efficacy of radiotherapy, chemotherapy, and observation as postoperative treatment modalities after STR of pediatric PAs, to identify the risk factors for the progression of PAs, especially after STR, and to evaluate the general clinical characteristics of PAs and survival outcomes. To accomplish our aims, we performed a PA-specific retrospective study consisting of all tumor locations in a single institute, where a single group of clinicians decided the treatment modalities for each patient.

Materials and Methods

1) Patients

We carried out a retrospective study of 95 cases of pediatric (defined as <18 years of age) PAs that occurred during a 30-year period (January 1983-December 2012) at Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea. The revised WHO classification system was used to classify tumor type. All patients had pathologically confirmed PAs at the time of diagnosis or progression detected via either biopsy or surgery. Four cases of malignant trans-

formation of PAs during follow-ups were not included in our analysis. The medical records of the remained 91 patients were reviewed for the following data: sex, age at diagnosis, tumor size, primary tumor location, presenting symptoms and signs, initial treatment modalities [GTR, STR, Gamma knife surgery (GKS), and observation], duration of follow-ups, and neurologic outcomes.

2) Treatment

GTR was performed if it would not result in significant neurologic deficits. GTR was defined as the removal of all tumor tissue during surgery and was approved only when both the surgeon's report and postoperative neuroimaging were concordant.

When GTR was not feasible, STR or observation was chosen by a group of clinicians.

GKS was performed in cases presenting with small (<3 cm in size) tumors or with possibilities of neurologic complications with other treatment modalities.

Patients treated via STR received the following postoperative treatment modalities: radiation therapy (PO-RT), chemotherapy (PO-CTx), or closed observation (PO-Obs), as recommended by a group of clinicians. For PO-RT, local tumor fields plus a 1-2-cm margin received a median dose of 49.3 Gy (45.0-50.4 Gy) with a median daily fraction size of 1.8 Gy. PO-CTx patients usually received carboplatin and vincristine (CV) [15]; other patients received procarbazine, carboplatin, and vincristine (PCV).

3) Statistical analysis

OS was measured from the date of histologic diagnosis to the date of death or last contact with a surviving patient. PFS was measured from the date of diagnosis to the date of the first failure of any type, death, or last contact with a patient who had responded. The Kaplan-Meier method was used to estimate OS and PFS rates. Survival estimates were compared via the log rank test. The Cox proportional hazards regression model was used for survival analyses of clinical variables such as age at diagnosis. All analyses were performed using SPSS software, version 21 (SPSS Inc., Chicago, IL, USA), and a *P*-value of <0.05 was considered statistically significant.

4) Ethics statement

This study was approved by the institutional review board of Severance Hospital (IRB No. 4-2014-0512).

Results

1) Patient demographics

The male-to-female ratio was 0.9 and the median age at diagnosis of PA was 8.9 years (range, 0.3-17.9) (Table 1). Among our 91 pediatric PA patients, 24 (26.4%) were younger than 5 years of age.

The main presenting symptoms were headache (65.9%), vomiting (28.5%), gait disturbance (22.0%), visual disturbance (18.6%) and seizure (6.5%). Incidental PAs were found in two cases after traumatic head injury. Regarding to treatment modalities, 82 (90%) received surgery as their initial treatment; 33 received GTR and 49 received STR. Three patients (3.3%) received GKS, and 6 (6.6%) were observed. During the follow-up period, 88 patients underwent 113 surgeries; once (N=69), twice (N=13), 3 times (N=6). During the follow-up period, 12 patients received GKS, 15 patients received RT, and 12 patients received a total of 13 cycles of chemotherapies. The chemotherapy regimens were as follows: CV (N=5), PCV (N=5), vinblastine, etoposide, 5-flurouracil and cyclophosphamide (N=3) [16].

2) OS and PFS in total group

At a median follow-up duration of 92 months (range, 4-302 months), 88 (96.7%) patients were alive, and 59 (63.4%) patients were progression-free. The 10-year OS and PFS estimates were 97.4±1.8% and 57.2±6.1%, respectively (Fig. 1). Three patients died during follow-up; as a result of tumor progression (N=1), perioperative shock (N=1) and bacterial meningitis related with ventriculo-peritoneal shunt (N=1).

3) OS and PFS on the basis of initial treatment modalities in total group

The 10-year OS rates for the initial treatment modalities were as follows: GTR, 100%; STR, 97.7±2.3%; GKS, 100%;

Table 1. Patient demographics (N=91)

Factors	Total (N=91)	Age<5 (N=24)	5≤Age<18 (N=67)	*P*-value
Sex[a]				0.531
Male	43 (47.3)	11 (45.8)	32 (47.8)	
Female	48 (52.7)	13 (54.2)	35 (52.2)	
Tumor size (cm)[b]		4.4±2.1 (1.0-8.0)	4.0±1.4 (1.0-6.0)	0.255
Location[a]				0.142
Cerebellar	45 (49.5)	12 (50.0)	33 (49.3)	
Supratentorial	12 (13.2)	1 (4.2)	11 (16.4)	
Brain stem	8 (8.8)	1 (4.2)	7 (10.4)	
Suprasellar	7 (7.7)	3 (12.5)	4 (6.0)	
Optic tract	14 (15.4)	7 (29.2)	7 (10.4)	
Spinal cord	2 (2.2)	0 (0.0)	2 (3.0)	
Thalamus	3 (3.3)	0 (0.0)	3 (4.5)	
Treatment modalities (N)[c]				
Surgery	113			
GTR	34			
STR	79			
GKS	12			
Radiotherapy	15			
Chemotherapy	12			
10-year OS (%)[d]	97.4±1.8	90.0±6.7	100.0±0.0	**0.005**
10-year PFS (%)[d]	57.2±6.1	41.8±11.5	63.3±7.0	**0.043**
Endocrinal dysfunction[a]	6 (6.6)	1 (4.2)	5 (7.5)	0.497
Follow up (years)[b]	7.8±6.5 (0.3-25.2)			

GKS, gamma knife surgery; GTR, gross total resection; N, numbers; OS, overall survival; PFS, progression free survival; STR, subtotal resection.
[a]data were shown as numbers (%). [b]data were shown as mean±standard deviations (range). [c]data included all numbers of treatment during follow-up. [d]data were shown as mean±standard errors.

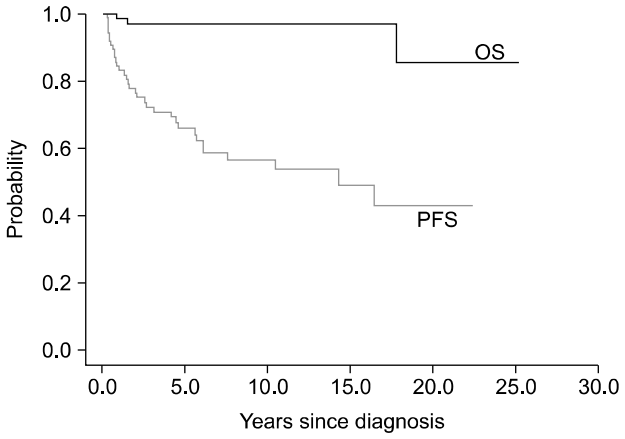

Fig. 1. Overall Survival and Progression Free Survival in total group (N=91).

and observation, 83.3±15.2% (*P*=0.081) (Fig. 2A). This result showed the tendency that GTR was superior to STR or observation, but did not reach to statistical significance due to small number of deaths (N=3). The 10-year PFS rates were as follows: GTR, 100%; STR, 38.6±8.0%; GKS, 50.0±35.4% and observation 16.7±15.2% (*P*<0.001) (Fig. 2B). No patients in the GKS group died, but 1 (33%) experienced disease progression. In the observation group, 5 (83.3%) patients progressed including 1 (16.7%) who died. In the STR group, 28 (57.1%) patients progressed including 2 (4.1%) who died.

4) OS and PFS on the basis of tumor locations in total group

The 10-year OS rates on the basis of primary tumor sites were as follows: optic tract, 92.3±7.4%; suprasellar region, 75.0±21.7%; and brain stem 50.0±35.4% (*P*=0.050) There were no deaths in cases of cerebellar, supratentorial, thalamic, or spinal cord tumors. The 10-year PFS rates were as follows: cerebellum, 69.1±7.6; supratentorial region, 72.0±17.8%; brain stem, 51.4±20.4%; suprasellar, 34.3±19.5%; and optic tract, 23.2±11.7% (*P*=0.006). The mean time to progression was significantly lower in suprasellar (5.6 years) and optic

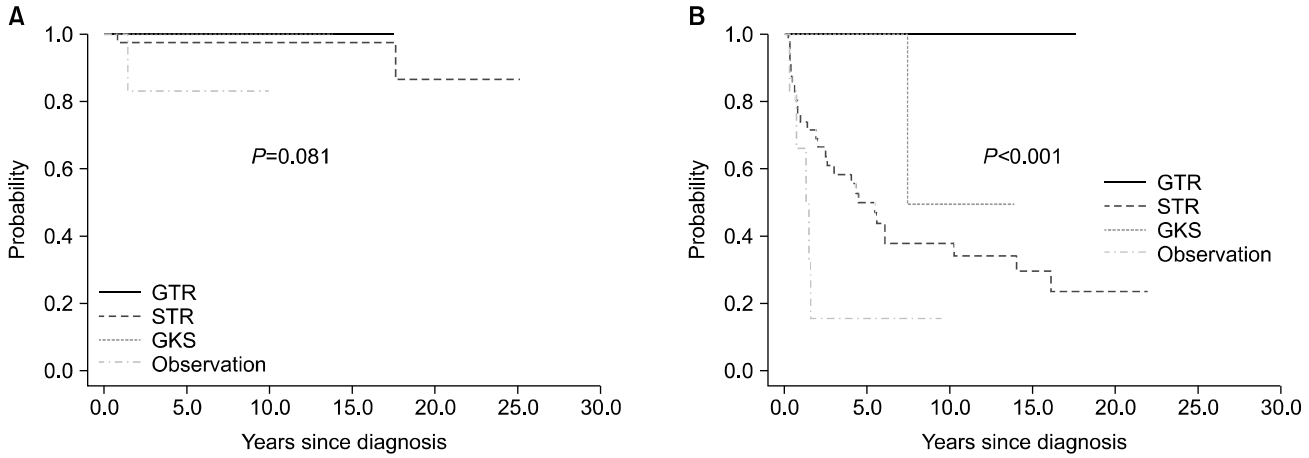

Fig. 2. Overall Survival and Progression Free Survival by Clinical Parameters in total group (N=91). (A) Overall Survival by initial treatment modalities. (B) Progression Free Survival by initial treatment modalities.

Table 2. Clinical parameters affecting the choice of initial treatment modalities in total group (N=91)

	GTR (N=33)	STR (N=49)	GKS (N=3)	Observation (N=6)	*P*-value
Age (year)[a]	10.0±4.8 (2.4-17.9)	8.3±4.4 (0.9-17.5)	14.4±2.4 (12.5-17.1)	4.8±4.6 (0.4-11.6)	**0.009**
Tumor size (cm)[a]	4.2±1.7 (1.0-8.0)	4.1±1.8 (1.0-8.0)	3.0±0.0 (3.0-3.0)	2.2±1.8 (0.5-7.0)	0.082
Tumor location[b]					**0.003**
Cerebellar	22 (48.9)	23 (51.1)	0 (0.0)	0 (0.0)	
Supratentorial	7 (58.3)	4 (33.3)	1 (8.3)	0 (0.0)	
Brain stem	1 (12.5)	5 (62.5)	0 (0.0)	2 (25.0)	
Suprasellar	1 (14.3)	5 (71.4)	0 (0.0)	1 (14.3)	
Optic tract	0 (0.0)	10 (71.4)	1 (7.1)	3 (21.4)	
Spinal cord	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	
Thalamus	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	

GKS, gamma knife surgery; GTR, gross total resection; STR, subtotal resection.
[a]data was shown as mean±standard deviations (range). [b]data was shown as numbers (%).

tract tumors (4.2 years) than in tumors at other sites (11.3 years).

5) OS and PFS on the basis of age at diagnosis in total group

The 10-year OS rates of the age groups were as follows: <5 years, 90.0±6.7%; 5 to <18 years, 100 (*P*=0.005). The 10-year PFS rates were as follows: <5 years, 41.8±11.5%; 5 to <18 years, 63.3±7.0% (*P*=0.043).

6) Clinical parameters affecting the choice of initial treatment modalities in total group

Tumor location was related to the choice of initial treatment modalities (*P*=0.003) (Table 2). Cerebellar tumors and supratentorial tumors were treated via GTR the most frequently, whereas tumors in the brain stem, suprasellar region, or optic tract were primarily treated via STR. Age was also related to the choice of initial treatment modalities. The median age was oldest in GKS group, and youngest in observation group (*P*=0.009). The tumor size was smaller in the observation group than in the GTR and STR groups However, this did not reach to statistical significance (*P*=0.082).

7) PFS on the basis of postoperative treatment modalities in the STR group

In STR group (N=49), 10-year-OS was good as 97.7%, but 10-year-PFS was low as 38.6% The 10-year PFS rates on the basis of postoperative treatment modalities were 71.1%,

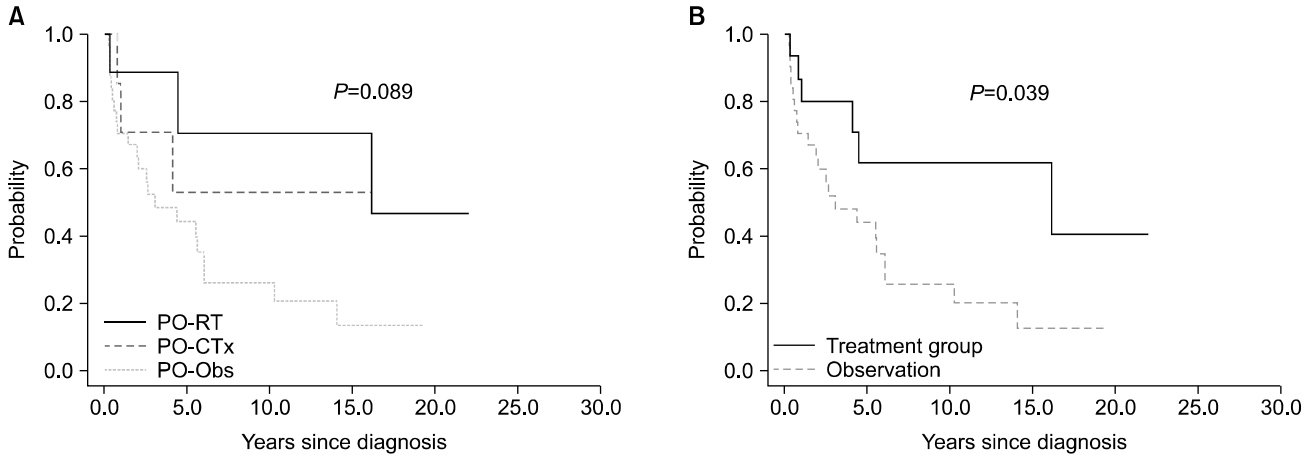

Fig. 3. Progression free survival comparison between treatment group and observation group in subtotal resected patients (N=49). (A) Progression Free Survival by postoperative treatment modalities in STR group. (B) Comparison of progression free survival between treatment group and observation group after STR. PO-CTx, postoperative chemotherapy; PO-Obs, observation after operation; PO-RT, postoperative radiotherapy.

Table 3. Clinical parameters affecting the choice of postoperative treatment modalities in STR group (N=49)

	PO-Obs (N=32)	PO-RT (N=10)	PO-CTx (N=7)	*P*-value
Age (year)[a]	8.0±4.7 (0.9-17.0)	8.4±3.0 (3.7-12.9)	10.0±4,8 (2.1-17.5)	0.553
Tumor size (cm)[a]	4.3±1.6 (1.5-8.0)	3.1±1.0 (2.0-5.0)	4.3±2.5 (1.0-8.0)	0.305
Tumor location[b]				**0.039**
Cerebellar, N=23 (46.9)	19 (82.6)	2 (8.7)	2 (8.7)	
Supratentorial, N=4 (8.2)	3 (75.0)	0 (0.0)	1 (25.0)	
Brain stem, N=5 (10.2)	2 (40.0)	3 (60.0)	0 (0.0)	
Suprasellar, N=5 (10.2)	3 (60.0)	0 (0.0)	2 (40.0)	
Optic tract, N=10 (20.4)	4 (40.0)	4 (40.0)	2 (20.0)	
Spinal cord, N=1 (2.0)	0 (0.0)	1 (100.0)	0 (0.0)	
Thalamus, N=1 (2.0)	1 (100.0)	0 (0.0)	0 (0.0)	

PO-CTx, postoperative chemotherapy; PO-Obs, observation after operation; PO-RT, postoperative radiotherapy.
[a]data was shown as mean±standard deviations (range). [b]data was shown as numbers (%).

53.6%, and 27.0% for the PO-RT, PO-CTx, and PO-Obs, respectively (*P*=0.089) (Fig 3A). The 10-year PFS rate was higher in patients who received postoperative treatment (either PO-RT or PO-CTx) after STR (62.5%) than in patients who received PO-Obs (27.0%; *P*=0.039) (Fig. 3B).

8) Clinical parameters affecting the choice of postoperative treatment modalities in the STR group

Tumors in cerebellar and supratentorial lesions were more commonly observed without further treatment after STR, whereas deep-seated tumors were more frequently treated after STR rather than just observed (*P*=0.039) (Table 3). Age and tumor size did not affect the choice of postoperative treatment modalities.

9) Prognostic factors determined by a multivariate analysis of PFS in the STR group

In a multivariate analysis of PFS in the STR group (N=49), postoperative treatments were favorable factors (PO-RT: HR, 0.13; 95% CI, 0.03-0.59; *P*=0.008; PO-CTx: HR, 0.20; 95% CI, 0.46-0.90; *P*=0.035) (Table 4). Suprasellar (HR, 7.54; 95% CI, 1.55-36.59; *P*=0.012) and optic tract tumors (HR, 5.71; 95% CI, 1.62-20.08, *P*=0.007) were poor prognostic factors. Age and sex were not prognostic factors for progression.

Table 4. Prognostic factors determined by a multivariate analysis of PFS in the STR group (N=49)

	Hazard ratio	95% Confidence interval	*P*-value
Postoperative treatment modalities			
PO-Obs	1		
PO-RT	0.13	0.03-0.59	**0.008**[a]
PO-CTx	0.20	0.46-0.90	**0.035**[a]
Location			
Cerebellar	1		
Supratentorial	1.33	0.35-5.13	0.679
Brain stem	0.62	0.08-4.94	0.651
Suprasellar	7.54	1.55-36.59	**0.012**[b]
Optic tract	5.71	1.62-20.08	**0.007**[b]
Spinal cord	3.36	0.35-32.13	0.293
Thalamus	1.18	0.13-9.31	0.919
Age			
5≤Age<18	1		
Age<5	1.74	0.68-4.48	0.250
Sex			
Male	1		
Female	1.16	0.40-3.31	0.786

PO-CTx, postoperative chemotherapy; PO-Obs, observation after operation; PO-RT, postoperative radiotherapy.
[a]stastically significant good prognostic factors. [b]stastically significant poor prognostic factors.

10) Endocrine dysfunction

Permanent endocrine dysfunction was occurred in six (6.6%) patients; panhypopituitarism (N=2), combined growth hormone and sexual hormone (luteinizing hormone and follicular stimulating hormone) deficiencies (N=2), pure growth hormone deficiency (N=1), and adrenocorticotropic hormone deficiency (N=1). Tumor locations were related with endocrine dysfunctions (*P*=0.039). Five of 31 (16.1%) deep located tumors showed endocrinal dysfunction; brain stem (N=2), suprasellar (N=2) and optic tract (N=1). One of 57 (1.7%) superficial tumors (included cerebellar and supratentorial) showed endocrine dysfunction. No endocrine dysfunction was occurred in 3 spinal tumors. Treatment modalities were not related with endocrine dysfunction, maybe due to insufficient number of events. One of six had received GTR, while other five patients received STR (*P*=0.502). Postoperative treatment after STR did not affect permanent endocrine dysfunction; 3 of 32 (9.3%) in PO-Obs group, 1of 10 (10%) PO-RT group, and 1 of 7 (14.3%) PO-CTx group (*P*=0.210). Age was not related with endocrine dysfunction.

Discussion

PAs are slowly growing WHO grade I tumors, which are generally associated with favorable prognosis. They account for approximately 15-20% of pediatric brain tumors [2,3], and commonly occur in the first two decades of life [5,17,18]. Our study included 91 pediatric PA patients, of which 24 (26.4%) were under the age of five. Tumor locations and clinical symptoms were not different between age groups. In our study, cerebellar tumors were the most prevalent location of PAs (49.5%), followed by the optic tract, supratentorial and brain stem.

Several studies have shown that the extent of resection is a main prognostic factor [6-10,19]. Our study also showed the importance of initial treatment modalities. Aggressive surgery (e.g., GTR) is the best approach for halting tumor progression and extending survival (7). After GTR, the next step is routine follow-up. Our Study showed no recurrence or death after GTR. Compared with patients receiving surgery, patients whose initial treatment modality was observation had the worst outcomes in our study; their 10-year OS and PFS rate was 83.3% and 16.7%, respectively. Observation is typically chosen for PAs in locations not readily accessible, such as the brain stem and optic tract.

Tumor locations are also prognostic factors for PA, mainly because they are related to the extent of resection [4,6,10,17]. Tumors in deep locations, where GTR is not feasible, have a worse prognosis than do tumors in more superficial locations [6,17]. In our study, brain stem, suprasellar, optic tract tumors were associated with tumor progression and reduced survival.

Age at diagnosis was a prognostic factor in some studies. LGG patients less than 5 or 7 years of age had an unfavorable prognosis [7,10].We found that an age less than 5 years was an unfavorable prognostic factor for both OS and PFS.

To treat or observe after STR is the one of the most perplexing problems to clinicians. Many authors recommend the "wait-and-see" policy, which means treatment only after re-progression of the PA and is based on the premise that

OS will be unaffected regardless of whether PFS significantly improves [4,20]. Although the OS rates were not statistically different between the treatment modalities in our study, longer PFS times are important. Tumor progression can result in significant neurologic morbidities [14], and shorter PFS times, especially in patients with brain tumors, negatively affect the quality of life of both patients and caregivers [21].

There had been many debates on the management of LGGs including PAs. Jakola et al. showed that early surgical resection improved survival compared with a "biopsy and watchful waiting strategy" [22]. Other reports of LGGs showed the efficacy of postoperative treatment for progression free survival benefit. The 1996 Hirntumorstudien study of pediatric WHO grade 1 and 2 gliomas showed that PO-RT and PO-CTx improved PFS rates and role of PO-CTx for deferred RT [13]. However, these studies had limitations that apply directly to PA patients who underwent STR patients as in our study. Many studies grouped heterogeneous pathologies such as LGGs or LGAs together and analyzed the efficacy of all treatment modalities together regardless of the clinical situation (e.g., initial, postoperative, or salvage treatment) or the extent of surgery, which is the most important prognostic factor for survival and progression. In addition, some reports only examined specific age groups or specific tumor locations, for example, the cerebellum, where GTR is usually amenable and thus the efficacy of the postoperative treatment is diminished.

Our study was limited to PAs and focused on patients who underwent STR. It compared the effects of postoperative treatment and observation just after STR, which is an unsolved problem among clinicians and patients. Post-STR treatment (PO-RT or PO-CTx) showed an approximate 35% benefit in PFS compared with PO-Obs. This means that 35% of patients remained progression-free for several years, which prevented further potential neurologic complications. Thus, for residual tumors after surgery, treatment appears to be a better option rather than observation.

Neurocognitive dysfunction and endocrine dysfunction are considerable factors, which could be related with tumor progression per se or treatment related toxicity [23]. Our study showed that treatment modalities after STR did not affect endocrine dysfunction, while tumor locations did. However, we could not suggest that whether PO-RT or PO-CTx do not affect endocrine dysfunction in our study, due to insufficient numbers of endocrine dysfunctions.

Our study had limitations. Although our cohort was relatively large for a single institute, which has homogenous treatment policies, our study is retrospective, and may have selection bias. And neurocognitive function was not evaluated fully in our study.

Nevertheless, it had strengths including its restriction to PA pathology, its focus on patients who underwent STR, and its inclusion of all tumor locations and all age groups of pediatric patients. In conclusion, postoperative treatment (either PO-RT or PO-CTx) after STR of PAs can prolong PFS, which will improve the patients' quality of life.

Acknowledgements

The authors would like to thank Dong-Su Jang, MFA, (Medical Illustrator, Medical Research Support Section, Yonsei University College of Medicine, Seoul, Korea) for his help with the illustrations.

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