Short Communication

Predicting survival with the Heidelberg prognostic model after salvage radiosurgery of previously irradiated progressive high-grade gliomas

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Abstract: The study aimed to determine which patients with previously irradiated progressive high-grade gliomas (PHGG) are likely to benefit from salvage stereotactic radiosurgery (SSRS) using the Heidelberg prognostication model (HPM). Twenty-five study participants with PHGG underwent SSRS between 2000 and 2010. There were 5 and 20 patients with determined low or high HPM prognostic scores, respectively. Overall median survival (MS) was 7 months (range, 1 to 32 months). The 6-, 12- and 24-month crude survival rates (CSR) were 60%, 28% and 16%, respectively. The MS and CSRs for the low-scoring patients were 20 months, 100%, 100% and 20%, respectively; for the 20 individuals with higher scores, the corresponding findings were 8 months, 75%, 35% and 10%, respectively. Among the evaluable 11 patients, the quality of remaining life after therapy was acceptable in approximately half of the cases. Acute and late toxicity were not observed in the retreated subjects. A trend towards improved survival, even if not statistically significant, was observed in the low HPM scoring patients. More documentation of favorable effects from the application of SSRS in people with PHGG is required to support its useful role as a second line treatment.

Keywords: Stereotactic radiosurgery; progressive high-grade glioma (PHGG); prognosis

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Introduction

Neurological deterioration is the most important cause of morbidity and mortality in people with previously irradiated, progressive high-grade gliomas (PHGG). This can be ascribed to the unpredictable rate of tumor growth. With the view that individuals with PHGG are not often expected to live long, choosing the right patients for salvage therapy is crucial. Prognostic factors, for example in brain metastases, have been defined to allow formulation of criteria for use in the selection of patients who may benefit from a particular form or forms of administered therapy. Recently, the Heidelberg prognostication model (HPM) was developed by Combs and colleagues (1) to determine survival after re-irradiation of high-grade gliomas. In the present study of an 11-year experience, salvage stereotactic radiosurgery (SSRS)] was used for treatment of the PHGGs, and the HPM scoring system was applied for its correlation with prognosis. Two questions were asked: (I) Was SSRS in these people worthwhile in terms of extended survival? (II) Was the HPM useful in the identification of patients who may benefit from SSRS?

Methods

A retrospective review of the radiation oncology data base identified 25 individuals treated with SSRS between 2000 and 2010 for previously irradiated PHGG. The initial treatment was multimodal (surgery, adjuvant

Table 1 Clinical characteristics, the Heidelberg prognostic model* and patient outcomes after salvage radiosurgery for progressive previously irradiated high-grade gliomas

Patient, no.	Age* (yrs)	Histology*	Interval* between treatments	Total score*	Survival in mos
1	1	2	0	3	2
2	1	2	1	4	32
3	1	2	1	4	9
4	0	2	1	3	24
5	0	2	1	3	8
6	0	2	0	2	6
7	1	2	0	3	27
8	1	2	1	4	25
9	1	2	1	4	1
10	0	2	1	3	4
11	0	2	1	3	3
12	1	2	0	3	5
13	0	2	1	3	17
14	0	2	0	2	14
15	1	2	1	4	13
16	0	2	0	2	4
17	1	2	1	4	8
18	1	2	0	3	4
19	1	1	1	3	5
20	1	2	0	3	3
21	0	2	0	2	2
22	1	2	0	3	10
23	0	2	1	3	7
24	1	2	1	4	8
25	0	1	0	1	7

*, Heidelberg prognostication scoring system includes for age group: score 0, <50 years and score 1, ≥50 years of age; for glioma histology group: score 1 for WHO grade III and score 2 for WHO grade IV tumor; for interval between primary radiotherapy and salvage radiosurgery: score 1 for ≤12 months and score 0 for >12 months interval.

chemoradiotherapy) in 20 patients or bimodal (surgery with adjuvant radiotherapy) in five subjects. Tumor progression (TP) or recurrence, identified on serial magnetic resonance imaging (both T1-weighted contrast-enhanced and T2-weighted images), was defined by an increased signal in new areas or a 25% increase in signal in pre-existing tumor sites within the brain. Given the radiographic challenge of distinguishing TP from radionecrosis, magnetic resonance spectroscopy was sometimes employed. PHGG was categorized as local if the progression was in the resection cavity or in-continuity with it, or less than 2 cm from the primary tumor margins (17 cases), and distant if the border of the recurrent lesion was more than 2 cm away from the previous tumor resection cavity (eight cases).

SSRS was administered alone in nine patients, with chemotherapy to ten patients or with prior gross tumor resection in six patients. The median applied margin dose, usually prescribed at the 50% isodose line, was 14 Gy (range, 11 to 20 Gy). Dose selection was influenced by several factors such as PHGG volume, tumor location in eloquent areas or juxtaposition to the anterior visual pathway or brainstem. The median target volume was 5.7 cm^3 (range, 0.7 to 26.3 cm^3); when the tumor volume was considerably large (>10 cm^3), the treatment target was limited only to the considered growing portion of the neoplasm.

In the HPM, clinicopathological factors were used in the generation of a prognostic score. These variables included histology, age and time between the initial and repeat radiotherapy. Numerical values were given as follows: When the patient's age was <50 or ≥50 years, the assigned scores were 0 and 1 respectively; when the tumor grade was III or IV, the assigned scores were 1 and 2, respectively; and when the time interval was ≤12 and >12 months, the assigned scores were 1 and 0, respectively. Summated scores were then correlated with ultimate longevity of the patients. The median survival and crude survival rates were the chosen expressions of prognosis.

Results

Table 1 displays the clinical characteristics and total HPM scores of the study participants. Fifteen patients were men and ten were women. The median age was 53 years (range, 16 to 81 years). Many (23 of 25; 92%) individuals possessed glioblastoma multiforme, including a case of gliosarcoma. Most of the tumors were unifocal in pattern (19 of 25; 76%). Fourteen people (56%) were symptomatic and needed palliation. All of the PHGGs were in the supratentorial compartment of the brain. The median interval between the initial radiotherapy and SSRS was ten months (range, 2 to 32 months). Local recurrence after

Table 2 The Heidelberg prognostication model after salvage stereotactic radiosurgery of progressive previously irradiated high-grade gliomas

Feature	Heidelberg prognostication model scoring system	
	Low score[¶] (n=5)	High score[§] (n=20)
Median survival (range)	20 (13 to 31) months	8 (1 to 32) months
Crude survival rate (P)		
6-month (P>0.50)	(5/5) 100%	(15/20) 75%
12-month (P<0.05)	(5/5) 100%	(7/20) 35%
24-month (P>0.08)	(1/5) 20%	(2/20) 10%

[¶], Score of 1 or 2; [§], Score of 3 or 4. Statistical analysis used the chi-square test and the Yates correction factor.

Table 3 Quality of life of patients after salvage stereotactic radiosurgery (SSRS) for progressive previously irradiated high-grade gliomas

Poor prognostic feature	Quality of Life*	
	Acceptable[¶] (n=5)	Poor[§] (n=6)
Older age (≥50 years)	2	4
World Health Organization grade IV glioma	5	6
Short interval between treatments (≤12 months)	3	3
Large tumor volume (≥10 cm^3)	3[a]	1[a]
Lower applied margin dose (≤15 Gy)	5	4
Overall median survival	5 months (range 2 to 8 months)	10.5 months (range 3 to 32 months)

*, Only 11 patients (of the 25 study participants treated by SSRS) were evaluable. Comparative statistical analysis was not performed given the small number of patients composing each subset. [¶], Acceptable meant the observed absence of neurologic deficit during the follow-up period; §Poor indicated neurological status deterioration during the follow-up period; [a], Information was available in three and four patients, respectively.

SSRS occurred in three patients (12%); two individuals were treated with repeat SSRS, while the remaining patient underwent salvage resection.

The study subjects were all deceased at the time of the clinical investigation. The overall median survival was seven months. The 6-, 12- and 24-month crude survival rates (CSR) were 60%, 28% and 16%, respectively. Prognosis associated with the HPM scoring system in this limited experience is revealed in *Table 2*. Admittedly, the uneven distribution of patients with different HPM scores (with a preponderance of high-scoring participants) precludes the drawing of a meaningful conclusion. No evidence was found to document the occurrence of adverse radiosurgery-related events such as radionecrosis or leukoencephalopathy. Quality of life (QOL) assessment after SSRS was possible in 11 patients (*Table 3*). Acceptable QOL (five patients) was defined by the absence of neurologic deficit during the follow-up period which ranged from two to eight months. On the other hand, QOL was declared poor [six patients] when neurological deterioration was observed during the follow-up period which extended from three to 32 months.

Discussion

The concept of repeat radiotherapy of PHGGs is intuitively rational for a disease that has the potential to be a life-threatening illness and for seriously affecting the quality of remaining life. This audit was performed because we consider it essential to identify which patients correctly need SSRS to avoid futile therapy, unnecessary toxicity, inappropriate resource expenditure and denial of potentially beneficial treatment. Given the confusing variety of potential prognostic factors, and the unanswered question of which patients benefit the most from re-irradiation of PHGGs, a simple method for classifying these individuals into a reasonable number of subgroups with different periods of survival is needed (2). In 2013, Combs and colleagues (1) used their database of 233 patients with

recurrent gliomas who were retreated with fractionated stereotactic radiotherapy. Tumor histology consisted of HGG (60%) and low-grade gliomas (40%). The median re-irradiation dose administered was 36 Gy given in 18 fractions; median survivals of 8, 20 and 24 months were observed in patients with grade IV, III and low-grade gliomas, respectively. After finding several significant prognostic factors and generating a scoring system, these researchers showed that patients with HPM 0 to 2 scores had the best prognosis, whereas those with 3 to 4 scores exhibited lower survivals after retreatment (3). Unlike those reported in two other HPM clinical investigations (1,4), we were unable to conclude with certainty that the prognosis in patients with HPM low scores is better than that of individuals with higher scores. However, the observations of a 12% failure rate after SSRS and the distinct possibility of maintaining a favorable QOL following SSRS seem congruent with the outcomes in other reports (5-8).

These results should be interpreted with caution because of several limitations. First, the retrospective design of the investigation could be responsible for selection bias, and the number of patients was small. Second, it was not possible to determine whether the few patients with symptoms and signs of PHGG improved after SSRS. Nonetheless, notwithstanding its failings, our short report permitted us to highlight the fact that there will be select patients with PHGGs whose life expectancy may be prolonged by the administration of SSRS. As additional data confirming the utility of the HPM are obtained, it is likely that we shall be able to select the most appropriate candidates for SSRS in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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