Validation of the Graded Prognostic Assessment Index for Surgically Treated Patients with Brain Metastases

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Abstract. *The purpose of this study was to evaluate the performance of the new Graded Prognostic Assessment (GPA) index, which was recently developed from data in the Radiation Therapy Oncology Group (RTOG) database, in patients treated with surgical resection of brain metastases and postoperative whole-brain radiotherapy. The authors analyzed 64 patients and assigned each patient to each of the four indices previously evaluated by the RTOG (recursive partitioning analysis class, Score Index for Radiosurgery, Basic Score for Brain Metastases and GPA). The present data confirm the validity of the scoring systems in surgically treated patients. Each of the four indices splits the dataset into prognostically different groups; in the GPA groups, median survival was 18.9, 9.8, 5.5, and 3.7 months, respectively ($p<0.05$). In conclusion, these results confirm the validity of the GPA index in a patient population that previously has not been assessed with this new tool.*

Sperduto *et al*. recently published an analysis of data from five randomized Radiation Therapy Oncology Group (RTOG) trials on treatment of brain metastases (1). They aimed at defining the most useful score by comparing the already well-known recursive partitioning analysis (RPA) classes originally described by Gaspar *et al*. 1997 (2), the Score Index for Radiosurgery (SIR) published by Weltman *et al*. 2000 (3), and the Basic Score for Brain Metastases (BSBM; Lorenzoni *et al*. 2004) (4). As RTOG radiosurgery (RS) trial 9508 allowed for substantial extension of their database, Sperduto *et al*. arrived at a new score, the Graded Prognostic Assessment (GPA). In the GPA system, three different values (0, 0.5 or 1) are assigned for each of the following four parameters: age (≥60, 50-59, <50 years), Karnofsky performance status (KPS; <70, 70-80, 90-100), number of brain metastases (>3, 2-3, 1), and extracranial metastases (present, not applicable, none). It was concluded that "GPA is the least subjective, most quantitative and easiest to use of the four indices" and that future trials should compare these scores and validate their findings. Our group was recently able to validate the performance of the GPA in patients treated with primary radiation therapy outside of clinical trials (paper submitted). In the present study, the same question was addressed in another group of patients, *i.e*. those treated with surgical resection and postoperative whole-brain radiotherapy (WBRT). Several groups have previously determined that the RPA classes define prognostically different subgroups in patients treated with surgery and WBRT (5-8).

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Patients and Methods

This study basically relies on the methods used by the RTOG in their analysis, though with a different target population. The authors included all adult patients with brain metastases from solid tumors treated with WBRT (median 30 Gy in 10 fractions) after surgical resection. The patients were entered into a database originally created by the first author before he moved to Norway. Only 2 patients were alive and censored at the last follow-up. As in other populations, the majority of patients had primary lung (non-small cell) or breast cancer. Overall survival distributions for each level of each index were calculated by using the Kaplan-Meier method. The day of first treatment (surgery) was used as the start date. The log-rank test was used to compare survival distributions of individual index level with all other levels by using a significance level of 0.05.

Results

The patient characteristics of the 64 cases are shown in Table I. Table II shows the survival results. In addition, Figure 1 and 2 display the survival curves for the GPA and SIR indices, respectively. The latter is shown because it has not often been evaluated in patients treated with resection and WBRT. All four indices split the dataset into groups with

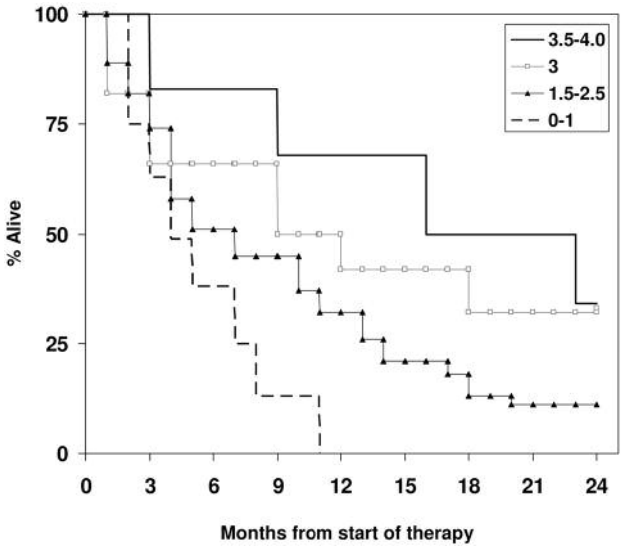

Figure 1. *Kaplan-Meier curves for overall survival for the Graded Prognostic Assessment (GPA) index.*

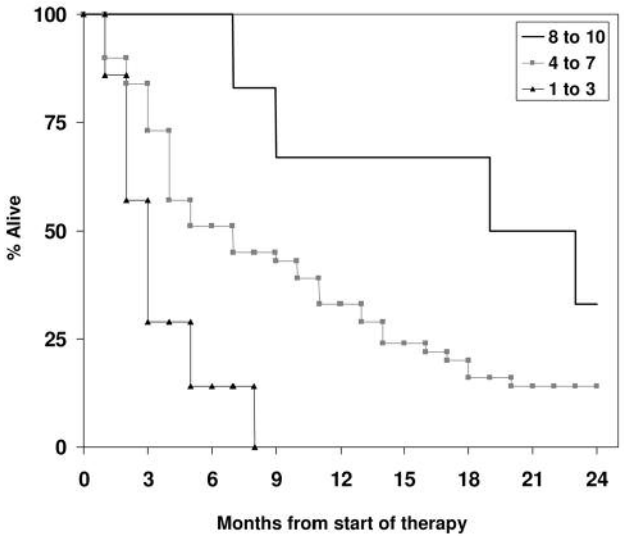

Figure 2. *Kaplan-Meier curves for overall survival for the Score Index for Radiosurgery (SIR).*

significantly different prognosis ($p<0.01$ for SIR and $p=0.05$-0.01 for the other three indices).

Discussion

This is, to the authors' best knowledge, the first analysis that validates the results of the recent RTOG publication (1) in a group of patients treated with a different approach, *i.e.* surgery and postoperative WBRT. As many patients in the authors' institution in Munich are treated with stereotactic radiosurgery, the number of patients in this study is limited. It was decided to include the SIR index in the present analysis, although the importance of the volume of the largest lesion is less obvious in patients treated with resection of that lesion as compared to radiosurgery. As shown in Figure 2, the SIR index clearly splits the dataset into prognostically different groups. However, 80% of the patients belonged to the intermediate group and only 9% and 11% to the favorable and unfavorable groups, respectively. It might be a drawback of all scoring systems that the most favorable prognostic group is very small (GPA ≥3.5: 9%; RPA class I: 17%; SIR 8-10: 9%; BSBM 3: 11%). Compared with the previous RPA studies in surgically treated patients (5-8), median survival in class I was better in the present cohort of patients (29 months *versus* 15-21 months). In class II, all other studies reported better results than the present one (7-11 months *versus* 5.5 months). In class III, the present data fit into those reported from the other trials that included class III (1.4-9 months *versus* 3.5 months). In the previous literature on brain metastases, the RPA classification was used more often than the BSBM and the SIR indices, probably because it is less time consuming and has been validated by several groups (9-16).

Table I. *Pretreatment characteristics of the 64 patients included in this study.*

Parameter	Number (%)
Female *vs.* male gender	22 *vs.* 42 (34 *vs.* 66)
Extracranial metastases present	33 (52)
Uncontrolled primary tumor	24 (38)
Single brain metastasis	54 (84)
Median Karnofsky performance status	70% (range 30-100)
Median age	55 years (range 36-74)

However, both RPA class II and III contain quite heterogeneous groups of patients. The factor determining class III is KPS<70, which might result from many different causes including the brain metastases themselves, advanced and treatment-refractory liver and lung metastases, atelectasis from primary lung cancer, surgery for pathological fracture in patients with bone metastases, anemia induced by chemotherapy and non-cancer-related comorbidity. As illustrated above, survival within the same RPA class varies by a factor of 2 between different studies (identical treatment approach). For these reasons, there obviously is a need for a better index than RPA.

The present analysis does not discourage the use of the new GPA in patients receiving surgery and WBRT, although the differences during the first four months of follow-up are largely negligible (Figure 1). As this might be caused by the small number of patients eligible for assignment to all four scores, it appears justified to continue exploring this new prognostic tool.

Table II. *Comparison of the survival results with the four different prognostic indices in all 64 patients.*

	RPA			BSBM				GPA				SIR		
	I	II	III	3	2	1	0	3.5-4	3	1.5-2.5	0-1	8-10	4-7	1-3
Number of patients (%)	11 (17)	35 (55)	18 (28)	7 (11)	23 (36)	30 (47)	4 (6)	6 (9)	12 (19)	38 (59)	8 (13)	6 (9)	51 (80)	7 (11)
Median survival (months)	29.0	5.5	3.5	20.3	7.0	3.2	2.0	18.9	9.8	5.5	3.7	20.2	6.0	2.0
% 6-Month survival	100	50	36	100	54	29	0	83	58	50	38	100	51	14
% 1-Year survival	91	24	11	80	38	16	0	67	42	32	0	67	33	0

RPA: recursive partitioning analysis class; BSBM: basic score for brain metastases; GPA: graded prognostic assessment; SIR: score index for radiosurgery.

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