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ORIGINAL ARTICLE

Validation of the graded prognostic assessment index for patients with brain metastases

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Abstract

Background. The purpose of this study is to evaluate the performance of the new "Graded Prognostic Assessment" (GPA) index, which recently was developed from data in the Radiation Therapy Oncology Group (RTOG) database, in patients with brain metastases treated outside of randomized clinical trials. *Material and methods.* The authors analyzed 232 patients with brain metastases and assigned these patients to the four indices previously evaluated by the RTOG (recursive partitioning analysis class, Score Index for Radiosurgery, Basic Score for Brain Metastases, and GPA). *Results.* The present data confirm the results of the RTOG analysis. Each of the four indices splits the data set into prognostically different groups. In the GPA groups, median survival was 10.3, 5.6, 3.5, and 1.9 months, respectively ($p < 0.01$). In the RTOG analysis, these figures were 11.0, 6.9, 3.8, and 2.6 months, respectively. *Conclusion.* These results confirm the validity of the GPA index in a patient population that most likely is more representative of the normal clinical situation than patients included in randomized trials.

Sperduto et al. have 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 prognostic 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 the 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 or1) are assigned for each of these four parameters: age ($\geq$ 60; 50–59; $<$50), 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. Therefore, the present analysis was performed.

Material and methods

This study basically relies on the methods used by the RTOG in their analysis, though with a different target population, i.e. patients treated in clinical routine outside of randomized trials. The authors included all adult patients with brain metastases from solid tumors treated with whole-brain radiotherapy (median 30 Gy in 10 fractions) with or without additional RS at two institutions (one in Norway and one in Germany) between 2002 and 2007. The patients were entered into a database, which originally was created by the first author before he moved to Norway. Survival updates are performed at regular intervals. The data were analyzed in April 2008. Only 6 patients were alive at last follow-up and thus censored (minimum follow-up 6 months, maximum 40 months, median

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8 months). As in other populations, the majority of patients had primary lung or breast cancer. Overall survival distributions for each level of each index were calculated by using the Kaplan-Meier method. The first day of radiotherapy 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 232 cases are shown in Table I. Radiosurgery was a component of treatment in 28 patients (12%). Due to missing information on primary tumor activity, not all patients could be assigned to RPA class, BSBM and SIR, respectively. The number of patients evaluated for RPA class was 208 (BSBM: 203, SIR: 222). Compared to RTOG's patients, the median age, KPS, number of lesions and volume are similar. Obvious differences exist, however, regarding controlled primary tumor (47% in this vs. 67% in RTOG's analysis) and presence of extracranial metastases (56% in this vs. 36% in RTOG's analysis). Thus, the present cohort is expected to have inferior survival. Table II shows the survival results. The median values for the GPA groups were 10.3 months, 5.6 months, 3.5 months and 1.9 months, respectively. In addition, Figure 1 displays the survival curves for the GPA index. All four indices split the dataset into groups with significantly different prognosis (borderline significance of $p = 0.05$ for the two intermediate groups in the GPA index, otherwise $p \leq 0.01$). Rather than using the SIR index in the same fashion as the RTOG authors, i.e. collapsed to 3 levels (8–10 points, 4–7 points, 0–3 points), separation into 4 levels appears feasible (8–10 points, 6–7 points, 4–5 points, 0–3 points). This results in median survival times of 8.7 months, 7.0 months, 2.7 months and 1.7 months in our patients ($p < 0.05$). One-year survival rates reach 44, 35, 12 and 2%. Yet, this 4-level SIR system is not superior to GPA.

Table I. Pretreatment characteristics of the 232 patients included in this study.

Parameter	Number (%)
Extracranial metastases present	131 (56)
Uncontrolled primary tumor	92 (40)*
Median Karnofsky performance status	70% (range 30–100)
Median age	57 years (32–81)
Median number of brain metastases	2 (1-approximately 50)
Median volume of the largest brain metastasis	11.6 ml (0.1–238)

*missing data in 29 patients (13%).

Discussion

This is, to the authors' best knowledge, the first analysis that validates the results of the recent RTOG publication [1]. Moreover, it extends the results to a different group of patients, i.e. those treated outside of randomized trials. The number of patients in this report is limited, although not tremendously different from that ultimately used by the RTOG authors, as two of their five trials did not collect the exact number of lesions at baseline and could therefore not be used to assign the patients to all 4 scoring systems. Eventually, 244 RTOG patients were available for the SIR score, compared to 222 in our database.

As a result of higher percentages of patients with uncontrolled primary tumor and known extracranial metastases, the unfavorable prognostic groups have lower median survival than the same groups in the RTOG database, e.g., RPA class II and III, the two unfavorable SIR groups, the 3 unfavorable BSBM groups, and the 3 unfavorable GPA groups. Yet 1-year survival is very similar for each of the groups if one compares the RTOG data with the present data. In the RTOG analysis, the GPA identified a group (GPA ≥ 3.5) with the longest survival (median 11.0 months) of any class in any of the four indices. In our patients, the median survival of that GPA group was 10.3 months.

It might be a drawback of all scoring systems that the most favorable prognostic group is very small (GPA ≥ 3.5: 9% of RTOG and 7% of present patients; RPA class I: 16% of RTOG and 11% of present patients; SIR 8–10: 13% of RTOG and 7% of present patients; BSBM 3: 28% of RTOG and 10% of present patients) and that all favorable groups actually contain a certain proportion of patients surviving for less than 2 months, while all unfavorable groups contain some patients surviving for 6–12 months. Clinical judgment is therefore required, e.g., in the decision to omit radiotherapy in patients with poor prognosis because presumed survival appears comparable to that with corticosteroids alone. In the previous brain metastases literature, the RPA classification has been used more often than the BSBM and the SIR indices, probably because it is less time consuming and has been validated by several groups [5–12]. 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 reasons (the brain metastases themselves, advanced and treatment-refractory liver and lung metastases,

Table II. Comparison of the survival results with four different prognostic indices in all 232 patients.

	RPA I	RPA II	RPA III	BSBM 3	BSBM 2	BSBM 1	BSBM 0	GPA 3.5–4	GPA 3	GPA 1.5–2.5	GPA 0–1	SIR 8–10	SIR 4–7	SIR 1–3
Number of patients (%)	22 (11)	123 (59)	63 (30)	20 (10)	61 (30)	88 (44)	34 (17)	17 (7)	36 (16)	108 (47)	71 (31)	16 (7)	145 (65)	61 (27)
Median survival in months	10.8	3.2	2.0	11.5	3.9	2.4	1.9	10.3	5.6	3.5	1.9	8.7	4.1	1.7
% 6-months survival	64	30	18	70	37	22	18	65	50	38	10	69	41	10
% 1-year survival	41	16	10	45	22	11	3	41	31	21	1	44	22	2

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

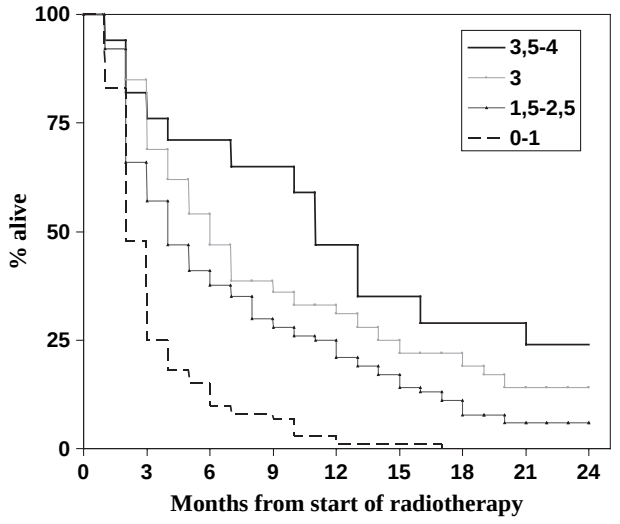

Figure 1. Kaplan-Meier curves for overall survival for the Graded Prognostic Assessment (GPA) index.

atelectasis from primary lung cancer, surgery for pathological fracture in patients with bone metastases, anemia induced by chemotherapy, non-cancer-related comorbidity etc.). For these reasons, there obviously is a need for a better index than RPA. The present analysis confirms the validity of the GPA index in a patient population that most likely is more representative of the normal clinical situation than patients included in randomized trials. It appears therefore justified to continue exploring this new prognostic tool.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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