Survival and prognostic factors of anaplastic gliomas and prognostic impact of the 2016 WHO classification

Je Beom Hong

Department of Medicine

The Graduate School, Yonsei University

Survival and prognostic factors of anaplastic gliomas and prognostic impact of the 2016 WHO classification

Directed by Professor Jong Hee Chang

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Je Beom Hong

August 2017

This certifies that the Master's Thesis of
Je Beom Hong is approved.

Thesis Supervisor : Jong Hee Chang

Thesis Committee Member#1 : Se Hoon Kim

Thesis Committee Member#2 : Seok Gu Kang

The Graduate School
Yonsei University

August 2017

ACKNOWLEDGEMENTS

I would like to express the deepest appreciation to Professor Jong Hee Chang, who has the attitude and the substance of a genius: he always devotes to the patient. Without his guidance and persistent help, this work would not have been possible.

I am highly indebted and thoroughly grateful to Professor Se Hoon Kim. As my academic advisor, his contribution to this study has been absolute from the beginning. I'd like to record here my acknowledgement to him for guiding and directing this study.

I would also like to thank Professor Seok Gu Kang for being an excellent guide throughout the study. I do not think I can ever repay the debt I owe him for his guidance and constant supervision as well as for providing necessary information regarding this study.

I am grateful to all members of the Department of Neurosurgery, Yonsei University, School of Medicine.

I should like to express my appreciation to my mother and father who backed me up while I was working. And, final votes of thanks must go to my wife, Yang Mi, whose support in every respect has stimulated me to work harder. Her patience and devotion have made me to do this work.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Survival and prognostic factors of anaplastic glioma and prognostic impact of the 2016 WHO classification

Je Beom Hong

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Jong Hee Chang)

Objective

To investigate the survival and prognostic factors in anaplastic gliomas and whether the updated 2016 WHO classification in anaplastic gliomas has more prognostically predictive impact for survival than 2007 WHO classification.

Methods

A total of 113 consecutive patients with newly diagnosed anaplastic gliomas by 2007 WHO classification at our hospital from Jan. 2001 to Dec. 2013 were enrolled in this study. We integrated the molecular profiles in each patient and reclassified the diagnosis with the molecular information according to 2016 WHO classification. The Kaplan Meier methods, a multivariate Cox proportional regression analysis, Contal and O'Quigley method and a time-dependent ROC curve method were used for statistical analysis.

Results

The overall survival of total group of anaplastic gliomas was 48.4 months, of which the AA, IDH-wildtype group was 21.5 months. The

progression free survival of total group was 31.8 months, of which the AA, IDH-wildtype group was 16.4 months.

Age, postoperative tumor volume, extent of resection measured in T2-weighted MRI, and deep location of tumor were factors associated with the overall survival. And cut off value of tumor resection were 99.96% in contrast enhanced T1-weighted MRI and 85.64% in T2-weighted MRI.

The 2016 WHO classification significantly increased predictability for survival across the entire follow-up period. The difference (iAUC of 2016 model – iAUC of 2007 model) was statistically significant (estimated difference was 0.024, 95% CI is 0.022–0.075).

Conclusion

We investigated the survival and prognostic factors in anaplastic gliomas and showed that 2016 WHO classification of tumors of the CNS may be more predictable in survival than 2007 WHO classification in patients with anaplastic gliomas.

Key words : anaplastic glioma, WHO classification, survival, prognosis

Survival and prognostic factors of anaplastic glioma and prognostic impact of the 2016 WHO classification

Je Beom Hong

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Jong Hee Chang)

I. Introduction

Anaplastic gliomas which are classified grade III malignant gliomas by World Health Organization (WHO) classification of tumors of the central nervous system represent up to 6~10% of all primary brain tumors in adults[1]. They have poor prognosis and remains challenging to treat despite the modern multimodal treatment. The established treatments for anaplastic gliomas are surgical resection followed by radiation therapy and chemotherapy.[2]

In 2007 WHO classification, anaplastic gliomas were anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA). In the new 2016 WHO classification, they are classified into anaplastic astrocytoma IDH mutant (AAm), *anaplastic astrocytoma IDH wild type* (AAw), anaplastic astrocytoma NOS (AAnos), anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted (AOmc), *anaplastic oligodendroglioma NOS* (AOnos), *anaplastic oligoastrocytoma NOS* (AOAnos).[3]

Many previous studies revealed the survival rate of anaplastic gliomas (Table 1).[4-11]

Table 1. Previous studies about survival of anaplastic gliomas*

Authors	Patients Group	Postoperative treatment	Patient number	OS	PFS	Year	Remark
Hildebrand et al.[4]	AA	RT + DBD / BCNU	94	27.3 m	14.8 m	2008	EORTC study 26882
		RT	99	23.9 m	12.4 m		
Wick et al.[5]	AG	RT	139	72.1 m	30.6 m	2009	NOA-04
		PCV / TMZ	135	82.6 m	31.9 m		
Chaichana et al.[6]	AA		165	34.5 m	33.1 m	2010	Needle Bx. excluded
	Enhancing AA		102	26.7 m	22.0 m		
	Nonenhancing AA		63	48.0 m	52.9 m		
Nuno et al.[7]	AA		1766	15 m		2013	SEER data
	AO		570	42 m			
Cairncross et al.[8]	AO, AOA	PCV + RT	148	4.6 yrs	-	2013	RTOG 9402
		RT	143	4.7 yrs	-		
		PCV+RT, 1p/19q noncodeleted	76	2.6 yrs	1.2 yrs		
		PCV +RT, 1p/19q codeleted	59	14.7 yrs	8.4 yrs		
		RT, 1p/19q noncodeleted	61	2.7 yrs	1.0 yrs		
		RT, 1p/19q codeleted	67	7.3 yrs	2.9 yrs		
Van den Bent et al.[10]	AO	PCV + RT	185	42.3 m	24.3 m	2013	EORTC brain tumor group study 26951
		RT	183	30.6 m	13.2 m		
		PCV + RT, 1p/19q noncodeleted	114	25.0 m	14.8 m		
		PCV + RT, 1p/19q codeleted	43	n.r.	156.8 m		
		RT, 1p/19q noncodeleted	122	21.1 m	8.7 m		
		RT, 1p/19q codeleted	37	111.8 m	49.9 m		
Rogne et al.[9]	AA		99	19 m		2014	
Wick et al.[11]	AG	RT	139	8 yrs	2.5 yrs	2016	Long-term analysis of NOA-04
		PCV or TMZ	135	6.5 yrs	2.7 yrs		

*AA, anaplastic astrocytoma; AG, anaplastic glioma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; BCNU, bichloroethylnitrosourea; Bx., biopsy; DBD, dibromodulcitol; EORTC, European Organisation for Research and Treatment of Cancer; m, months; n.r., not reached; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PFS, progression free survival; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SEER, Surveillance, Epidemiology, and End Results; TMZ, temozolomide; yrs, years

And the established prognostic factors are patient age, symptom duration, preoperative neurological status, Karnofsky performance status (KPS), tumor location, extent of resection, preoperative magnetic resonance imaging (MRI) characteristics of the tumor and various molecular markers.[2,3,5-8,10,12-15]

Extent of resection has been known as an important prognosticator in anaplastic gliomas.[7,9,16,17] However, many studies focused on only contrast enhanced part of T1-weighted MRI despite considerable cases of anaplastic gliomas are not enhanced or partially enhanced in contrast enhanced T1-weighted MRI. In our study,

we investigated the tumor volume and extent of resection in different MRI sequence each – contrast enhanced T1-weighted MRI and T2-weighted MRI respectively.

The aim of this study was 1) to identify survival rate and prognostic factors in patients with anaplastic gliomas; 2) to determine the prognostically meaningful cut off value of resection volume in each MRI sequences and 3) to reveal whether the updated 2016 WHO classification in anaplastic gliomas has more prognostically predictive impact for survival than 2007 WHO classification.

II. Materials and Methods

1. Study design

We performed a retrospective analysis of the medical records and MRI features of 113 consecutive patients with anaplastic gliomas who were newly diagnosed at our institute between 2000 and 2013 without any prior therapy neither radiation nor chemotherapy. We excluded the patient with gliomatosis cerebri (more than 3 lobes involved), midline location and malignant transformation from previous low grade gliomas. Medical records reviewed included gender, age at first diagnosis, preoperative KPS score, postoperative treatment (radiation therapy, chemotherapy) (Table 2).

Table 2. Baseline patient characteristics*

Characteristic	AAw	AAm	AOmc	Total
Patients number (%)	72 (63.7%)	15 (13.3%)	26(23.0%)	113 (100%)
Age (years, median, range),	44.0 (7-82)	35.0 (18-71)	46.0 (27-66)	42.9 (7-82)
Sex (female/male)	32/40	9/6	11/15	51/67
Preoperative KPS (median, range)	80 (40-90)	80 (80-100)	80 (70-100)	80 (40-100)
Postoperative treatment				
CCRT	5 (4.4%)	1 (0.9%)	0 (0%)	6 (5.3%)
CCRT → CT	15 (13.3%)	1 (0.9%)	9 (8.0%)	28 (24.8%)
RT → CT	17 (15.0%)	7 (6.2%)	6 (5.3%)	26 (23.0%)
RT	25 (22.1%)	5 (4.4%)	11 (9.7%)	41 (36.3%)
CT	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)
None	10 (8.8%)	1 (0.9%)	0 (0%)	51 (45.1%)
Chemotherapy regimen				
PCV	11 (9.7%)	0 (0%)	4 (3.5%)	15 (13.3%)
TMZ	24 (21.2%)	7 (6.2%)	10 (8.8%)	44 (38.9%)
Others†	2 (1.8%)	0 (0%)	1 (0.9%)	3 (2.7%)
MGMT promoter				
Methylated	27 (23.9%)	12 (10.6%)	25 (22.1%)	64 (56.6%)
Unmethylated	44 (39.0%)	3 (2.7%)	1 (0.9%)	48 (42.5%)
Missing	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
Tumor location				
Deep	26 (23.0%)	4 (3.5%)	3 (2.7%)	33 (29.2%)
Superficial (%)	38 (33.6%)	10 (8.8%)	22 (19.5%)	70 (61.9%)
Preoperative tumor volume				
T1 CE volume (cm^3, mean, range)	13.1 (0-117.8)	2.7 (0-14.8)	20.9 (0-112.2)	13.9 (0-117.8)
T2 volume (cm^3, mean, range)	42.5 (0.8-212.2)	89.5 (13.5-232.9)	76.5 (6.2-154.4)	67.6 (0.7-232.9)
Postoperative tumor volume				
T1 CE volume (cm^3, mean, range)	0.57 (0-24.4)	0 (0-0)	0.2 (0-2.5)	1.3 (0-24.4)
T2 volume (cm^3, mean, range)	7.94 (0-166.5)	5.1 (0-27.3)	3.2 (0-14.5)	10.0 (0-166.5)
Extent of resection				
T1 CE volume (%, range)	28.6 (0-100)	100 (100-100)	76.7 (41.2-100)	88.1 (0-100)
T2 volume (%, range)	32.4 (0-100)	85.3 (52.7-100)	92.0 (76.5-100)	87.5(7.3-100)

* AAm, anaplastic astrocytoma IDH mutant; AAw, *anaplastic astrocytoma IDH wild type*; AOmc, anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted; Bx., biopsy; CCRT, concurrent chemo-radiation therapy; CE, contrast-enhancing; CT, chemotherapy; GTR, gross total resection; NTR, near total removal; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy; STR, subtotal resection; TMZ, temozolomide

†Others include fluorouracil (5-FU)+carboplatin, Vincristine, lomustine (CCNU)

2. Histopathologic review

We investigated the molecular profiles including 1p/19q codeletion, O-6-methylguanine-DNA methyltransferase (MGMT) methylation, isocitrate dehydrogenase (IDH) mutation status for all patients.

In this study, we analyzed 113 cases classified as grade III gliomas in the 2007 WHO classification into the new 2016 WHO classification using only the molecular information, ignoring the previously made histologic information. The cases in which IDH are wild type were classified as AAw. The cases in which chromosome 1p/19q were not co-deleted and IDH was mutated were classified as AAm. And the cases with IDH mutation and chromosome 1p/19q co-deletion were classified as AOmc. Our classification criteria according to molecular information is presented in Tale 3. As a result, of the total of 113 cases, 72 cases were classified into AAw, 15 cases into AAm, and 26 cases into AOmc (Table 3). All pathologic and molecular information were reviewed by a single pathologist (S.H.Kim).

Table 3. New classification using molecular information

	1p/19q non-codeleted	1p/19q codeleted	
IDH wild	anaplastic astrocytoma IDH wild type (AAw) (72)		72
IDH mutant	anaplastic astrocytoma IDH mutant (AAm) (15)	anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted (AOmc) (26)	41
	77	36	113

3. Imaging study evaluation

Tumor volume and extent of resection measured in contrast enhanced T1-

weighted MRI sequence and T2-weighted MRI sequence were analyzed respectively. We used ABC ellipsoid measurement methods (4/3 π ABC) for volume measure, where A, B and C are the three maximal radii of the tumor in 3-D coordinate system. Tumor volume was estimated by the area of increased signal intensity on contrast-enhanced T1-weighted MRI for enhancing lesions, and increased signal intensity on T2-weighted MRI for non-enhancing lesions.

As for the tumor location, deep lesions were defined as those that involved deep inside the cortex. And superficial lesions were defined as those that involved only the cortex outside the insula.

4. Statistical analysis

All statistical procedures were performed using SAS for Windows (version 9.4, Cary, NC, USA) with the exception of the time-dependent receiver operating characteristic (ROC) analysis, which was performed using R package for Windows (version 3.3.0). Age, preoperative KPS score, tumor volume, and extent of tumor resection were considered as a continuous variable.

Overall survival (OS) was defined as time from operation date to death by any cause or last follow-up. Progression free survival (PFS) was defined as time from the operation date to radiologic signs of progression or deterioration of patient's neurologic status, or death. Kaplan-Meier curves and log-rank tests were used to find the overall survival (OS) and progression free survival (PFS).

To determine factors associated with progression free survival and overall survival, a univariate and a multivariate Cox proportional regression analysis with stepwise methods (entry and exit criteria of $p<0.05$) were performed using time from surgery to progression or death. Contal and O'Quigley method was used to calculate the cut-off point of extent of resection.

To further evaluate the predictability of 2016 WHO classification across the entire follow-up period, we applied a time- dependent ROC curve method for censored survival data.[18] We then compared the global concordance probability

(integrated area under the curve, iAUC) of the 2016 model with 2007 model; iAUC is a weighted average of the AUC across a period of follow-up and a measure of predictive accuracy of a model over follow-up. All statistical tests were two-tailed. A value of $p< 0.05$ was considered statistically significant.

III. Results

1. Patient Characteristics and Classification

Clinical information of total 113 patients are listed in Table 2, stratified by 2016 WHO classification. Patients number in AAw group was 72 (63.7%), 15 (13.3%) in AAm group, and 26 (23.0%) in AOmc group. Median age at first diagnosis in total group was 42.9 years (range 7-82 years). Postop treatment modalities are also presented in table 2. MGMT promotor methylation was detected in 64 cases (56.6%) in whole group, 27 cases (23.9%) in AAw subgroup, 12 cases (10.6%) in AAm subgroup, 25 cases (22.1%) in AOmc subgroup (Table 2).

The summarized number of changes from 2007 WHO classification to 2016 WHO classification are presented in Table 4. A total of 57 anaplastic astrocytoma (AA) patients in the 2007 classification were classified by the new 2016 classification as 53 patients of AAw; 3 patients of AAm; 1 patient of AOmc. A total of 27 anaplastic oligoastrocytoma (AOA) patients were newly classified as 9 patients of AAw; 10 patients of AAm; 8 AOmc. And 29 AO patients were newly classified as 10 patients of AAw; 2 patients of AAm; 17 patients of AOmc (Table 4).

Table 4. Comparison of 2007 WHO classification with 2016 WHO classification (Number of changes) *

2016 WHO / 2007 WHO	AAw (72)	AAm (15)	AOmc (26)	Total (113)
AA (57)	53	3	1	57
AOA (27)	9	10	8	27
AO (29)	10	2	17	29

* AA, anaplastic astrocytoma; AAm, anaplastic astrocytoma IDH mutant; AAw, *anaplastic astrocytoma IDH wild type*; AO, anaplastic oligodendroglioma; AOmc, anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted; AOA, anaplastic oligoastrocytoma

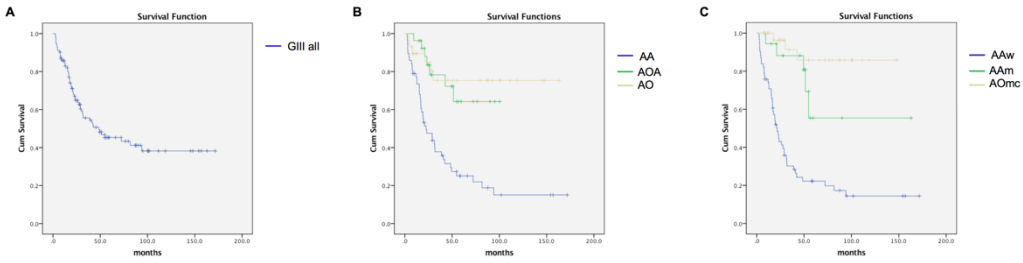
2. Volumetric analysis

Mean preoperative tumor volume was 13.9 cm^3 (range 0 - 117.8) and 67.6 cm^3 (range 0.7 - 232.9) in contrast enhanced T1-weighted MRI and T2-weighted MRI sequence respectively. Mean postoperative tumor volume was 1.3 cm^3 (range 0 - 24.4) and 10.0 cm^3 (range 0 - 166.5) in contrast enhanced T1-weighted MRI and T2-weighted MRI sequence respectively. The extent of resection measured in contrast enhanced T1-weighted MRI was 88.1% (range 0-100%) and 87.5%(7.3-100%) in T2-weighted MRI sequence (Table 2). In our study the biopsy was performed in 25 patients (22.1%).

3. Survival

After median follow-up period of 59.5 months, median OS was 48.4 months (95% CI: 15.1-81.7) in entire group, 22.5 months (95% CI: 11.1-33.9) in AA subgroup and 21.5 months (95% CI:17.2-25.8) in AAw subgroup (Figure. 1, Table 5). The Median OS was not reached in other subgroups since more than half of the patients were still alive at the time of last follow-up. Overall survival at 1,2,3,4,5 year are presented in table 5. PFS was 31.8 months (95% CI: 17.6-46.2) in entire group, 19.1 moths (95% CI: 14.0-24.1) in AA subgroup, 16.4 months (95% CI: 12.6-21.0), in AAw subgroup and 130.0 months in AOmc subgroup (Figure. 2, Table 6). Progression free survival at 1,2,3,4,5 year are presented in Table 6.

Figure. 1 Overall Survival



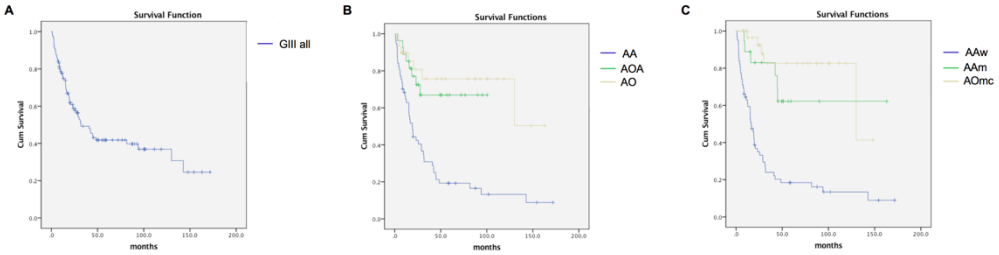
A. Kaplan-Meier representation of overall survival time for the entire group of 113 patients.
B. Overall survival of subgroups according to 2007 WHO Classification.
C. Overall survival of subgroups according to 2016 WHO Classification.

Table 5. Overall Survival*

Group		Median	1yr	2yr	3yr	4yr	5yr
GIII all		48.4 mos	84.8%	64.9%	55.6 %	50.7%	45.3%
2007	AA	22.5 mos	78.9%	60.6%	41.7%	25.1%	15.1%
	AOA	n.r.	78.3%	64.2%	64.2%	64.2%	64.2%
	AO	n.r.	80.3%	75.3%	75.3%	75.3%	75.3%
2016	AAw	21.5 mos	74.1%	64.0%	46.6%	28.3%	14.4%
	AAm	n.r.	69.3%	55.4%	55.4%	55.4%	55.4%
	AOmc	n.r.	96.3%	85.9%	85.9%	85.9%	85.9%

* AA, anaplastic astrocytoma; AAm, anaplastic astrocytoma IDH mutant; AAw, *anaplastic astrocytoma IDH wild type*; AO, anaplastic oligodendroglioma; AOmc, anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted; AOnos, *anaplastic oligodendroglioma NOS;* AOA, anaplastic oligoastrocytoma; GIII, grade III glioma; mos, months; yr, year

Figure. 2 Progression Free Survival



A. Kaplan-Meier representation of progression free survival time for the entire group of 113 patients
B. Progression free survival of subgroups according to 2007 WHO Classification.
C. Progression free survival of subgroups according to 2016 WHO Classification

Table 6. Progression Free Survival *

Group		Median	1yr	2yr	3yr	4yr	5yr
GIII all		31.8 mos	76.7%	58.7%	49.2%	43.1%	41.8%
2007	AA	19.1 mos	64.7%	42.4%	30.9%	19.3%	19.3%
	AOA	n.r.	85.2%	72.5%	66.9%	66.9%	66.9%
	AO	n.r.	89.7%	80.7%	75.6%	75.6%	75.6%
2016	AAw	16.4 mo	80.6%	64.5%	45.7%	25.8%	9.0%
	AAm	n.r.	88.9%	83.0%	83.0%	62.2%	62.2%
	AOmc	130.0 mo	96.4%	92.4%	82.6%	82.6%	82.6%

* AA, anaplastic astrocytoma; AAm, anaplastic astrocytoma IDH mutant; AAw, *anaplastic astrocytoma IDH wild type*; AO, anaplastic oligodendroglioma; AOmc, anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted; AOnos, *anaplastic oligodendroglioma NOS;* AOA, anaplastic oligoastrocytoma; GIII, grade III glioma; mos, months; yr, year

4. Prognostic factors

In univariate analysis, age, preoperative KPS score, location of tumor, postoperative tumor volume in contrast enhanced T1 weighted MRI and T2 weighted MRI, extent of resection in contrast enhanced T1 weighted MRI and T2 weighted MRI were statistically significant prognostic factors for overall survival and progression free survival (Table 7). After multivariate analysis, age, postoperative tumor volume in contrast enhanced T1 weighted MRI and T2 weighted MRI, extent of resection measured in T2 weighted MRI and tumor location were statistically significant prognostic factor for overall survival (Table 8). With regard to progression free survival, age, postoperative tumor volume measured in T1 contrast enhanced MRI, extent or resection in T2 weighted MRI and tumor location were statistically significant prognostic factors (Table 8).

Table 7. Univariate analysis of prognostic factors*

Variables	OS		PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.021 (1.005-1.038)	0.0106	1.018 (1.003-1.034)	0.0204
Sex	1.271 (0.753-2.146)	0.3700	1.453 (0.877-2.408)	0.1473
Preop. KPS score	0.915 (0.874-0.958)	0.0001	0.932 (0.895-0.970)	0.0005
Deep location	2.941 (1.728-5.006)	<.0001	3.102 (1.850-5.201)	<.0001
Preop. T1 CE Vol.	1.006 (0.998-1.015)	0.1530	1.005 (0.996-1.013)	0.2843
Preop. T2 Vol.	0.996 (0.991-1.001)	0.0800	0.996 (0.991-1.000)	0.0628
Postop. T1 CE Vol.	1.161 (1.092-1.234)	<.0001	1.122 (1.063-1.185)	<.0001
Postop. T2 Vol.	1.020 (1.009-1.030)	0.0002	1.015 (1.006-1.024)	0.0015
EOR. (T1 CE %)	0.984 (0.973-0.996)	0.0068	0.985 (0.974-0.996)	0.0095
EOR. (T2 %)	0.976 (0.965-0.988)	<.0001	0.977 (0.966-0.989)	<.0001

*CE, contrast enhancing; EOR, extent of resection; HR, hazard ratio; KPS, Karnofsky performance status; OS, overall survival; PFS, progression free survival; Postop., postoperative; Preop., preoperative; Vol., volume

Table 8. Multivariate analysis of prognostic factors*

Variables	OS		PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.035 (1.004-1.067)	0.0281	1.035 (1.005-1.065)	0.0217
Postop. T1 CE Vol.	1.404 (1.189-1.657)	<.0001	1.147 (1.079-1.220)	<.0001
Postop. T2 Vol.	0.945 (0.914-0.977)	0.0007		
EOR. (T2 %)	0.940 (0.915-0.966)	<.0001	0.967 (0.953-0.981)	<.0001
Deep location	2.884 (1.191-6.983)	0.0189	2.702 (1.097-6.658)	0.0307

*CE, contrast enhancing; EOR, extent of resection; HR, hazard ratio; OS, overall survival; PFS, progression free survival; Postop., postoperative; Vol., volume

5. Cut off value of extent of resection

In cut off value analysis using Contal and O'Quigley method, age of 50 or younger, complete resection of enhanced portion (99.96%), and more than 85.64% resection of non-enhanced tumor portion have prognostic impact on overall survival in patient with anaplastic gliomas (Table 9). About the progression free survival, age of 55 or younger, 72.72% resection of contrast enhanced portion, 84.88% resection of non-enhanced tumor portion have prognostic impact.

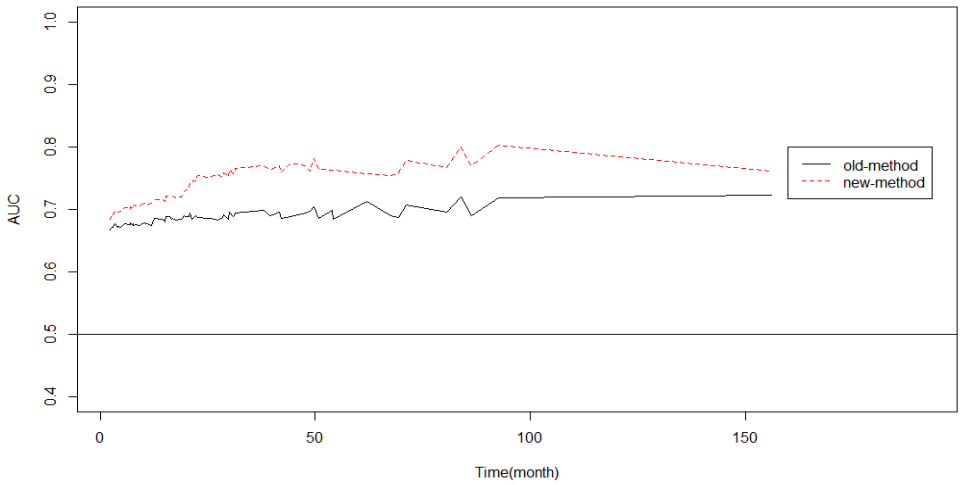
Table 9. Cut off point (Contal and O'Quigley method)

Variables	OS		PFS	
	Cut point	p-value	Cut point	p-value
Age	≥51	0.0001	≥55	0.0003
Extent of resection (%, T1 contrast enhanced)	≥99.957	0.0001	≥72.727	0.0002
Extent of resection (%, T2)	≥85.635	<.0001	≥84.88	<.0001

6. Prognostic impact of WHO 2016 classification

Time-dependent ROC curve demonstrated that concordance probability (iAUC) increased from 0.708 (2007 WHO classification model) to 0.745 (2016 WHO classification model). On visual inspection, the 2016 WHO Classification model had a higher iAUC throughout the entire follow-up period than the 2007 WHO Classification model (Figure. 3). To calculate the difference in iAUC between the 2016 WHO Classification model and the 2007 WHO Classification model, bootstrap resampling tests were performed for 1,000 times. The difference (iAUC of 2016 model – iAUC of 2007 model) was statistically significant (estimated difference was 0.024, 95% CI is 0.022–0.075). These findings suggest that the 2016 WHO classification to the survival increases the predictive accuracy for mortality.

Figure 3: iAUC (Age, sex adjusted overall survival)



Time-dependent receiver operating curve analysis derived from the Cox regression models with 2016 WHO classification model and 2007 WHO classification model. The area under the curve (AUC) indicated predictive accuracy at the indicated time. Throughout the study period, the 2016 WHO classification model was superior to the 2007 WHO classification in distinguishing patients who will survive from those who will not.

IV. Discussion

1. Survival and Prognostic Factors

When multiple cox regression analysis was performed on all factors including molecular markers, IDH mutation was the only prognostic factor (P= 0.0294, HR= 0.196 (0.045-0.849)). Therefore, our study confirms that IDH mutation is a stronger factor than tumor volume, extent of resection and all other factors.[19]

To investigate other prognostic factors, we performed cox regression analysis of known prognostic factors including age, KPS, tumor location, tumor volume and extent of resection except molecular markers. Because considerable proportion of anaplastic gliomas does not show contrast enhancement in T1-weighted MRI[13,20,21], we analyzed tumor volume and extent of resection according to different MRI sequences – contrast enhanced T1 and T2 respectively. Although the extent of resection of contrast enhanced lesion on T1-weighted MRI was not statistically significant in multiple cox regression analysis, extent of resection in T2-weighted MRI was a statistically significant prognostic factor in multivariate analysis.

In addition, As revealed in other papers, postoperative tumor volume and extent of resection were found to be important prognostic factors (Table 7,8).[21] So, we investigated the cut off value of extent of resection on each MRI sequence (Table 9). The cut off value of extent of resection affecting overall survival was 99.99% in contrast enhanced T1-weighted MRI and 85.6% in T2-weighted MRI. Therefore, we think that complete resection of enhanced lesion on T1-weighted MRI and more than 85.6% resection of high signal lesion in T2-weighted MRI are important in anaplastic gliomas. The strength of our study is that we suggest the cut off value of volumetric extent of resection according to different MRI sequences.

2. 2016 WHO classification

Overall survival of existing anaplastic glioma was reported to vary from 15

months to 27.3 months in AA and from 21 months to 14.7 years in AO.[4-11] This implies that there are heterogeneous groups and that there is a need to renew the classification. Changes from previous histopathologic classification to integrated molecular classification have been mandated in modern outcome analyses. And recently, a new classification using molecular information has been shown to provide a high prognostic value in biological and clinical analysis.[11,22] Our study also showed a superiority of a 2016 WHO classification over the 2007 WHO classification in anaplastic gliomas using iAUC (Figure. 3). 2016 WHO classification in anaplastic gliomas used IDH and 1p/19q molecular information only, but in the future, other molecular informations such as ATRX, MGMT, CIMP, PTEN, TERT is thought to lead further development.[11,22]

Because our study is a retrospective study, there are some limitations. There may be surgical bias in treatment which are non-standardized postoperative adjuvant treatment, different surgeon's preference considering tumor location and extent. However, our study has the significance that we have evaluated the usefulness of the new 2016 WHO classification in which we classified anaplastic glioma using the molecular information only comparing histologic 2007 WHO classification. And we still give information that extensive surgery is important in this molecular era.

V. Conclusion

The median OS was 48.4 months in total anaplastic glioma group and 21.5 months in AAw group. And we revealed that complete resection (more than 99.96%) of tumor volume measured in contrast enhanced T1-weighted MRI and more than 85.6% of tumor resection measured in T2-weighted MRI have prognostic impact on the patient survival in anaplastic gliomas. Therefore, gross-total resection of at least contrast enhance lesion should be performed to prolong survival in anaplastic gliomas patients.

And we showed that WHO 2016 classification may be more predictable of survival in patients with grade III gliomas than 2007 WHO classification.

References

1. Wick W. Anaplastic gliomas: an emerging entity. Eur J Cancer 2011;47 Suppl 3:S357-8.

2. Paleologos NA, Merrell RT. Anaplastic glioma. Curr Treat Options Neurol 2012;14:381-90.

3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803-20.

4. Hildebrand J, Gorlia T, Kros JM, Afra D, Frenay M, Omuro A, et al. Adjuvant dibromodulcitol and BCNU chemotherapy in anaplastic astrocytoma: results of a randomised European Organisation for Research and Treatment of Cancer phase III study (EORTC study 26882). Eur J Cancer 2008;44:1210-6.

5. Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol 2009;27:5874-80.

6. Chaichana KL, Kosztowski T, Niranjan A, Olivi A, Weingart JD, Laterra J, et al. Prognostic significance of contrast-enhancing anaplastic astrocytomas in adults. J Neurosurg 2010;113:286-92.

7. Nuno M, Birch K, Mukherjee D, Sarmiento JM, Black KL, Patil CG. Survival and prognostic factors of anaplastic gliomas. Neurosurgery 2013;73:458-65; quiz 65.

8. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013;31:337-43.

9. Rogne SG, Konglund A, Scheie D, Helseth E, Meling TR. Anaplastic astrocytomas: survival and prognostic factors in a surgical series. Acta Neurochir (Wien) 2014;156:1053-61.

10. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013;31:344-50.

11. Wick W, Roth P, Hartmann C, Hau P, Nakamura M, Stockhammer F, et al. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. Neuro Oncol 2016; doi:10.1093/neuonc/now133.

12. Stupp R, Reni M, Gatta G, Mazza E, Vecht C. Anaplastic astrocytoma in adults. Crit Rev Oncol Hematol 2007;63:72-80.

13. Wang Y, Wang K, Wang J, Li S, Ma J, Dai J, et al. Identifying the association between contrast enhancement pattern, surgical resection, and prognosis in anaplastic glioma patients. Neuroradiology 2016;58:367-74.

14. Roth P, Wick W, Weller M. Anaplastic oligodendroglioma: a new treatment paradigm and current controversies. Curr Treat Options Oncol 2013;14:505-13.

15. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol 2010;120:707-18.

16. McCrea HJ, Bander ED, Venn RA, Reiner AS, Iorgulescu JB, Puchi LA, et al. Sex, Age, Anatomic Location, and Extent of Resection Influence Outcomes in Children With High-grade Glioma. Neurosurgery 2015;77:443-52; discussion 52-3.

17. Wang YY, Wang K, Li SW, Wang JF, Ma J, Jiang T, et al. Patterns of Tumor Contrast Enhancement Predict the Prognosis of Anaplastic Gliomas with IDH1 Mutation. AJNR Am J Neuroradiol 2015;36:2023-9.

18. Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. Biometrics 2005;61:92-105.

19. Jungk C, Scherer M, Mock A, Capper D, Radbruch A, von Deimling A, et al. Prognostic value of the extent of resection in supratentorial WHO grade II astrocytomas stratified for IDH1 mutation status: a single-center volumetric analysis. J Neurooncol 2016;129:319-28.

20. Scott JN, Brasher PM, Sevick RJ, Rewcastle NB, Forsyth PA. How often are nonenhancing supratentorial gliomas malignant? A population study. Neurology 2002;59:947-9.

21. Keles GE, Chang EF, Lamborn KR, Tihan T, Chang CJ, Chang SM, et al. Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg 2006;105:34-40.

22. Tabouret E, Nguyen AT, Dehais C, Carpentier C, Ducray F, Idbaih A, et al. Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort. Acta Neuropathol 2016;132:625-34.

23. Pessoa IA, Sagica FE, Anselmo NP, Brito JR, de Oliveira EH. IDH1 and IDH2 mutations in different histologic subtypes and WHO grading gliomas in a sample from Northern Brazil. Genet Mol Res 2015;14:6533-42.

24. Siegal T. Clinical impact of molecular biomarkers in gliomas. J Clin Neurosci 2015;22:437-44.

ABSTRACT (IN KOREAN)

역형성 신경교종에서 생존율과 예후인자 분석 및 2016 WHO 분류의 예후적 의의

<지도교수 장 종 희>

연세대학교 대학원 의학과

홍 제 범

목적

역형성 신경교종에서 생존율과 예후 인자를 조사하고 새로운 2016 WHO 분류가 2007 WHO 분류보다 역형성 신경교종에서 예후를 더 잘 예측할 수 있는지 알아보고자 하였다.

방법

2001년 1월부터 2013년 12월까지 본원에서 2007 WHO 분류에 따라 3등급 신경교종으로 진단받은 113명의 환자분들을 대상으로 연구를 진행하였다. 분자생물학적 검사결과를 조사하였으며 그 결과를 바탕으로 2016 WHO 분류에 따라 새로이 분류하여 연구를 진행하였다. 통계기법으로 카플란 마이어 생존분석(Kaplan Meier methods), 다중 콕스 회귀분석 (multivariate Cox proportional regression analysis), 콘탈 오퀴글리 분석(Contal and O'Quigley method) 그리고 시간 종속 ROC 곡선(time-dependent ROC curve method)을 이용하였다.

결과

전체 역형성 신경교종에서서의 생존율은 48.4 개월이었으며

역형성 성상세포종, IDH-야생형에서는 생존율이 21.5 개월이었다. 무진행생존율은 전체 그룹에서 31.8 개월이었으며 역형성 성상세포종, IDH-야생형에서는 16.4 개월이었다. 나이, 수술 후 종양 부피, T2 자기공명영상에서 측정된 절제 범위, 종양의 깊은 위치가 생존율에 영향을 미치는 요소로 연구되었다. 예후에 영향을 미치는 종양 절제 정도의 절단값은 조영증강 T1 자기공명영상에서 99.96% 였으며, T2 자기공명영상에서 85.64% 였다. 새로운 2016 WHO 분류는 전체 추적기간에서 기존의 2007 WHO 분류보다 예후를 더 잘 예측한다고 연구되었다. (예측 차이값은 0.024, 95% 신뢰구간에서 0.022–0.075).

결론

이번 연구를 통해서 역형성 신경교종의 생존율과 예후인자를 알 수 있었으며 역형성 신경교종에서 2007 WHO 분류보다 2016 WHO 분류가 더 예후를 잘 예측한다는 결론을 얻을 수 있었다.

핵심되는 말 : 역형성 교종, WHO 분류, 생존율, 예후 인자