의학석사 학위논문

성인 다형성 황색 성상세포종의 임상결과

Clinical Experience and Outcomes of Adult Pleomorphic Xanthoastrocytoma

울산대학교 대학원

의 학 과

변준호

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이 논문을 의학석사 학위 논문으로 제출함

2017년 11월

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Abstract

Introduction: PXA is known for clinically indolent tumor, however clinical behavior of PXA is not uniform. The predicting factors of aggressive behaviors of PXA have not been fully elucidated. The purpose of this report is to demonstrate the experiences and clinical outcomes of PXA in our institution, to find prognostic factors of PXA.

Method: Our institutional database was searched for patients aged 18 years or older who underwent surgery and were diagnosed with PXA between 2002 and 2016. Total of 25 patients were identified and analyzed.

Result: There were 8 (32%) male and 17 (68%) female patients. Mean age was 29.9. Most common presenting symptoms was seizure. Most common location of PXA was temporal lobe (11, 44%). Mean tumor size was 33.6 mm (range: 10 to 70 mm). 21 (84%) patients were diagnosed as PXA, WHO grade II and 4 (16%) patients were diagnosed anaplastic PXA, WHO grade III. The perilesional edema was seen on 13 patients (52%). Twenty-one (84%) patients underwent GTR, 4 (16%) of patients underwent STR. Seven (28%) patients received adjuvant radiation therapy. No patient received adjuvant chemotherapy. Recurrence occurred in 11

(44%) patients. High grade transformation was observed in 4 patients (36.4%). Six (24%) patients were died during follow up period. The OS rate of PXA in 1,2,3,5,7 and 10 years were 100%, 89.5%, 89.5%, 89.5%, 61.4% and 40.9% and OS rate of anaplastic PXA in 1,2,3,5,7,10 years were 100%, 100%,100%, 0%, 0% and 0%. The PFS rate of PXA in 6 months, 1,2,3,5 and 7 years were 90.5%, 81%, 70.5%, 65.1%, 65.1% and 52% and PFS rate of anaplastic PXA in 6 months, 1,2,3,5 and 7 years were 100%, 75%, 50%, 50%, 0% and 0%. The differences of OS and PFS between PXA and anaplastic PXA were not statistically significant. (p value= 0.379 and 0.213, respectively. We did comparison the advanced MR imaging (DWI, PWI) and PET finding between PXA and anaplastic PXA. This result failed to show statistical significance. We analyzed the impact of advanced MR findings and PET findings to recurrence rate of PXA grade II. In recurrence group, There were no differences of DWI, PWI and PET findings between recurrence and non-recurrence group. Tumor size larger than 40mm, solid with mixed cystic and hemorrhagic tumor, presence of perilesional edema were poor prognostic factors for PFS (HR=4.394, 11.846, 15.239, p value=0.036, 0.013, 0.01 respectively) were poor prognostic factors in univariate analysis. In multivariate analysis, only

perilesional edema was significant poor prognostic factor. (HR=20.523, *p* value=0.009) We did comparison characteristics between post-treatment silent PXA grade II group and recurrent PXA (grade II) group. In recurrent PXA grade II group, the rate of presence of peritumoral edema was 87.5%, while in silent PXA grade II group, the rate of presence of peritumoral edema was 23.1%. This difference showed statistically significance. (p value= 0.008). A PXA grade II grading system was constructed using the 3 variable, size, peritumoral edema and tumor type. Score 1 to 2 were classified low risk and score 3 to 4 were high risk. Tumor progression and recurrence was predicted according to PXA grade II group, 5-year progression-free survival was 80.2% in low risk group and 20% in high risk group. (*p value*= 0.025)

Conclusion:. To our limited knowledge, tumor size, solid plus cyst and hemorrhage tumor type and peritumoral edema of PXA is associated with poorer progression free survival in univariate analysis. DWI, PWI and PET findings of PXA can't expect clinical behavior and grade of the PXA. PXA show high recurrence rate, thus close follow up is needed. In the future, multicenter larger size prospective study should be needed.

Keywords

Pleomorphic xanthoastrocytoma, peritumoral edema, recurrence, outcome, scoring system

차 례

표 및그림목차

Introduction

Pleomorphic xanthoastrocytoma (PXA) was first described by Kepes et al. in 1979.[1,2] This rare neoplasm accounts for 1% of all astrocytic tumors.[3] It was firstly added to the World Health Organization (WHO) classification of tumors in 1993.[4] The latest updated 2016 WHO classifications reclassified PXA and "anaplastic PXA" which requires 5 or more mitoses per 10 high-power fields and necrosis maybe present. Both of PXA and anaplastic PXA are corresponded grade II and grade III.[5]

PXA is known for clinically indolent tumor, however clinical behavior of PXA is not uniform. Giannini et al. investigated 71 patients of PXA, they reported favorable outcomes of 81% 5 years overall survival and 72% 5 years recurrence free survival.[6] However, some authors reported the fatal outcomes and malignant transformation potential of PXA, the early report of Weldon-Linne et al, they reported fatal outcome of PXA which death of 21 months after diagnosis and other series reported 35% of the malignant transformation of PXA[7,8]. The recurrence rates of PXA was reported 29 to 33% and overall mortality rate 15 to 30%.[3,9] From the recent report of Oh et al., they reported that favorable 10-year survival rate of 94%, while

78% patients experienced recurrence.[10]

Studies of imaging aspects of PXA demonstrated that theses tumor are often involve supratentorial region and frequently located on temporal lobe.[6] Solid, cystic, mixed solid and cystic tumor can be present on imaging and solid portion usually show intense enhancement after the use of contrast.[11,12] Kepes et al. reported superficial cortical located tumor showed favorable outcomes and according to previous published study, high mitotic index ≥ 5/10HPF, extent of resection;non-gross total resection, old age, BRAF V600E non-mutant are associated with poorer prognosis of PXA.[1,10,13] Etzl et al. insisted positron emission tomography (PET) findings was associated with aggressive clinical behaviors of PXA.[1,14] However, the predicting factors of aggressive behaviors of PXA have not been fully elucidated.

Conventional MR findings, diffusion weighted magnetic resonance image (DWI-MRI), perfusion-weighted MRI, and PET scan are used for radiological differential diagnosis of brain neoplasm recently. For now, there have been lack of study for relation between adult PXA's conventional magnetic resonance imaging (MRI) findings, diffusion weighted MRI, perfusion weighted MRI, brain PET scan findings and its clinical impacts.

The purpose of this report is to demonstrate the experiences and clinical outcomes of PXA in our institution, to find prognostic factors of PXA, potential value of radiologic findings as an indicator of recurrence and aggressive behavior.

Materials and method

This study was approved by our institutional review board. Our institutional database was searched for patients aged 18 years or older who underwent surgery and were diagnosed with PXA between 2002 and 2016. Only newly diagnosed cases were enrolled and those of underwent surgery in other institution, recurrent tumors with unavailable information on primary tumor were excluded. Thus, a total of 25 patients were identified and analyzed. All patient clinical, radiological and surgical records were obtained and reviewed. The histologic specimens were reexamined by our institutional neuropathologist, who reclassified the "PXA and "Anaplastic PXA" following the 2016 WHO classification of Central Nervous System Tumors.

The extent of resection was defined as following criteria. Gross total resection (GTR) was defined as tumor was removed totally under the gross examinations, Subtotal resection (STR)

was defined as tumor was remained in grossly but less than 10% of tumor was leaved. Biopsy was defined as obtained tissue for histopathologic examination and remained over 10% of the tumor.

The size of the tumor was defined by the maximal tumor diameter in the two dimensions. The type of tumor was classified 4 subtypes, solid, solid plus cystic portion, hemorrhagic tumor and solid plus cystic, hemorrhagic tumor. The PXA is known for circumscribed astrocytoma, the extent of perilesional edema was defined high signal intensity lesion on T2-weighted MRI of adjacent the circumscribed lesion. We also obtained the findings of diffusion weighted image (DWI), perfusion weighted image (PWI) of MRI and brain fludeoxyglucose F18 (FDG)-positron-emission tomography (PET) scan.

Diffusion MR imaging, performed using a spin-echo sequence with *b*_0 and *b*_1000 seconds/mm2. ADC maps were generated with a monoexponential fit on a voxel-to-voxel basis for all imaging planes. When diffusion MR imaging was available, DWI image and apparent diffusion coefficient (ADC) map were checked simultaneously. High signal intensity on DWI and low signal intensity on ADC was considered “diffusion restriction”.

Perfusion weighed image was obtained as a DSC study (1700/31.5/90, FOV 24 cm; section thickness 5 mm; matrix 128*128; no gap). Gadovist 0.1 ml/kg, 1 mmol/l concentration was injected at

5 ml/s for each of the DSC studies. The DSC was followed by a post-gadolinium threedimensional

T1 fast spoiled gradient echo (FSPGRE) (8.5/4.2, FA 20, FOV 22 cm, matrix 270*270, NEX 1).

The PET scans were performed with fluorodeoxyglucose (FDG), a measure of cerebral glucose use. The scanner produces 31 transaxial slices with a center-to-center slice separation of 3.4 mm, a 10.8-cm axial field of view, and in-plane resolution of 5.8 to 7.7 mm full width at half maximum in the center of the field of view and an axial resolution of 5.0 to 7.1 mm full width at half maximum. Attenuation correction was performed using a standard ellipse fitting method with an attenuation coefficient of 0.95 cm-1 or measured attenuation using an external 68Ge ring source with 20 minutes of data acquistion. An infusion of 0.143 mCi per kilogram body weight of FDG was administered.

Initial follow-up involves clinical evaluation and MRI at 1 month after surgery, 6 months, 1 year and check annually thereafter.

Subgroup comparison was performed using Student T-test, Mann-whitney test, Chi-square test and Fisher's exact test. We also investigated the overall survival (OS) and progression-or recurrence free survival (PFS) of our patients as well as prognostic factors. The OS period was defined as the time between the date of the initial diagnosis and the date of death and the PFS period was defined as the time between the date of the initial treatment and the date of tumor recurrence or progression based on radiologic findings. OS and PFS were analyzed using Kaplan-Meier survival analysis and subgroup comparisons were performed using log rank test. Prognostic factor including age, sex, histology, tumor size, tumor type, extent of resection, calcification, perilesional edema, DWI, PWI and PET findings for OS and PFS was analyzed using Cox-proportional Hazard model. All statistical analysis was conducted using SPSS ver. 18.0 (SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

Result

Patient demographics

There were 8 (32%) male and 17 (68%) female patients. Mean age was 29.9 years (range: 18 to 60 years). Most common presenting symptoms was seizure (48%) following headache (32%), motor weakness (8%), visual disturbance (4%), dizziness (4%). Most common location of PXA was temporal lobe (11, 44%), following frontal lobe (7, 28%), occipital lobe (2, 8%), cerebellum (2 ,8%), suprasellar area (1, 4%), fourth ventricle (1, 4%), and thalamus (1, 4%). Mean tumor size was 33.6 mm (range: 10 to 70 mm). We divided 4 subgroup of tumor type, solid type tumor composed 12 (48%), solid plus cystic portion was 10 (40%), hemorrhagic tumor was 1 (4%) and solid plus cystic with hemorrhagic tumor was 2 (8%). 21 (84%) patients were diagnosed as PXA, WHO grade II and 4 (16%) patients were diagnosed anaplastic PXA, WHO grade III. The detailed basal demographic findings of adult PXA was described on Table 1.

Table 1. Basal demographic findings of patients of adult pleomorphic xanthoastrocytoma (PXA)

Sex	Male	8 (32%)
	Female	17 (68%)
	Male : Female ratio	0.47
Age (years)	Mean	29.9 (range: 18 to 60)
	Median	29
Presenting Symptoms	Seizure	12 (48%)
	Headache	8 (32%)
	Motor weakness	2 (8%)
	Visual disturbance	1 (4%)
	Dizziness	1 (4%)
	Incidental findings	1 (4%)
Tumor location	Frontal	7 (28%)
	Temporal	11 (44%)
	Parietal	0
	Occipital	2 (8%)
	Cerebellum	2 (8%)
	Suprasellar	1 (4%)
	4^{th} ventricle	1 (4%)
	Thalamus	1 (4%)
Tumor size (mm)	Mean	33.6 (range: 10 to 70)
	Median	30
Tumor type	Solid	12 (48%)
	Solid + cyst	10 (40%)
	Hemorrhagic tumor	1 (4%)
	Solid + cyst and hemorrhage	2 (8%)
Histology	PXA* (WHO† grade II)	21 (84%)
	Anaplastic PXA (WHO grade III)	4 (16%)

* PXA: pleomorphic xanthoastrocytoma, †WHO: World Health Organization

Radiologic findings

Brain computed tomography (CT) scan was examined in 21 of 25 patients. Seven (33.3%) of patients presented isodense, 13 (61.9%) patients presented hyperdense and 1 (4.8%) presented hypodense mass. On T1-WI, 22 (88%) patients showed low signal intensity lesion, 2 (8%) patients showed iso-signal intensity and 1 (4%) patients showed mixed signal intensity. On T2-WI, 24 (96%) showed high signal intensity lesion, 1 (4%) patient showed mixed-signal intensity. 24 (96%) patients showed enhancement on gadolinium enhanced T1-WI. Calcification of the tumor was noted on 3 (12%) patients. The perilesional edema was seen on 13 patients (52%). We divided two subgroup of perilesional edema according to extent, larger than 1cm and smaller than 1 cm size, 9 (36%) patients showed larger than 1cm size edema and 4 (16%) patients showed smaller than 1cm size edema.

15 of 25 patients were examined DWI. 10 of 15 (66.7%) patients showed diffusion restriction of the tumor on DWI and 5 of 15 (33.3%) patients did not show diffusion restriction on DWI.

13 of 25 patients were examined PWI, 10 of 13 (76.9%) patients showed increased perfusion of the tumor and 3 (23.1%) patients did not show increased perfusion of the tumor. 15 of 25 patients was examined brain PET scan, 12 of 15 (80%) patients showed increased FDG uptake of the tumor, 3 of 15 (20%) patients did not show increased FDG uptake of the tumor. The detailed radiologic findings of PXA was described on Table 2 and Figure 1.

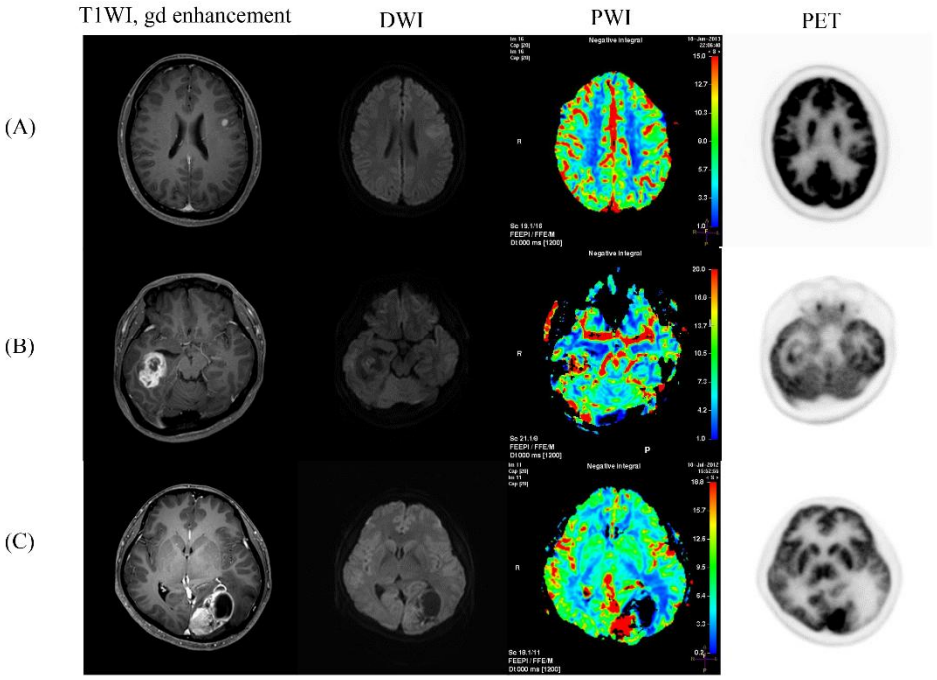
Table 2. Image findings of patients of adult pleomorphic xanthoastrocytoma

CT* scan (21 of 25 patients)	Isodense	7 (33.3%)
	Hyperdense	13 (61.9%)
	Hypodense	1 (4.8%)
MR† T1-WI€	Low-signal intensity	22 (88%)
	Iso-signal intensity	2 (8%)
	High-signal intensity	0
	Mixed-signal intensity	1 (4%)
MR T2-WI £	Low-signal intensity	0
	Iso-signal intensity	0
	High-signal intensity	24 (96%)
	Mixed-signal intensity	1 (4%)
MR T1-WI gadolinium enhancement	No-enhancement	1 (4%)
	Enhancement	24 (96%)
Calcification	Present	3 (12%)
	Absent	22 (88%)
Peritumoral edema	Absent	12 (48%)
	Present	13 (52%)
	≤1cm	4 (16%)
	>1cm	9 (36%)
MRI-DWI†† (15 of 25 patients)	Diffusion restriction	10 (66.7%)
	No diffusion restriction	5 (33.3%)
MRI-PWI€€ (13 of 25 patients)	Normal perfusion	3 (23.1%)
	Hyperperfusion	10 (76.9%)
Brain PET ¥ scan (15 of 25 patients)	No hypermetabolic lesion	3 (20%)
	Hypermetabolic lesion	12 (80%)

*CT: computed tomography, † MR: magnetic resonance imaging, € T1-WI: T1 weighted image, £ T2-WI: T2 weighted image, † † DWI: diffusion weighted image, € € PWI:

perfusion weighted image, ￥PET: positron emission tomography

Figure 1. Radiologic findings of adult pleomorphic xanthoastrocytoma



Legend: (A) frontal lobe PXA: T1WI gadolinium(gd) enhancement MRI show small enhancing nodule on left frontal lobe, this lesion show diffusion restriction on DWI and increasing perfusion on PWI. PET scan shows focal hypermetabolic lesion on left frontal lobe with adjacent cortical hypometabolism. (B) Temporal lobe PXA: T1WI gd enhancement image show irregular shape enhancing lesion on right temporal lobe. This lesion show diffusion restriction on DWI and increasing perfusion on PWI. PET scan shows hypermetabolism. (C) Occipital lobe PXA the tumor contain cystic portion and show strong enhancement of solid portion of the tumor. Diffusion restriction and hyperperfusion are seen on DWI and PWI. PET scan shows hypermetabolism.

Treatment and prognosis

Twenty-one (84%) patients underwent GTR, 4 (16%) of patients underwent STR. Seven (28%) patients received adjuvant radiation therapy, these patients were composed of 4 patients of anaplastic PXA, 1 patient of after GTR for PXA grade II (diagnosed PXA with anaplastic features according to 2007 WHO classification), 2 patients of after STR for PXA grade II). No patient received adjuvant chemotherapy. Recurrence occurred in 11 (44%) patients, 10 of 11 (90.9%) patients were local recurrence, 1 of 12 (9.1%) patient was distant recurrence. High grade transformation was observed in 4 patients (36.4%). Postoperative surgical complication was occurred in 2 patients (8%), 2 patients' postoperative complication were epidural hematoma (EDH). Seizure control rate after surgery was 100% (12 of 12 patients). Six (24%) patients were died during follow up period. All patients' cause of death was disease progression. Mean follow up period was 51.4 months (range: 2 to 112 months). Detailed of treatment of outcomes of adult PXA patients were described on Table 3.

The OS rate of PXA in 1,2,3,5,7 and 10 years were 100%, 89.5%, 89.5%, 89.5%, 61.4% and 40.9% and OS rate of anaplastic PXA in 1,2,3,5,7,10 years were 100%, 100%,100%, 0%, 0%

Table 3. Treatment outcomes of patients of adult PXA

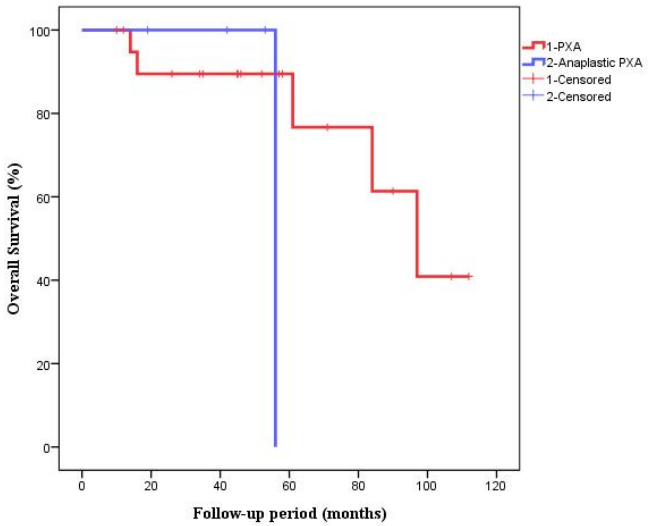
Extent of resection	GTR*	21 (84%)
	STR†	4 (16%)
Adjuvant treatment	Radiation therapy	7 (28%)
	Chemotherapy	0
Recurrence	Absent	14 (56%)
	Present	11 (44%)
	Local recurrence	10 (90.9%)
	Distant recurrence	1 (9.1%)
	High grade transformation	4 (36.4%)
Postoperative complications	Postoperative EDH€	2 (8%)
Seizure control	Improvement	12/12 (100%)
Death		6 (24%)
Follow up period (months)	Mean	51.4 (range: 10 to 112)
	Median	46

*GTR: gross total resection, † STR: subtotal resection, € EDH: epidural hematoma

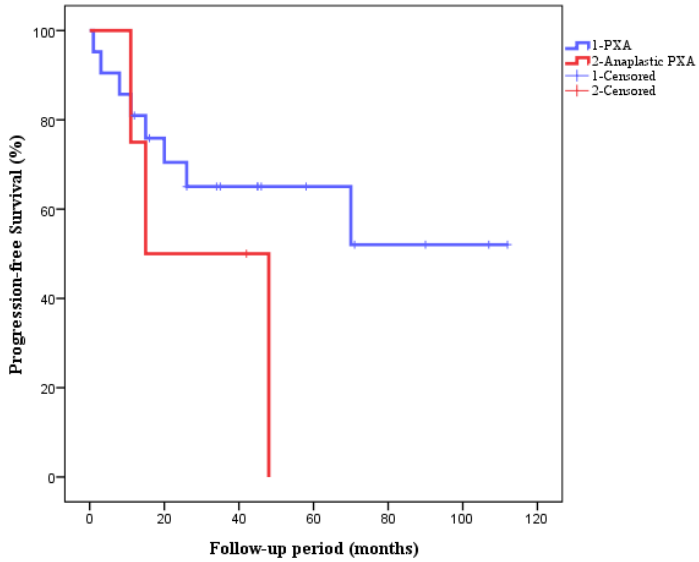
and 0%. The PFS rate of PXA in 6 months, 1,2,3,5 and 7 years were 90.5%, 81%, 70.5%, 65.1%, 65.1% and 52% and PFS rate of anaplastic PXA in 6 months, 1,2,3,5 and 7 years were 100%, 75%, 50%, 50%, 0% and 0%. The differences of OS and PFS between PXA and anaplastic PXA were not statistically significant. (p value= 0.379 and 0.213, respectively.) The Kaplan Meier survival analysis was described on Figure 2.

We did comparison the advanced MR imaging (DWI, PWI) and PET finding between PXA and anaplastic PXA. In PXA grade II group, diffusion restriction on DWI was shown in 6 of 11 patients (54.5%), increasing perfusion on PWI was shown in 6 of 9 patients (66.7%) and 8 of 11 patients (72.7%) showed hypermeatbolism on brain PET scan. While, in anaplastic PXA group, all examined patients showed diffusion restriction on DWI, increasing perfusion on PWI and hypermetabolism on brain PET scan. This result failed to show statistical significance. (p value= 0.231, 0.497 and 0.516, respectively) We analyzed the impact of advanced MR findings and PET findings to recurrence rate of PXA grade II. In recurrence group, diffusion restriction on DWI was shown in 3 of 5 patients (60%), increasing perfusion on PWI was shown in 3 of 4 patients (75%) and hypermetabolism was shown in 4 of 6 patients (66.7%). In

Figure 2. **Overall and progression-free survival of patients of adult pleomorphic xanthoastrocytoma.**



Histology	1-year	2-year	3-year	5-year	7-year	10-year	P value
PXA	100%	89.5%	89.5%	89.5%	61.4%	40.9%	
Anaplastic PXA	100%	100%	100%	0%	0%	0%	0.379



Histology	6 months	1-year	2-year	3-year	5-year	7-year	P value
PXA	90.5%	81%	70.5%	65.1%	65.1%	52%	
Anaplastic PXA	100%	75%	50%	50%	0%		0.213

non-recurrence group, 3 of 6 patients (50%) showed diffusion restriction on DWI, 3 of 5 (60%) patients showed increasing perfusion on PWI and 4 of 5 patients (80%) showed hypermetabolism on brain PET scan. There were no differences of DWI, PWI and PET findings between recurrence and non-recurrence group. (p value= 1.000, 1.000, 1.000, respectively). The detailed was described on Table 4 and 5.

We analyzed prognostic factors for OS and PFS of adult PXA including age, sex, histology, size, tumor type, extent of resection, presence of calcification, perilesional edema, diffusion restriction on DWI, increasing perfusion on PWI and hypermetabolism on brain PET scan. In univariate analysis, we failed to find risk factors for OS. Tumor size larger than 40mm, solid with mixed cystic and hemorrhagic tumor, presence of perilesional edema were poor prognostic factors for PFS (HR=4.394, 11.846, 15.239, p value=0.036, 0.013, 0.01 respectively) were poor prognostic factors in univariate analysis. In multivariate analysis, only perilesional edema was significant poor prognostic factor. (HR=20.523, p value=0.009) The detailed was described on Table 6.

We did comparison characteristics between post-treatment silent PXA grade II group and

Table 4. The differences of advanced MR imaging and brain PET findings between PXA grade II and anaplastic PXA.

Modality		PXA grade II	Anaplastic PXA	P value
Diffusion weighted MR imaging	Diffusion restriction	6/11 (54.5%)	4/4 (100%)	0.231
	No diffusion restriction	5/11 (45.5%)	0/4	
Perfusion weighted MR imaging	Normal perfusion	3/9 (33.3%)	0/4	0.497
	Hyperperfusion	6/9 (66.7%)	4/4 (100%)	
Brain PET	No hypermetabolism	3/11 (27.3%)	0/4	0.516
	Hypermetabolism	8/11 (72.7%)	4/4 (100%)	

Table 5. The differences of advanced MR imaging and brain PET findings between recurrence group and non-recurrence group of PXA grade II.

Modality		Recurrence group	Non-recurrence group	P value
Diffusion weighted MR imaging	Diffusion restriction	3/5 (60%)	3/6 (50%)	1.000
	No diffusion restriction	2/5 (40%)	3/6 (50%)	
Perfusion weighted MR imaging	Normal perfusion	1/4 (25%)	2/5 (40%)	1.000
	Hyperperfusion	3/4 (75%)	3/5 (60%)	
Brain PET	No Hypometabolism	2/6 (33.3%)	1/5 (20%)	1.000
	Hypermetabolism	4/6 (66.7%)	4/5 (80%)	

Table 6. Univariate and multivariate analysis of risk factors of adult pleomorphic xanthoastrocytoma

		Univariate analysis				Multivariate analysis			
		Overall Survival		Progression-Free Survival		Overall Survival		Progression-Free Survival	
		HR*	*p* value	HR	*p* value	HR	*p* value	HR	*p* value
Age (years)	≥ 30	6.658	0.08	2.518	0.147				
Sex	Male								
	Female	55.517	0.259	6.046	0.089				
Histology	PXA grade II								
	Anaplastic PXA	2.836	0.399	2.288	0.231				
Size	> 40mm	1.709	0.559	**4.394**	**0.036**			1.767	0.544
Location	Cortical								
	Deep	2.889	0.247	2.162	0.265				
Tumor type	Solid								
	Solid + cyst	1.043	0.964	0.830	0.799				
	Hemorrhagic tumor	0.000	0.995	4.510	0.193				
	Solid + cyst and hemorrhage	0.000	0.993	**11.846**	**0.013**			2.108	0.522
Extent of resection	GTR†	24.618	0.678	1.686	0.621				
	STR€								
Radiologic findings	Calcification (+)	0.029	0.387	0.493	0.509				
	Peritumoral edema								
	Absence								
	Presence	71.619	0.248	**15.239**	**0.01**			**20.523**	**0.009**

Advanced MRI findings	Diffusion restriction	1.544	0.712	1.140	0.876
	Hyperperfusion	26.605	0.778	0.915	0.936
PET ￥findings	Hypermetabolism	3.108	0.330	3.585	0.255

*HR: hazard ratio, †GTR: gross total resection, €STR: subtotal resection, ￥PET: positron emission tomography

recurrent PXA (grade II) group. We compared sex, age, tumor location, tumor size, tumor type, presence of calcification, presence of peritumoral edema, extent of resection and adjuvant treatment between two groups. All parameter except perilesional edema did not show difference. In recurrent PXA grade II group, the rate of presence of peritumoral edema was 87.5%, while in silent PXA grade II group, the rate of presence of peritumoral edema was 23.1%. This difference showed statistically significance. (p value= 0.008). The detailed was described on Table 7.

Proposed PXA grade II grading system

A PXA grade II grading system was constructed using the 3 variable, size, peritumoral edema and tumor type. Size, solid plus cyst and hemorrhagic type and peritumoral edema were weighted by the beta coefficient estimates in the univariate analysis of prognostic factors. The grades were assigned that ranged from 1 to 4 points. (Table 8) Score 1 to 2 were classified low risk and score 3 to 4 were high risk. Tumor progression and recurrence was predicted according to PXA grade II group, 5-year progression-free survival was 80.2% in low risk group and 20% in high risk group. (*p value*= 0.025) The difference of PFS between low-risk and high-risk

Table 7. Comparison characteristics of post-treatment silent PXA (grade II) and recurrent PXA (grade II) group.

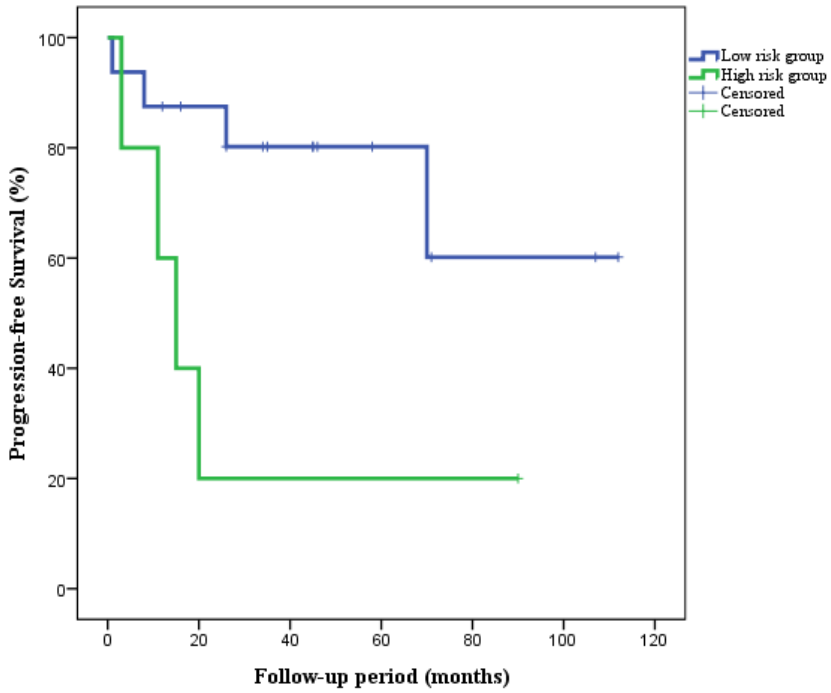
		Silent group (N=13)	Recurrence group (N=8)	P value
Sex	Male	7 (53.8%)	1 (12.5%)	
	Female	6 (46.2%)	7 (87.5%)	0.085
Age (years)	Mean	25.8	33.6	0.121
Tumor location	Frontal	2 (15.4%)	3 (37.5%)	0.067
	Temporal	8 (61.5%)	1 (12.5%)	
	Parietal	0	0	
	Occipital	1 (7.7%)	1 (12.5%)	
	Cerebellum	0	2 (25%)	
	Suprasellar	1 (7.7%)	0	
	4^{th} ventricle	1 (7.7%)	0	
	Thalamus	0	1 (12.5%)	
Tumor size (mm)	<40mm	11 (84.6%)	4 (50%)	0.146
	>40mm	2 (15.4%)	4 (50%)	
Tumor type	Solid	6 (46.2%)	3 (37.5%)	0.225
	Solid + cyst	7 (53.8%)	3 (37.5%)	
	Hemorrhagic tumor	0	0	
	Solid + cyst and hemorrhage	0	2 (25%)	
Calcification	Absent	11 (84.6%)	8 (100%)	0.505
	Present	2 (15.4%)	0	
Peritumoral edema	Absent	10 (76.9%)	1 (12.5%)	
	Present	3 (23.1%)	7 (87.5%)	**0.008**
Extent of resection	GTR*	11 (84.6%)	7 (87.5%)	
	STR†	2 (15.4%)	1 (12.5%)	1.000
Adjuvant treatment	Radiation therapy	2/13 (15.4%)	1/8 (12.5%)	1.000

Follow up period (months)	Mean	56.4	48.0	0.612

*GTR: gross total resection, † STR: subtotal resection

group was demonstrated on Figure 4.

Figure 3. **Progression-free survival difference of patients of adult pleomorphic xanthoastrocytoma according to low and high risk group in suggestive scoring system**



	6 months	1-year	2-year	3-year	5-year	7-year	P value
Low risk group	93.8%%	87.5%	87.5%	80.2%	80.2%	60.2%	
High risk group	80%	60%	20%	20%	20%		0.025

Discussion

PXA was first described by Kepes et al. and it was added firstly WHO classification of the tumors 1993.[1,4] In 2007, the WHO classification classified PXA as a grade II tumor and mentioned about "with anaplastic features". PXA with anaplastic features demonstrated variable levels of necrosis and/or ≥5 mitoses per high power field(HPF).[15] However, in 2007 WHO classifications, PXA and PXA with anaplastic features are both classified grade II tumor. The latest updated 2016 WHO classification of the tumors reclassified PXA and anaplastic PXA which requires 5 or more mitoses per 10 high-power fields and anaplastic PXA categorized the WHO grade III tumors.[5]

Clinical and histologic finding

PXA is known for very rare, low grade glial neoplasm and usually occur in younger age group, so symptomatic control and long-term survival outcomes are most important consideration when manage PXA. In our series, mean age of patients was 29.9 years and show temporal lobe predilection (44%). Most common presenting symptom was seizure (48%). PXA is already known for that presented by seizure and show its location of temporal lobe predilection.[3] Our

study shows consistent result compared to previously published study. In our study, 21 of 25 (84%) patients were PXA and 4 of 25 (16%) patients were anaplastic PXA, WHO grade III. However, we did not find the survival differences between PXA and anaplastic PXA, we suspect that this finding comes from the lack of sufficient patient number of anaplastic PXA; our study only included 4 patients of anaplastic PXA, the number of patients of anaplastic PXA is too small to obtain meaningful result. During follow up period, 11 (44%) of patients experienced recurrence. 5-year progression or recurrence free survival rates of PXA and anaplastic PXA were 65.1% and 0%. In our series recurrence group, 4 (36.4%) patients of PXA grade II underwent malignant transformation to anaplastic PXA (3 patients) and glioblastoma multiforme (1 patient). The recurrence rate and malignant transformation potential of PXA in our study are similar to previous report.

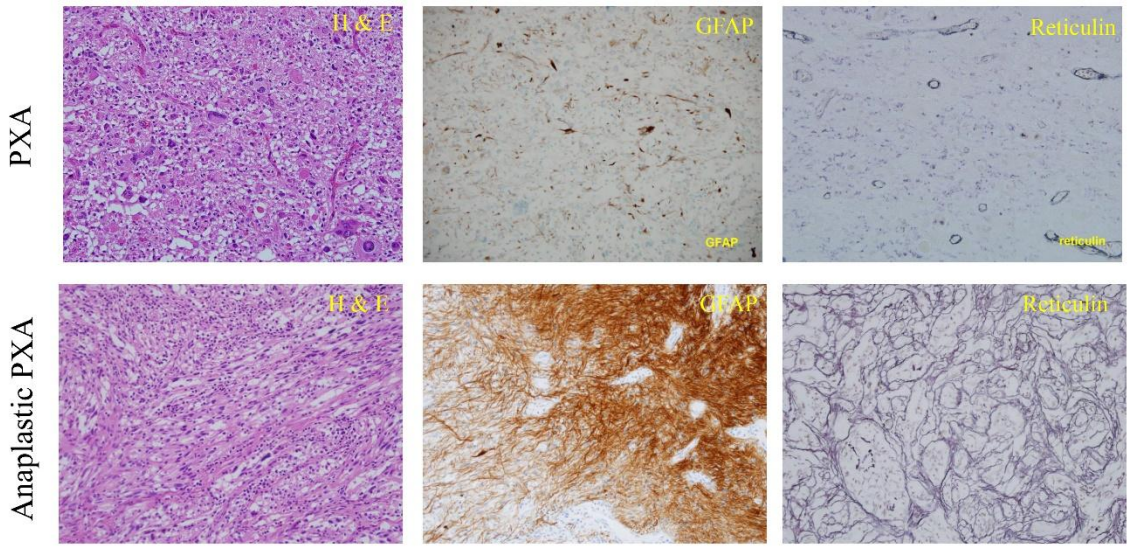
Histological criteria of PXA include pleomorphic tumor cells with giant nuclei, xanthomatous cell, abundant reticulin fiber deposition in the stroma. The presence of GFAP suggests astrocytic origin. In anaplastic PXA, significant mitotic activity (5 or more mitoses per 10 HPF) should be seen. (Figure 4) Necrosis and endothelial proliferation can be seen on PXA. Pahapill

et al. reported the necrosis of PXA associated to poorer overall survival.[16] Also, Nasuha et al. reported that the typical histological features including absence of mitoses, necrosis and endothelial proliferation were generally considered to be the reason for the slow growth of PXA.[17] However, Nakajima et al. reported the case of PXA grade II which transform to glioblastoma without mitosis, necrosis and endothelial hyperplasia in initial histology. The clinical impact of necrosis and endothelial hyperplasia still debate.

Radiological findings

In the imaging aspects of PXA, Lucato mentioned that the features of PXA is variable and the key is in the name of PXA.[18] Consistent with the name "pleomorphic," the imaging features of PXAs are varied and it make preoperative diagnosis difficult. Yu et al. reported MR findings of 19 patients of PXA, in their report, 89.4% of tumors were located in the brain surface and other 10.6% of tumors located deeper area. They divided tumor into 3 morphological subgroup, 21% of tumors were cystic, 36.8% of tumors were mixed cystic-solid, and 42.1% were solid.

Figure 4. Histopathologic findings of adult pleomorphic xanthoastrocytoma



Legend: Spindly element are intermingled with mono- or multinucleated giant astrocytes, the nuclei show great variation in size and staining. Large xanthomatous cells showing intracellular accumulation of lipids. In anaplastic PXA, significant mitotic activity (5 or more mitoses per 10 HPF seen). GFAP stains generally make the astrocytic character and are usually positive in PXA. Reticulin is important pathologic marker of PXA. (best seen using silver impregnation).(x 100, respectively). H & E: hematoxylin and eosin stain, GFAP: glial fibrillary acidic protein, HPF: high power field.

Solid components of tumors were low signal intensity or iso-signal intensity on T1-WI and slightly hyperintense on T2-WI. 89.4% of tumors showed contrast enhancement.[19] In our series, 80% of tumors located brain surface and 20% of tumors located deeper area. The unusual location was 2 (8%) cerebellum, 1 (4%) suprasella, 1 (4%) fourth ventricle, and 1 (4%) thalamus. We divided tumors morphological type into 4 subgroup, solid, solid with cyst, hemorrhagic, solid with hemorrhage and cyst. Most common type of tumor was solid (12, 48%) following solid with cyst 10 (40%), hemorrhagic tumor 1 (4%) and solid with hemorrhage and cyst 2 (8%). The tumors morphological type isn't associated with the OS and PFS. Solid with hemorrhage and cyst type is poor prognostic factor of PFS in univariate analysis (HR: 11.846, p=0.013), it did not show statistical significance on multivariate analysis. In comparison of silent and recurrent group of grade II PXA, all of solid with cyst and hemorrhagic tumor experienced recurrence, however it didn't show statistical significance.

On MRI T1-WI, 96.3% of tumors showed low-signal intensity or iso-signal intensity. On MRI T2-WI, 96% of tumors showed high signal intensity. Our results of MRI findings are consistent with previously report.

Peritumoral cerebral edema can be seen in brain tumor patient. The developing mechanism of peritumoral edema is known for vasogenic, but there are suggestive complex mechanism.[20,21] In our study, 52% of tumors showed peritumoral edema. We divided this extent of peritumoral edema larger than 1cm and smaller than 1cm. 4 (16%) of tumors showed peritumoral edema smaller than 1cm and 9 (36%) of tumors showed larger than 1cm perilesional edema. Schoeneggera et al. reported that peritumoral edema is the independent poor prognostic factor in high grade glioma.[22] In early report of Tien et al., they speculate that peritumoral edema is related to aggressive clinical behavior of PXA, however they only experienced 1 case of tumor with peritumoral edema underwent recurrences.[12] In our study, peritumoral edema is independent poor prognostic factor of progression-free survival. Presence of peritumoral edema's hazard ratio (HR) was 20.523, *p* value was 0.009 in multivariate analysis. We divided the extent of peritumoral edema into larger than 1cm and smaller than 1cm, the lack of adequate patient number, thus we analyzed the difference between absence and presence of peritumoral edema. In comparison between non-recurrent (silent) PXA grade II and recurrent PXA, the rate of tumor with peritumoral edema was

significantly higher in recurrent PXA group. (87.5% versus 23.1%, *p* value=0.008) From our result, we strongly speculate that peritumoral edema in PXA tumor associated with recurrence. The cause of peritumoral edema was extravasation of the fluid through flaw of the brain tumor microvasculature. However, some authors described the cause of peritumoral edema is complex and suggest the role of vascular endothelial growth factor.[20,21] For now, the role of peritumoral edema in recurrence of PXA haven't been unveiled. The mechanism and clinical impact of peritumoral edema of PXA research should be needed.

Diffusion weighted MR image (DWI) has been used extensively in the evaluation of brain tumors. DWI help to evaluate tumor grading, differential diagnosis of the tumor.[23] High signal intensity on DWI and low Apparent diffusion coefficient (ADC) value in the brain tumor reflect high cellularity. High cellularity suggest high grade tumor among the glial neoplasm.[24] In our study, 15 of 25 patients were examined DWI. 4 of 4 (100%) of anaplastic PXA showed diffusion restriction on DWI. However, 6 of 11 (54.5%) patients of PXA also showed diffusion restriction on DWI. In PXA (WHO grade II) group, there was no difference of diffusion restriction rate between recurrence group and non-recurrence group.

Perfusion MRI findings can implicate higher grade tumor and can distinguish treatment effects from the true tumor progression.[25] In our study, 13 of 27 patients were examined PWI. 4 of 4 (100%) anaplastic PXA showed increasing perfusion on PWI. 6 of 9 (66.7%) patients of PXA showed increasing perfusion on PWI. The differences of PWI findings did not show statistical significance. In PXA (WHO grade II) group, there was no difference of increasing perfusion rate between recurrence group and non-recurrence group.

According to our result, although the limited result and knowledge, DWI and PWI can't expect the aggressiveness and higher grade of PXA. PXA is very rare and unique circumscribed astrocytic neoplasm, as mentioned above, it showed variable clinical and radiologic findings. In our limited knowledge, there are no pathognomonic radiological findings of PXA, only peritumoral edema of PXA was associated with the PFS in multivariate analysis.

Brain PET study have been used widely to evaluate brain tumor and PET findings of glioma may provide an independent measure of the aggressiveness of a brain tumor and it may play role of supplement pathologic grading.[26] PET is adjunct radiological tool of brain tumor, in

the recent PET have been used with DWI, PWI to make differential diagnosis of the PXA. However, in our study, brain PET findings could not differentiate the tumor grade (PXA grade II versus anaplastic PXA) and it also failed to predict the aggressiveness. Thus, its ability to predict aggressive clinical behavior of the tumor could not adopt directly in PXA patients.

Treatment and prognosis of PXA

In our study, 21 (84%) patient underwent GTR, 4 (16%) patients underwent STR. 7 patients underwent postoperative radiation therapy (RT). The standard treatment guideline of PXA have not been established. In our institution, after GTR of PXA grade II, we did not give further treatment such as RT and chemotherapy. However, in anaplastic PXA, postoperative adjuvant RT was given to patients routinely even though the tumor was resected gross totally.

Perkins et al. reported in their SEER analysis, extent of resection is the independent prognostic factors of PXA.[27] Giannini et al. reported EOR of PXA is single factor associated recurrence free survival but no OS.[6] However, some authors also reported EOR did not associated with OS and PFS. [3,10] In our study, EOR did not affect the OS and PFS of PXA.

Thus, for now, EOR is equivocal factors for OS and PFS.

The effectiveness of RT and chemotherapy for PXA are still controversial. Several authors reported that adjuvant RT showed no beneficial for prognosis of PXA.[3,10,13,28] However, because of the higher recurrence rate of PXA, we can't help considering the adjuvant RT and chemotherapy. In our series, adjuvant RT was given to 7 patients, 4 patients of anaplastic PXA, 1 patient of after GTR for PXA grade II (diagnosed PXA with anaplastic features according to 2007 WHO classification previously), 2 patients of after STR for PXA grade II) and no patient received chemotherapy as primary adjuvant therapy. In our study, 3 patients of PXA grade II received adjuvant RT, one patient experienced recurrence. And 3 of 4 patient of anaplastic PXA those who received RT experienced recurrence during follow up periods.

Chemotherapy for PXA has been generally considered ineffective.[1,3,6] In our institution, we did not give the chemotherapy as a primary adjuvant therapy, we used the chemotherapy as salvage therapy for recurrent disease. We only used temozolomide and vascular endothelial growth factor inhibitor-bevacizumab after recurrence. Cartmill et al. reported the benefit of vincristine and carboplatin chemotherapy for 1 case of recurrent PXA,[29] and Koga reported

the case report that nimustine and temozolomide for disseminated recurrent PXA achieved long term control.[30] These 2 reports were case report, thus we interpreted the result of study cautious. The efficacy of chemotherapy for PXA is still controversial, the future study should include the effect of RT and chemotherapy for PXA.

Giannini et al. investigated 71 patients of PXA, they reported favorable outcomes of 81% 5 years overall survival and 72% 5 years recurrence free survival.[6] However, not only the recurrence rates of PXA was reported 29 to 33% and overall mortality rate 15 to 30%,[3,9] but also PXA can undergo malignant transformation and progression rates was known for 10 to 38%.[3,31] From recent report of Oh et al. PXA show 78% of recurrence rate and 28% of malignant transformation.[10]

In our series, 6 (24%) deaths were occurred during mean follow-up periods of 51.4 months and recurrence was occurred in 11 (44%) patients. The 10-year survival rate was 40.9% in PXA grade II. 65.1% of 5-year PFS rate of PXA grade II, 50% of 3-year PFS rate of anaplastic PXA. It is higher recurrence rate than other low-grade glioma. Considering high recurrence rate of PXA, close follow up of PXA patients and regular brain imaging are needed.

There are still debate, the reported prognostic factors PXA in the previous literature were age, mitotic index, necrosis on histology, EOR, BRAF V600E mutation.[2,32] In our study, we failed to find the prognostic factors of overall survival. Tumor size, solid with cyst and hemorrhage type and peritumoral edema were statistically significant poor prognostic factor of PFS in univariate analysis, however only peritumoral edema was statistically significant poor prognostic factors of PFS in multivariate analysis. Age, EOR, histologic grade, adjuvant therapy were not prognostic factors in our study.

In comparison between non-recurrent (silent) PXA grade II and recurrent PXA grade II group, the difference of tumor location showed borderline statistical significance (p value= 0.067) and difference of peritumoral edema showed statistical significance (p value= 0.008).

We suggested the scoring system of predicting the recurrence of PXA grade II. We included the variables of age, tumor type (solid plus cyst and hemorrhge) and peritumoral edema. Our scoring system could expect the higher recurrence rate in our series. And the progression free survival differences between low risk group and high-risk group was statistically significant (p value= 0.025). Of course, there are many flaws in this retrospectively designed study and

this scoring system should be complemented. Nonetheless this proposed scoring system was firstly suggested and meaningful differences was noted in our study.

Limitations

Due to its rarity, our study contains only 25 patients. And study was retrospectively designed, thus precluding fully meaningful analysis and possibly containing selection bias. Additionally, this is single institutional series and span 14 years for study period and the variable length of follow-up data makes it difficult to reveal the definitive clinical characteristics of PXA and draw conclusions of best treatment strategies and outcomes. We only contain 4 patients of anaplastic PXA and all patient was not examined uniform preoperative imaging study and immunohistochemical study.

Conclusion

PXA is very rare glial neoplasm. PXA show variable clinical and radiological behaviors. To our limited knowledge, tumor size and peritumoral edema of PXA is associated with poorer progression free survival in univariate analysis. DWI, PWI and PET findings of PXA can't expect clinical behavior and grade of the PXA. In comparison of silent PXA grade II and

recurrent PXA grade II, the differences of rate of harboring peritumoral edema showed statistical significance and tumor location showed borderline significance. Suggested scoring system could predict the higher recurrences in our series. PXA show high recurrence rate, thus close follow up is needed. In the future, multicenter larger size prospective study should be needed.

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