Gamma Knife Stereotactic Radiosurgery and Bevacizumab can be Safely Used to Prolong Survival for Focally Recurrent Glioblastoma

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Introduction

There has been promising retrospective data, which suggests a survival benefit with the use stereotactic radiosurgery (SRS) and bevacizumab in the treatment of glioblastoma (GBM) recurrences. The existing data is derived from small cohorts, which has limited analysis of the concomitant therapies efficacy.

Methods

We retrospectively reviewed our experience with SRS and bevacizumab for the treatment of focal GBM recurrence during 2009 - 2015. Outcomes include overall survival (OS), progression-free survival (PFS), and radiation-related adverse events. Kaplan-Meier methods and multivariate Cox proportional hazards models were applied for survival analysis.

Results

Within a median of 13.7 months after diagnosis, a total of 45 GBM patients underwent SRS and bevacizumab treatment. Median age was 57 years (range: 20 - 78 years) and 63.3% were female. The median KPS at recurrence was 80 (range: 40 - 100). 65% of patients had single radiosurgery target (range: 1 - 4) and median target volume and margin dose were 2.2 cm3 (range: 0.1 - 25.2 cm3) and 17.0 Gy (range: 13 - 24 Gy), respectively. Median PFS and OS were 9.3 and 31.0 months following diagnosis, and 5.2 and 13.3 months after SRS, respectively. Factors associated with poor outcomes were KPS = 70, SRS dose < 18 Gy, and use < 2 chemotherapy agents prior SRS. No radiation-related adverse events occurred.

Conclusions

SRS and bevacizumab can be safely used to treat focal GBM recurrence. KPS, radiation dose, and multi-agent chemotherapy use prior to SRS demonstrated significant impact on PFS. Bevacizumab may provide clinically relevant radioprotection.

Learning Objectives

1. Understand the natural history of recurrent glioblastoma.

2. Describe the mechanism of radiation injury and bevacizumab's role in suppressing its manifestations.

3. Understand the role of radiosurgery and bevacizumab in focally recurrent glioblastoma.

References

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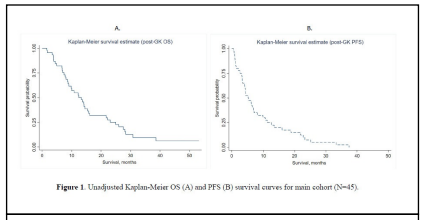

Figure 1. Unadjusted Kaplan-Meier OS (A) and PFS (B) survival curves for main cohort (N=45).

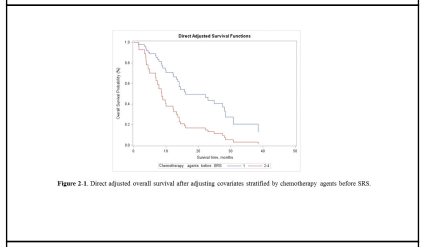

Figure 2-1. Direct adjusted overall survival after adjusting covariates stratified by chemotherapy agents before SRS.

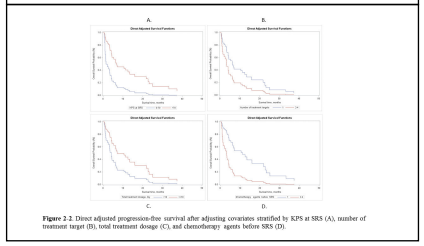

Figure 2-2. Direct adjusted progression-free survival after adjusting covariates stratified by KPS at SRS (A), number of treatment target (B), total treatment dosage (C), and chemotherapy agents before SRS (D).

Table 1. Patient characteristics in total cohort, OS cohort and PFS cohort.

Characteristics	Total cohort N (%)	OS cohort N (%)	PFS cohort N (%)
Total	45 (100)	39 (100)	31 (100)
Age at SRS, years			
20-60	28 (62)	25 (64)	21 (68)
>60	17 (38)	14 (36)	12 (34)
Gender			
Male	21 (47)	21 (54)	17 (49)
Female	24 (53)	18 (46)	18 (51)
KPS at SRS			
≤ 70	12 (27)	12 (31)	11 (31)
>70	28 (62)	27 (69)	24 (69)
Unknown	5 (11)	-	-
Number of craniotomies			
1	28 (58)	22 (56)	20 (57)
2-4	19 (42)	17 (44)	15 (43)
Number of treatment targets			
1	29 (64)	26 (67)	23 (66)
2-4	16 (36)	13 (33)	12 (34)
Time from diagnosis to SRS, months			
3.4-13.6	23 (51)	20 (51)	18 (51)
13.6-47.9	22 (49)	19 (49)	17 (49)
Total treatment volume, cm^3			
<5	33 (73)	27 (69)	24 (69)
≥5	12 (27)	12 (31)	11 (31)
Total treatment dosage, Gy			
<18	28 (62)	23 (59)	21 (60)
≥18	17 (38)	16 (41)	14 (40)
Chemotherapy agents before SRS			
1	23 (52)	20 (51)	18 (51)
2-4	21 (48)	19 (49)	17 (49)
Chemotherapy agents after SRS			
1-2	19 (42)	15 (38)	13 (37)
3-5	25 (58)	24 (62)	22 (63)
Unknown	1 (2)	-	-

Abbreviations: SRS, stereotactic radiosurgery; OS, overall survival after the first SRS; PFS, progression-free survival after the first SRS; KPS, Karnofsky performance score.

Table 2. Multivariate Cox proportional hazards models of OS and PFS.

Predictors	OS cohort (N=39)[a] HR	95%CI	P	PFS cohort (N=31)[b] HR	95%CI	P
Age at SRS, years						
20-60	1.00	-	-	1.00	-	-
>60	1.07	0.48 - 2.35	0.866	1.93	0.75 - 5.00	0.173
Gender						
Male	1.00	-	-	-	-	-
Female	0.99	0.46 - 2.14	0.978	2.75	1.10 - 6.93	0.031
KPS at SRS						
≤ 70	1.00	-	-	1.00	-	-
>70	0.50	0.19 - 1.35	0.172	0.14	0.05 - 0.44	0.001
Number of craniotomies						
1	1.00	-	-	1.00	-	-
2-4	1.00	0.48 - 2.08	0.992	0.41	0.19 - 0.89	0.025
Number of treatment targets						
1	1.00	-	-	1.00	-	-
2-4	2.20	0.89 - 5.44	0.088	2.94	1.09 - 7.94	0.033
Time from diagnosis to SRS, months						
3.4-13.6	1.00	-	-	1.00	-	-
13.6-47.9	1.50	0.60 - 3.07	0.455	2.34	0.94 - 5.73	0.062
Total treatment volume, cm^3						
<5	1.00	-	-	1.00	-	-
≥5	1.97	0.71 - 5.45	0.195	0.85	0.29 - 2.52	0.774
Total treatment dosage, Gy						
<18	1.00	-	-	1.00	-	-
≥18	0.55	0.24 - 1.24	0.147	0.31	0.13 - 0.72	0.010
Chemotherapy agents before SRS						
1	1.00	-	-	1.00	-	-
2-4	3.18	1.31 - 7.72	0.011	6.26	2.29 - 17.09	0.000
Chemotherapy agents after SRS						
1-2	1.00	-	-	1.00	-	-
3-5	0.90	0.40 - 2.31	0.835	0.88	0.34 - 2.12	0.786

Abbreviations: SRS, stereotactic radiosurgery; OS, overall survival after the first SRS; PFS, progression-free survival after the first SRS; KPS, Karnofsky performance score; HR, hazard ratio; 95%CI, 95% confidence interval.
a. Adjusted age KPS at SRS, gender, number of craniotomies, number of treatment targets, time from diagnosis to SRS, treatment volume, treatment dosage, and chemotherapy agents before after SRS in OS cohort.
b. Adjusted age KPS at SRS, gender, number of craniotomies, number of treatment targets, time from diagnosis to SRS, treatment volume, treatment dosage, and chemotherapy agents before after SRS in PFS cohort.

Table 3. Survival statistics by KPS at SRS, SRS dosage, and chemotherapy agents before SRS*.

Survival statistics	Death/Total N (%)	Median OS (months, IQR)	1-year OS % (95%CI)	2-year OS % (95%CI)
OS (N=39)				
Total	34/39 (87.2)	13.3 (8.9 - 24.9)	55.3 (38.1 - 69.3)	26.3 (13.7 - 40.8)
Chemotherapy agents before SRS				
1	17/20 (85.0)	14.5 (9.0 - 28.3)	70.0 (45.1 - 85.3)	40.0 (19.3 - 60.1)
2-4	17/19 (89.5)	7.8 (3.8 - 14.1)	38.9 (17.5 - 60.0)	12.5 (0.8 - 42.3)
	Progression/Total N (%)	Median PFS (months, IQR)	6-month PFS % (95%CI)	1-year PFS % (95%CI)
PFS (N=31)				
Total	28/31 (100.0)	4.5 (2.1 - 12.6)	45.7 (28.9 - 61.1)	25.7 (12.8 - 40.8)
KPS at SRS				
0-70	11/11 (100.0)	3.3 (0.3 - 10.6)	36.4 (11.2 - 62.7)	18.2 (2.9 - 44.2)
>70	24/24 (100.0)	5.4 (2.1 - 12.6)	50.0 (28.5 - 67.8)	28.2 (13.8 - 47.9)
Number of treatment targets				
1	23/23 (100.0)	6.1 (2.4 - 21.8)	56.5 (34.3 - 73.8)	34.8 (16.6 - 53.7)
2-4	12/12 (100.0)	3.4 (1.0 - 5.4)	25.0 (6.0 - 50.5)	8.3 (0.5 - 31.1)
Total treatment dosage, Gy				
<18	21/21 (100.0)	4.1 (2.1 - 6.6)	33.3 (14.9 - 53.1)	14.3 (2.6 - 32.1)
>=18	14/14 (100.0)	7.1 (1.3 - 21.8)	64.3 (34.3 - 83.3)	42.9 (17.7 - 66.0)
Chemotherapy agents before SRS				
1	18/18 (100.0)	8.6 (4.4 - 22.7)	61.1 (35.3 - 79.2)	38.9 (17.3 - 60.8)
2-4	17/17 (100.0)	3.4 (1.2 - 6.1)	29.4 (10.7 - 51.2)	11.8 (2.0 - 33.2)

Abbreviation: OS, overall survival; PFS, progression-free survival; IQR, interquartile range; 95%CI, 95% confidence interval.
*. The differences of Kaplan–Meier survival proportions across covariates were tested by using log-