MGMT Gene Promoter Methylation as a Potent Prognostic Factor in Glioblastoma Treated with Temozolomide-Based Chemoradiotherapy: A Single-Institution Study

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Directed by Professor Jaeho Cho

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ABSTRACT

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Purpose: Recently, cells deficient in O^6-methylguanine–DNA methyltransferase (MGMT) were found to show increased sensitivity to temozolomide (TMZ). We evaluated whether hypermethylation of *MGMT* was associated with survival in patients with glioblastoma multiforme (GBM).

Methods and Materials: We retrospectively analyzed 93 patients with histologically confirmed GBM and who received involved field radiotherapy with TMZ from 2001 to 2008. The median age was 58 years (range, 24-78). Surgical resection was total in 39 patients (42%), subtotal in 30 patients (32%), partial in 17 patients (18%), and only a biopsy was performed in seven patients (8%). Post-operative radiotherapy began within 3 weeks of surgery in 87% of the patients. Radiotherapy doses ranged from 50-74 Gy (median 70 Gy). MGMT gene methylation was determined in 78 patients; MGMT was unmethylated in 43 patients (55%) and methylated in 35 patients (45%). The median follow-up period was 22 months (range, 3-88) for all patients.

Results: The median overall survival (OS) was 22 months, and progression-free

survival (PFS) was 11 months. MGMT gene methylation was an independently significant prognostic factor for both OS (p=0.002) and PFS (p=0.008) in multivariate analysis. The median OS was 29 months for the methylated group, and 20 months for the unmethylated group. In 35 patients with methylated MGMT genes, the 2-year and 5-year OS rates were 54% and 31%, respectively. Six patients with combined prognostic factors of methylated MGMT genes, ≤50 years, and total/subtotal resections are all alive 38-77 months after operation, whereas the median OS in eight patients with unmethylated MGMT genes, >50 years, and less than subtotal resection was 13.2 months.

Conclusion: We confirmed that MGMT gene methylation is a potent prognostic factor in patients with GBM. Our results suggest that early post-operative radiotherapy and a high total/subtotal resection rate might further improve the outcome.

Key words: glioblastoma, O^6-methylguanine-DNA methyltransferase, methylation, prognostic factor, radiotherapy

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I. INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive and common primary brain tumor in adults. Median survival is 14.6 months with radiotherapy plus temozolomide (TMZ) and 12.1 months with radiotherapy alone in a multicenter trial.[1] Age, performance status, extent of surgical resection, and mental status are the most consistently reported prognostic factors.[2] In addition, since 2000 the promoter methylation status of the O^6-methylguanine–DNA methyltransferase (MGMT) gene has been suggested as a predictive factor in GBM, especially in patients who receive chemoradiation with alkylating agents.[3,4] [4] In prognostic factor analyses of the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) trial 26981-22981, methylated MGMT was associated with improved survival in patients whose tumors were resected and who received radiotherapy and TMZ.[5] The MGMT gene is located on chromosome 10q26 and encodes a DNA repair protein that removes alkyl groups from the O^6

position of guanine, an important site of DNA alkylation.[1] Epigenetic MGMT gene silencing by promoter methylation is associated with loss of MGMT expression and diminished DNA repair activity, which results in increased sensitivity to TMZ and longer overall survival (OS).[6]

There are few studies about MGMT gene promoter methylation in Korean patients with GBM.[7] We evaluated whether MGMT gene promoter methylation is associated with survival in patients with GBM who were treated in a single institution.

II. MATERIALS AND METHODS

1. Patient characteristics

Between January 2001 and December 2008, 165 patients with newly diagnosed GBM were treated with post-operative radiotherapy at Yonsei University Health System. Of these, 93 patients with histologically proven GBM (WHO grade 4) and who received involved field radiotherapy with TMZ were selected for this study. Seventy-two patients were excluded: 49 were treated with radiotherapy alone without chemotherapy; six were operated on at other hospitals; four discontinued radiotherapy due to poor performance; one refused completion of radiotherapy; two died from complications during radiotherapy including aspiration pneumonia and tumor progression; two were not followed up after radiotherapy; four were treated with a chemotherapy

regimen other than TMZ (Lomustine, Carmustine, Vincristine); three had pathologic features of glioblastoma with oligodendroglial components; and one was excluded due to pediatric age.

Two pathologists independently examined specimens. All patients were followed-up until death or time of analysis. Median follow-up period was 22 months (range, 3-88 months), and median age was 58 years (range, 24-78). Gender distribution showed male preponderance (1.27:1). Karnofsky performance status (KPS) at the beginning of radiotherapy was over 60% in 84 patients (90%). All patients underwent surgery after imaging studies.

2. Treatment

Gross total resection (GTR) was achieved in 39 patients. Subtotal resection (STR) or partial removal was performed in 30 and 17 patients, respectively. In seven patients, only biopsy was performed. Three-dimensional conformal radiotherapy was used to treat 86 patients (92%) with 2 Gy per fraction. Seven patients (8%) were treated with intensity-modulated radiation therapy using tomotherapy with 2.5 Gy per fraction (Table 1). The definition of subtotal resection was resection of a gross tumor by 75% or more. Partial resection was defined as resection of a gross tumor by less than 75%. Post-operative radiotherapy was started 10-67 days after operation (median 16 days, mean 18.4 days). We wanted to begin radiotherapy within 2 weeks of

Table 1. Clinical profiles according to MGMT gene promoter methylation status

	No. of patients (%)	Methylated n=35 (38%)	Unmethylated n=43 (46%)	Unknown n=15 (16%)	Sig.
Age		28-71 (Median: 57)	24-78 (Median: 56)	28-76 (Median: 60)	0.644
≤50 years	28 (30)	11 (31)	14 (33)	3 (20)	
>50 years	65 (70)	24 (69)	29 (67)	12 (80)	
Gender					
Male	52 (56)	19 (54)	25 (58)	8 (53)	
Female	41 (44)	16 (46)	18 (42)	7 (47)	0.921
KPS					
≤80	72 (77)	29 (83)	32 (74)	11 (73)	
>80	21 (23)	6 (17)	11 (26)	4 (27)	0.620
Extent of resection					
Total	39 (42)	14 (40)	21 (49)	4 (27)	
Subtotal	30 (32)	12 (34)	13 (30)	5 (33)	
Partial	17 (18)	8 (23)	6 (14)	3 (20)	
Biopsy	7 (8)	1 (3)	3 (7)	3 (20)	0.374
RT total dose (Gy)					
<60	3 (3)	0 (0)	2 (5)	1 (7)	
60-69	41 (44)	14 (40)	19 (44)	8 (53)	
≥70	49 (53)	21 (60)	22 (51)	6 (40)	0.832
RT fraction dose (Gy)					

2 (3D-CRT)	86 (92)	33 (94)	40 (93)	13 (87)	
2.5 (Tomotherapy)	7 (8)	2 (6)	3 (7)	2 (13)	0.634

Abbreviations: Sig.=statistical significance, KPS=Karnofsky performance status scale, RT=radiotherapy, 3D-CRT=three-dimensional conformal radiotherapy.

operation, and post-operative radiotherapy was started within 3 weeks of operation in 87% of the patients. Patients were treated with thermoplastic immobilization masks to ensure adequate immobilization during therapy and reproducibility. We followed the protocol of RTOG 98-03 trial to define the target volume for radiotherapy.[8] The gross tumor volume (GTV) included the resection cavity and any gross residual tumor as observed with immediate postoperative magnetic resonance imaging (MRI). A 1.5-cm margin was added to the GTV for microscopic extension (clinical target volume), and an additional 0.3-cm margin was added for setup uncertainty (PTV1). A subsequent boost was given to PTV2, which was defined as the GTV plus a 0.3-cm margin. The total dose of radiotherapy was 50-74 Gy (median 70 Gy). We gradually increased the radiotherapy dose from 60 Gy to 70 Gy until 2005, and thus, most patients (60%) received >66 Gy. Forty-nine patients (53%) received ≥70 Gy. Three patients (3%) received <60 Gy (Table 1).

The current standard regimen is radiotherapy plus continuous daily TMZ (75 mg/m^2 of body-surface area per day, 7 days per week from the first to last day of radiotherapy), followed by six cycles of adjuvant TMZ (150-200

mg/m^2 for 5 days during each 28-day cycle).[1] Since December 2006, 54 patients received TMZ chemotherapy with this current standard regimen. In 39 patients (42%) treated before 2006, the TMZ regimens were different from the current standard regimen in daily dose, administration days, and adjuvant TMZ regimen. Inconsistent TMZ regimens that were different from the current standard included TMZ with other chemotherapy agents (Lomustine, Carmustine, Vincristine, n=18), TMZ administered after radiotherapy (n=15), TMZ daily dose different from the current standard TMZ treatment (n=24), and TMZ administered concurrently with radiotherapy, but not daily during radiotherapy (n=21).

3. MGMT gene promoter methylation assessment

A retrospective analysis evaluated the MGMT gene promoter methylation status. Genomic DNA was isolated from paraffin-embedded samples from 84 patients. The DNA methylation status of CpG islands at the MGMT promoter was determined by methylation-specific polymerase chain reaction (MSP) as previously described, with some modifications.[3,4] [4] Annealing temperature was 59°C. Low-quality DNA yielding uncertain polymerase chain reaction (PCR) results was discarded. Unmethylated control DNA and methylated control DNA with bisulfite treatment (Qiagen, Duesseldorf, Germany) were used as negative and positive controls, respectively. PCR products were separated on 8% polyacrylamide gels, stained

with ethidium bromide, and examined under ultraviolet illumination. Investigators performing these assays were blinded to clinical information.

Among 84 patients from whom paraffin-embedded samples were available for MSP, the MGMT gene promoter was methylated in 35 (38%) and unmethylated in 43 (46%). In the remaining six patients, the methylation status could not be determined. Therefore, the percent of methylation was 44.9%. Clinical profiles according to MGMT gene promoter methylation status are presented in Table 1. Patients were divided into two groups according to MGMT methylation status. No significant differences in clinical variables were found between the two groups.

1. Treatment response

MRI with contrast was performed in all patients within 48 hours of operation to evaluate surgery success. Most patients (83%) were followed up with MRI at 1 month after radiotherapy, and every 3 months during the first 2 years or when disease progression was suspected. Disease progression was defined as radiologic (25% or greater increase in the size of the largest perpendicular diameter of contrast-enhancing tumor or any new tumor on MRI or computed tomography [CT]), neurologic, or clinical.[9]

Patients with transient progressive lesions (neuroradiological enhancement) within the first 3 months after the end of radiotherapy were regarded as showing pseudoprogression.[10] Radiation necrosis (RN) is seen on

CT and MRI as a ring-enhancing mass with edema and mass effect, findings similar to tumor recurrence.[11,12] [12] Diagnostic imaging including positron emission tomography or magnetic resonance spectroscopy and/or surgical pathology consistent with cerebral RN was also used to define RN.

4. Statistical analysis

Progression-free survival (PFS) and OS were measured from the time of surgery to disease progression or death, respectively, or date of last follow-up, and analyzed using the Kaplan-Meier method. The log-rank test was employed to compare MGMT promoter methylation status, methylated versus unmethylated MGMT, and test the significance of the following prognostic variables: age, gender, extent of surgery, total dose of radiotherapy, and performance status. Multivariate analysis was performed using the Cox proportional hazards model. Comparison of patient characteristics was carried out using the chi-square test for categorical variables (age, gender, KPS, extent of resection, total dose of radiotherapy, and fraction dose of radiotherapy). P values ≤ 0.05 were considered statistically significant.

III. RESULTS

1. Treatment outcome

At the time of analysis, 70 patients had died 3-50 months after surgery (median 17 months), and 23 patients were alive 21-88 months after surgery (median 31 months). Among the 93 patients, pseudoprogression occurred in 11 patients (12%). RN was noted in 29 patients (31%). Disease progression or recurrence was noted in 73 patients (78%) 1-42 months after radiotherapy (median 11 months). Repeat operations were performed in 14 patients (15%). In one patient who underwent a repeat operation 74 months after initial treatment, pathologic examination revealed no tumor cells, but necrotic tissues (blood clots and fibrinous exudate). She is alive without evidence of recurrence 88 months after diagnosis (Table 2).

Table 2. Prognostic factors in overall survival and progression-free survival, univariate analysis

Variables	No. of patients (%)	Overall Survival (months)			Progression-Free Survival (months)		
		Median (95% CI)	2 yr (%)	p	Median (95% CI)		p
Age							
≤50 years	28 (30)	30 (13-47)	57	0.001	15 (8-22)		0.190
>50 years	65 (70)	18 (16-20)	27		10 (7-13)		

Gender						
Male	52 (56)	18 (13-23)	30	0.248	10 (7-13)	0.190
Female	41 (44)	24 (17-31)	45		11 (6-16)	
KPS						
≤80	72 (77)	18 (14-22)	34	0.077	10 (8-12)	0.503
>80	21 (23)	24 (17-31)	45		15 (5-25)	
RT total dose (Gy)						
≤ 60	31 (33)	19 (15-23)	28	0.726	12 (5-19)	0.793
>60	62 (77)	22 (17-27)	39		10 (8-12)	
RT fraction dose (Gy)						
2	86 (92)	20 (15-25)	35	0.196	10 (8-12)	0.391
2.5	7 (8)	25 (17-33)	57		20 (0-49)	
Extent of resection						
GTR+STR	69 (74)	23 (21-25)	38	0.049	14 (10-18)	0.005
Partial+Biopsy	24 (26)	15 (10-20)	33		7 (5-9)	
MGMT gene						
Methylated	43 (38)	29 (16-42)	54		18 (9-27)	
Unmethylated	35 (46)	20 (16-24)	27	0.002	9 (6-12)	0.017
Unknown	15 (16)	14 (9-20)	17		6 (5-7)	

CI=confidence interval, KPS=Karnofsky performance status scale, RT=radiotherapy, GTR=Gross total resection, STR=Subtotal resection

Table 3. Prognostic factors in overall survival and progression-free survival, multivariate analysis

Prognostic factors	No. of patients	Overall Survival			Progression-Free Survival		
	(%)	HR	95% CI	p	HR	95% CI	p
Age							
≤50 years	28 (30)						
>50 years	65 (70)	2.3	1.3-4.0	0.006	1.3	0.8-2.2	0.290
KPS							
≤80	72 (77)						
>80	21 (23)	1.6	0.8-3.1	0.147	1.2	0.7-2.1	0.581
Extent of resection							
GTR+STR	69 (74)						
Partial+Biopsy	24 (26)	1.4	0.8-2.4	0.231	2.0	1.2-3.4	0.010
MGMT gene promoter							
Methylated	43 (38)						
Unmethylated	35 (46)	1.8	1.2-2.5	0.002	1.6	1.1-2.2	0.008
Unknown	15 (16)						

HR=hazard ratio, CI=confidence interval, KPS=Karnofsky performance status scale, GTR=Gross total resection, STR=Subtotal resection

2. Patient survival

The median PFS was 11 months, and the 3-year PFS rate was 19% in 93 patients. For PFS, the extent of resection (p=0.010) and MGMT gene promoter methylation status (p=0.008) were independently significant

prognostic factors (Tables 2 and 3). The PFS was 14 months for patients with GTR or STR, and 7 months for partial resection or biopsy (p=0.005). The median PFS times of methylated, unmethylated, and unknown MGMT gene promoter groups were 18 months, 9 months, and 6 months, respectively (p=0.017). Age, KPS, gender, total dose of radiotherapy, radiotherapy fraction dose, and pseudoprogression were not significant prognostic factors for PFS (Table 3).

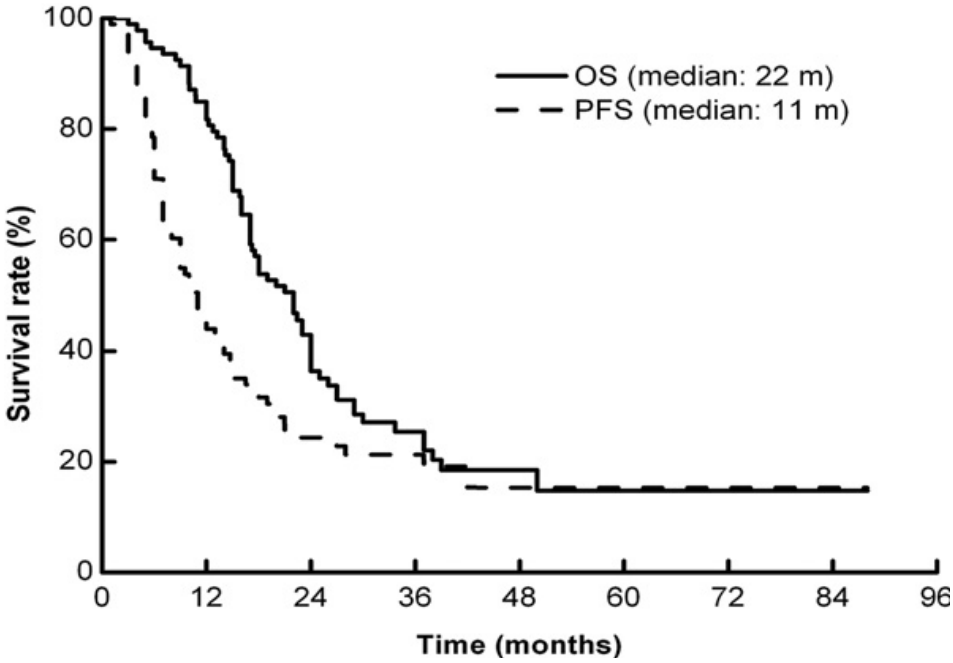

Figure 1. Overall survival (OS) and progression-free survival (PFS) in 93 patients with glioblastoma.

The median OS was 22 months, the 3-year OS rate was 22% in 93 patients, and the 5-year OS rate was 15% (Figure 1). Age and MGMT gene promoter methylation status were significant prognostic factors in both univariate and multivariate analyses (Tables 2 and 3). The median survival time and 2-year survival rates were 30 months and 57% in patients younger than 50 years and 18 months and 27% in patients older than 50 years, respectively (p=0.001). Patients who underwent GTR or STR showed a median survival of 23 months and a 2-year survival rate of 38%. However, patients who received partial resection or biopsy only showed a median survival of 15 months and a 2-year survival rate of 33% (p=0.049). Median survivals of the methylated, unmethylated, and unknown groups were 29 months, 20 months, and 14 months, respectively (Figure 2. A, p=0.002). In the 35 patients with methylated MGMT promoters, the 3- and 5-year survival rates were 43 and 31%, respectively. KPS, gender, total dose of radiotherapy, fraction dose of radiotherapy, and pseudoprogression were not significant prognostic factors. Long-term survivors (more than 3 years) were more frequently seen in the methylated group (11 of 35 patients in the methylated group vs. 4 of 43 patients in the unmethylated group).

To assess the impact of radiation dose and chemotherapy regimen, ninety patients were divided into three groups according to total dose of radiation and TMZ regimens; 60 Gy and the current TMZ regimen, over 60 Gy and the current TMZ regimen, and over 60 Gy and inconsistent TMZ regimen.

Three patients with low total dose of radiation (under 60 Gy) were excluded. There was no statistically significant difference in OS among the three groups (p=0.991).

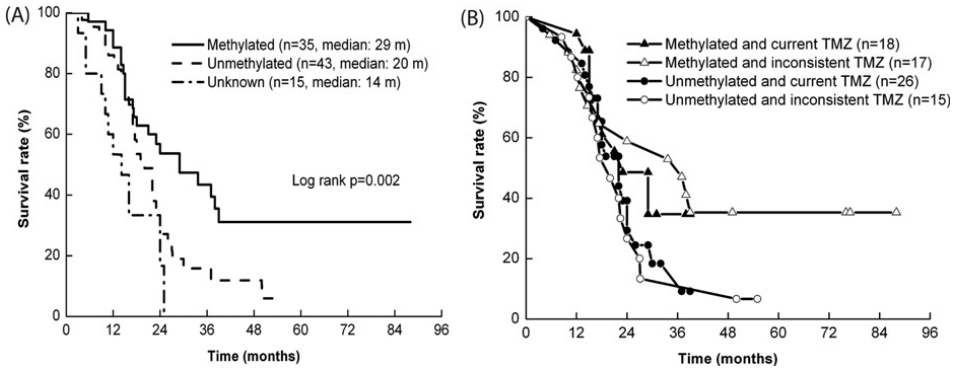

Figure 2. (A) Overall survival rates, according to O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation status (n=93). (B) Overall survival rates, according to MGMT gene promoter methylation status and temozolomide (TMZ) regimens (n=76).

Patients were classified according to the three most significant prognostic factors in our current study, and treatment outcome was analyzed (Table 4). The six patients with combined prognostic factors of having a methylated MGMT gene, ≤50 years, and total/subtotal resections are all alive 38-77 months after operation. However, the median OS in the eight patients with an unmethylated MGMT gene, >50 years, and who underwent less than a subtotal resection was 13.2 months.

Table 4. Overall survival related to three significant prognostic factors

Methylation Status (n=78)	Age (years)	Extent of Resection		Median OS (months) (95% CI)
Methylated (n=35)	Age ≤50 (n=11)	GTR+STR	(n=6)	all alive (38-77)
		Partial+biopsy	(n=5)	38 (15.5-62.4)
	Age >50 (n=24)	GTR+STR	(n=20)	21 (10.6-31.3)
		Partial+biopsy	(n=4)	12 (0.0-24.3)
Unmethylated (n=43)	Age ≤50 (n=14)	GTR+STR	(n=13)	24 (17.9-30.0)
		Partial+biopsy	(n=1)	15 (18.7-26.1)
	Age >50 (n=29)	GTR+STR	(n=21)	18 (11.0-24.9)
		Partial+biopsy	(n=8)	13.2 (5.2-19.2)

CI=confidence interval, GTR=Gross total resection, STR=Subtotal resection

IV. DISCUSSION

Age, performance status, Mini-Mental Status Examination, extent of resection, detection of pseudoprogression, tumor location, and no corticosteroid treatment at baseline were considered prognostic factors in previous reports. Among these, age, performance status, and extent of resection are the most consistently reported prognostic factors for patients with GBM.[2] In this study, age and MGMT gene promoter methylation were independent prognostic

factors for OS, and extent of resection and MGMT gene promoter methylation were independent prognostic factors for PFS. Gender, KPS, total dose of radiotherapy, radiation necrosis, and pseudoprogression did not show significant correlation with patient survival.

The EORTC trial 26981/22891 and NCIC trial CE.3 was a prospective, randomized study to compare radiotherapy alone and radiotherapy plus TMZ in a total of 573 patients from 85 centers. Monika et al. evaluated the MGMT methylation status in a total of 307 of 573 patients, and reported that the median OS was 21.7 months in patients with a methylated MGMT gene promoter and 12.7 months in patients with an unmethylated MGMT gene promoter.[13] In our study, the median OS was 29 months with MGMT gene methylation and 20 months with unmethylation. One possible explanation for improved survival in our current study is the superior GTR/STR rate. Approximately three-fourths (74%) of our patients underwent GTR or STR, and their median survival time was 23 months. In the EORTC trial 26981/22891 and NCIC trial CE.3, the extent of resection was categorized into biopsy, partial debulking surgery, and complete debulking surgery. Approximately 40% of patients underwent complete debulking surgery, although the definition of complete removal and partial removal was not clearly described. On the other hand, in our institution, the extent of resection was determined by post-operative MRI taken within 48 hours of operation in all patients. Another possible explanation of better survival in our current study is the early start of

post-operative radiotherapy. The median estimated cellular doubling time of GBM is 17 days. As the tumor enlarges and sends out satellite growths, a regional miss is more likely in the radiation treatment.[14] Some authors have reported that delay in the time from surgery to start of radiotherapy is associated with a poor survival rate.[15] Irwin et al. reported that every additional week of delay until start of radiotherapy increases the risk of death (hazard ratio) by 8.9% (95% confidence interval, 2.0-16.1%). In the EORTC trial 26981/22891 and NCIC trial CE.3, the median time from diagnosis to the start of radiotherapy was 5 weeks (range, 1.7-12.9 weeks). In our current study, post-operative radiotherapy was started within 3 weeks of operation in 87% of patients. The current study was conducted in a single institution, and consistent surgical and radiotherapy techniques may have contributed to better survival compared with reports from multi-institution studies.

Most previous dose-escalation studies for GBM have failed to show an improvement in survival.[16,17] [17] Before introducing TMZ, we tried to escalate the radiation dose from 60 Gy to 70.2 Gy. In the report by Cho et al.,[18] the median survival in 42 patients who received a higher dose of radiation (63-70.2 Gy, median 66 Gy) was 21±5.03 months, whereas median survival in 33 patients who received a lower radiation dose (50.4-59.4 Gy, median 59.4 Gy) was 14±0.94 months. Because Cho et al. conducted a retrospective study with historical comparison, improved survival could possibly be attributed not only to a higher radiation dose but also to improved surgical and radiotherapy

techniques. In the current study, there was no significant difference in the median OS between patients who received 60 Gy radiation plus TMZ and patients who received over 60 Gy radiation plus TMZ (p=0.991). One possible explanation is the higher radiotherapy dose effect was compromised by adding TMZ. The effects of adding TMZ and escalating the radiation dose require further investigation.

From the EORTC trial 26981/22891 and NCIC trial CE.3, MGMT gene promoter methylation has gained interest as a potential predictive marker for improved response to chemotherapy, particularly alkylating agents such as TMZ. However, it is still not entirely clear whether MGMT promoter methylation is truly a prognostic marker, indicative of the natural history of disease, or truly a predictive marker of sensitivity to chemotherapy or radiation.[19,20] [20] In the same EORTC trial, in patients who were treated with radiotherapy alone, MGMT promoter methylation showed a strong correlation with improved survival. This finding suggested that MGMT promoter methylation was a general prognostic marker for radio-sensitivity, in addition to a predictive marker for chemo-sensitivity. Rivera et al. assessed the MGMT methylation status and treatment outcome in 225 patients with GBM who were treated with radiotherapy alone and found that methylation of the MGMT gene promoter correlated with improved OS.[20] In our current study, 39 patients received radiotherapy with inconsistent TMZ. We questioned whether the outcome was different according to the TMZ regimen. We observed that OS

was consistently better in patients with a methylated MGMT promoter than in those with an unmethylated MGMT promoter irrespective of the TMZ regimen (Figure 2. B). Our results suggest that MGMT promoter methylation might be predictive of response to radiation and a general prognostic factor in GBM.

In conclusion, we confirmed that MGMT gene methylation status and age are potent prognostic factors in patients with GBM. Our results also suggested that maximum surgical resection and early start of post-operative radiotherapy might further improve the outcome.

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ABSTRACT(IN KOREAN)

Temozolomide-Based Chemoradiotherapy를 받은 아교모세포종 환자에서, 중요한 예후 인자로써의 MGMT Gene Promoter Methylation: 단일 기관 연구

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목적: 최근, O^6-methylguanine-DNA methyltransferase (MGMT)가 결핍된 세포는 temozolomide 치료에 더 민감한 것으로 알려졌다. MGMT gene의 hypermethylation이 아교모세포종 환자에서 생존율과 관련이 있는 지 평가하고자 하였다.

대상 및 방법: 2001년부터 2008년까지, temozolomide와 함께 involved field radiotherapy를 받은, 조직학적으로 확진된 93명의 환자를 후향적으로 분석하였다. 나이의 중앙값은 58세였다 (범위, 24-78). 수술적 절제 범위는 전절제가 39명 (42%), 아전절제가 30명 (32%), 부분절제가 17명 (18%), 조직검사만 시행된 경우가 7명 (8%)

이었다. 방사선 치료는 87%의 환자에서 수술 후 3주 이내에 시작하였다. 방사선 치료 선량은 50-74 Gy (중앙값 70 Gy)였다. MGMT gene methylation 여부는 78명의 환자에서 확인할 수 있었다; 43명이 (55%) unmethylated, 35명이 (45%) methylated 소견이었다. 중앙 추적 기간은 22개월 (범위, 3-88)이었다.

결과: 중앙 생존기간은 22개월, 무진행 생존기간은 11개월이었다. MGMT gene methylation은 다변량 분석에서 생존율 (p=0.002)과 무진행 생존율 (p=0.008) 모두에서 중요한 예후 인자였다. Methylated 군의 중앙 생존기간은 29개월이었고, unmethylated 군은 20개월이었다. Methylated된 35명의 환자에서 2년 생존율, 5년 생존율은 54%, 31%였다. methylated MGMT gene, ≤50 세, 전절제/아전절제 시행 받은 6명의 환자는 수술 후 38-77개월째에 모두 살아있는 상태이다. 반면, unmethylated MGMT gene, >50 세, 수술적 절제 범위가 아전절제보다 적었던 8명의 환자는 중앙 생존기간이 13.2 개월이었다.

결론: 본 연구에서 MGMT gene methylation이 아교모세포종 환자에서 중요한 예후인자임을 확인하였다. 이 결과는 수술 후 조기에 방사선 치료를 시작하는 것과 수술적 절제 범위가 아전절제 이상인 경우가 더 좋은 예후를 보임을 나타낸다.

핵심되는 말 : 아교모세포종, O^6-methylguanine-DNA methyltransferase, methylation, 예후인자, 방사선치료