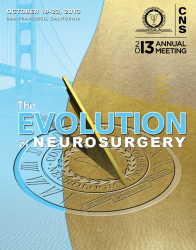


The Role of Stereotactic Radiosurgery and its Combination with Temozolomide as a Salvage Treatment of Recurrent Glioblastoma

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Introduction: After the use of radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ), the survival in patients with newly diagnosed glioblastoma multiforme (GBM) have improved. Stupp et al. reported the standard treatment schedule for GBM and the increased median survival from 12.1 to 14.5 months. Despite advances in first-line therapy, almost all of GBM recurred within a few months. Therefore, GBM is still an incurable disease and its prognosis is dismal [2,3]. For increasing survival, improvement in salvage treatment for GBM at recurrence is essential. However, there is no standard of salvage management so far and the available options are limited.

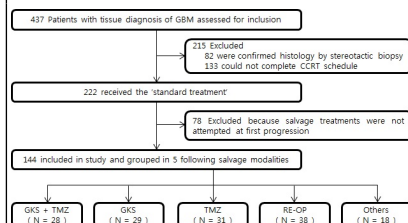
In this retrospective study, we reviewed our experience with various kinds of salvage treatment to determine which modality is the most effective for improving survival and what factors are correlated with prognosis. Especially, we paid attention to combination of GKS and concurrent TMZ and its superiority than other modalities in patients with recurrent GBM.

Methods: Between January 2002 and December 2011, we included 144 patients into this study whom were received standard treatment at first diagnosis and salvage treatment at the time of first progression. We defined 'standard treatment' as debulking surgery (not including biopsy only) at first diagnosis and followed by concomitant chemoradiation (CCRT) regimen (continuous delivery of 75 mg/m² of TMZ for 6weeks combined with fractionated external beam RT) and conventional adjuvant TMZ (150 mg/m² to 200 mg/m² given 5 days of each 28-day cycle upto 6 cycles). And we grouped these patients into 5 categories according to salvage modalities. The diagram of patient selection is shown in figure.

Results: The median overall survival (OS) and progression free survival (PFS) from the time of progression were showed in followed figures and tables. In the multivariate analysis, performance status, age, recurrence pattern, and time to 1st progression were influenced in prognosis of patients with recurrent GBM

Conclusions: The GKS with concomitant TMZ attained survival advantage in the treatment of recurrent GBM in comparison with GKS alone or TMZ alone. Survival outcome of radiosurgery was compatible with re-operation in the salvage situation. To treat recurrent GBM, both local and systemic modalities are important as like in initial treatment. Combination with GKS and systemic TMZ is a good strategy for managing recurrent GBM.

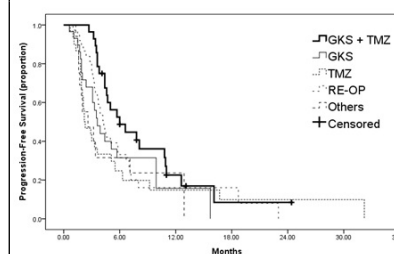
Flow diagram of patient selection



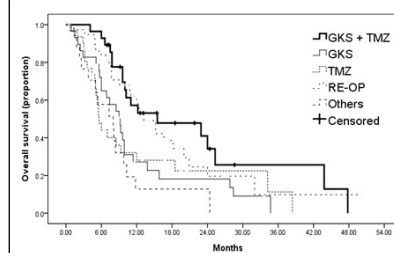
144 patients were included for survival analysis according to 5 salvage modalities. All of included patients in this study were received one of salvage treatments at first progression after 'standard treatment (debulking surgery followed by CCRT and conventional TMZ administration)'.

Learning Objectives: By the conclusion of this session, participants should be able to : Identify an effective combination of local (stereotactic radiosurgery) and systemic (temozolomide chemotherapy) treatments for managing recurrent glioblastoma

PFS



OS



PFS and 6-PFS according to salvage modalities

	PFS, months (median, 95% CI)	6-PFS, percent (95% CI)	P value (vs. GKS + TMZ)
GKS + TMZ	6.0 (3.4 – 8.6)	48.8 (39.2 – 58.4)	N/A
GKS	3.6 (2.6 – 4.6)	31.5 (22.2 – 40.8)	0.071
TMZ	2.3 (1.2 – 3.4)	16.4 (16.4 – 29.0)	0.021
RE-OP	4.3 (3.5 – 5.1)	33.2 (25.2 – 41.2)	0.092
Others	2.6 (0.6 – 4.5)	31.6 (19.0 – 44.2)	0.030

GKS + TMZ group showed the significantly longer estimated PFS (6.0 months) and nearly half of patients were survived in 6 months.

OS and 6-OS according to salvage modalities

	OS, months (median, 95% CI)	6-OS, percent (95% CI)	P value (vs. GKS + TMZ)
GKS + TMZ	15.5 (0.7 – 30.2)	92.9 (88.0 – 97.8)	N/A
GKS	9.2 (6.8 – 11.5)	72.1 (63.7 – 80.5)	0.009
TMZ	5.6 (4.8 – 6.3)	44.1 (34.7 – 53.5)	0.005
RE-OP	13.2 (9.5 – 16.9)	78.3 (78.3 – 90.1)	0.511
Others	9.9 (8.5 – 11.2)	57.8 (45.6 – 70.0)	0.001

GKS + TMZ group showed prolonged OS compared with other groups significantly except RE-OP group.

Prognostic factors of patients with GBM at progression

* Hazards ratio (p value, 95% CI)

Variables	PFS	OS
Age (< vs. ≥ 65years)	2.151 (0.017, 1.150 – 4.025)	0.897 (0.706, 0.509 – 1.580)
Gender (male vs. female)	0.950 (0.799, 0.641 – 1.408)	1.087 (0.681, 0.731 – 1.618)
ECOG (good vs. poor)	1.691 (0.020, 1.086 – 2.633)	2.146 (0.001, 1.351 – 3.409)
Resection (total vs. subtotal)	0.816 (0.335, 0.539 – 1.234)	0.889 (0.577, 0.588 – 1.345)
Recurrence (local vs. distant)	0.843 (0.464, 0.533 – 1.332)	1.791 (0.013, 1.132 – 2.834)
Time to 1 st progression (< vs. ≥ 9months)	0.625 (0.625, 0.741 – 1.648)	1.507 (0.047, 1.005 – 2.259)

Good performance status was important for improving both OS and PFS. Old age, distant recurrence pattern, short period to first progression were risk factors for decreasing PFS or OS.