

Validation of a Graded Prognostic Model in Patients With Brain Metastases Treated With Whole-brain Radiotherapy Instead of Radiosurgery

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Abstract. *Background/Aim:* The aim of this study was to analyze the survival predictions obtained from a recent graded prognostic model developed and validated in Japan. *Patients and Methods:* This was a retrospective single-institution analysis of 249 patients, managed with whole-brain radiotherapy for brain metastases. The sum of scores was calculated as in the Japanese study. The following parameters were included: number of brain metastases, volume of the largest lesion, sex, Karnofsky performance status, primary cancer type, control of primary cancer, and presence of extra-cerebral metastases. *Results:* Median overall survival was 3.0 months (95% CI= 2.6-3.4 months). The median sum of scores was 12, range=0-29. Statistically significant differences were observed between all prognostic strata. *Conclusion:* The graded prognostic model is also applicable to patients treated with whole-brain rather than stereotactic radiotherapy.

Parallel to changes in the treatment of brain metastases from solid tumors, more advanced prognostic models have been developed (1-6). In recent years, different models for different types of primary tumors have been proposed, e.g., melanoma- or renal cell carcinoma-specific prognostic scores (7-12). Nevertheless, a universally applicable score can still be considered advantageous due to its less complicated assignment in a busy working environment. Both three- and four-tiered scores have been validated and sometimes used

for stratification in prospective clinical studies. Recently, Sato *et al.* have published a graded prognostic model for patients surviving 3 years or more after stereotactic radiosurgery (13). These authors assigned scores for seven statistically significant factors, *i.e.*, number of brain metastases 1 vs. 2-4 vs. ≥ 5 (score; 6/1/0), volume of the largest lesion <10 ml vs. ≥ 10 ml (4/0), female/male sex (5/0), Karnofsky performance status (KPS) $\geq 80\%$ vs. $<80\%$ (5/0), primary cancers of breast/lung/gastrointestinal tract/other (1/0/3/0), controlled primary cancer vs. uncontrolled primary cancer (8/0) and presence of extra-cerebral metastases vs. no extra-cerebral metastases (5/0). Patients were categorized into four strata according to the sum of scores, *i.e.*, 0-9, 10-19, 20-29 and 30-36. The 3-year survival rates ranged between 0.7 and 45.1%. The median survival was 3.6, 6.8, 15.0 and 32.8 months, respectively. Relatively similar results were obtained in patients irradiated at a different institution in the same country (Japan), *i.e.* in a validation cohort (13). The aim of the present study was to provide additional data about the performance of this new prognostic model. In order to challenge its validity in several ways, patients managed in a different geographical region and with a different strategy (primary whole-brain radiotherapy, WBRT) were selected.

Patients and Methods

Analogous to previous validation studies (14-16), a single-institution database that includes all patients with unresected parenchymal brain metastases from histologically verified extracranial primary tumors managed with first-line WBRT was analyzed; both completed and interrupted treatment courses were included (according to the intention-to-treat principle; no previous prophylactic or other brain irradiation). The fractionation regimen was at the discretion of the treating physician. Further treatment for new or recurrent brain metastases was individualized. The strategies consisted of salvage surgery, stereotactic radiotherapy, systemic therapy or best supportive care (BSC). Systemic treatment was usually prescribed as judged appropriate by the patients' medical oncologists. The patients were treated between January 01, 2007 and

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December 31, 2019. Extracranial staging consisted of computed tomography (CT). If clinically relevant, other modalities were added to clarify CT findings, *e.g.*, isotope bone scan, ultrasound, positron emission tomography *etc.* The sum of scores was calculated as described by Sato *et al.* (outlined in the previous paragraph) (13). Overall survival (time to death) from the first day of radiotherapy was calculated employing the Kaplan–Meier method, and different groups were compared using the log-rank test (SPSS 25, IBM Corp., Armonk, NY, USA). Only three patients were censored after median 4 months of follow-up. Date of death was known in all other patients. Univariate Cox regression was employed to analyze the validity of the prognostic score.

Results

The study included 249 patients, whose baseline data are shown in Table I. Median overall survival was 3.0 months [95% confidence interval (CI)=2.6-3.4 months]. The median sum of scores was 12, range=0-29. The Cox regression analysis showed that the prognostic score (continuous variable) predicted overall survival [$p=0.0001$, Chi-square 26.4, Exp(B) 0.948]. As shown in Figure 1, the Kaplan-Meier survival curves were significantly different ($p=0.0001$ pooled over all strata). None of the study patients had a favorable sum of scores, *i.e.*, 30-36 points. Patients with 0 points ($n=8$) had a median survival of 1.8 months (maximum 3.7 months). The respective figures were 2.1 months (5.0 months) for those with 1 point ($n=7$).

Discussion

The validity of the new four-tiered score has already been demonstrated by Sato *et al.* (13). Their study included patients treated with stereotactic radiosurgery and was methodologically different from previous prognostic studies because the endpoint of interest was 3-year survival. The present results confirm the validity of the score in a very different population, both geographically and with regard to radiotherapy. Sato *et al.* reported a median survival time of 8.0 months and a median sum of scores of 15 (13). These figures illustrate that the WBRT study patients represent a negative selection (3.0 months, sum of scores 12). The study institution’s policy was to offer surgery or stereotactic radiosurgery to patients with favorable prognostic features and brain metastases eligible for such treatment. Interestingly, the poor-prognosis group (0-9 points) had a median survival of 2.8 months, whereas Sato *et al.* reported 3.6 and 3.8 months, respectively (development and validation cohort). This relatively small difference increased with increasing sum of scores (20-29 points: 7.0 months after WBRT *vs.* 15.0 and 15.7 months in the Sato *et al.* study). In other words, stereotactic radiosurgery is increasingly beneficial in patients with better prognostic features, both regarding the higher likelihood of local

Table I. Patient characteristics.

Baseline parameter	Number	Percent
Female gender	122	49
Male gender	127	51
Non-small cell lung cancer	104	42
Breast cancer	29	12
Malignant melanoma	24	10
Small cell lung cancer	25	10
Renal cell cancer	22	9
Colorectal cancer	18	7
Other primary tumors	27	11
No extracranial metastases	39	16
Extracranial metastases	210	84
Controlled primary tumor	158	63
Uncontrolled primary tumor	91	37
Single brain metastasis	31	13
Two, three or four brain metastases	101	41
More than four brain metastases	117	47
Volume of the largest lesion <10 ml	58	23
Volume of the largest lesion ≥10 ml	191	77
Performance status ≥80	61	24
Performance status <80	188	76
Incomplete radiotherapy	12	5
Prescribed 10 fractions of 3 Gy without boost	179	72
Prescribed equivalent dose lower than 10 fractions of 3 Gy	49	20
Prescribed equivalent dose higher than 10 fractions of 3 Gy	21	8
Median age, range (years)	65, 28-90	
Median Karnofsky performance status, range	70, 30-100	

Equivalent dose was calculated with alpha/beta value 10 Gy, higher doses than 10 fractions of 3 Gy were due to sequential or simultaneous integrated boost or administration of 15 fractions of 2.5 Gy.

control and the lower likelihood of neurocognitive decline [endpoints that were not studied here, but in previous clinical trials reviewed in (17-19)].

In contrast to other prognostic models (20-22), the present one is not well suited to predict extremely short survival (even patients with 0-1 points sometimes survived for more than 3 months). This fact is not surprising, given that 3-year survival was the landmark chosen by the Japanese group. Limitations of the present study include the relatively small number of patients and its retrospective design. Strengths of our study include the completeness of data (both baseline and follow-up) and the real-world setting (all age groups, different disease burden, inclusion of patients who failed to complete treatment). It is reassuring that a validation study in a vastly different setting was able to confirm the applicability of the score published by Sato *et al.*

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

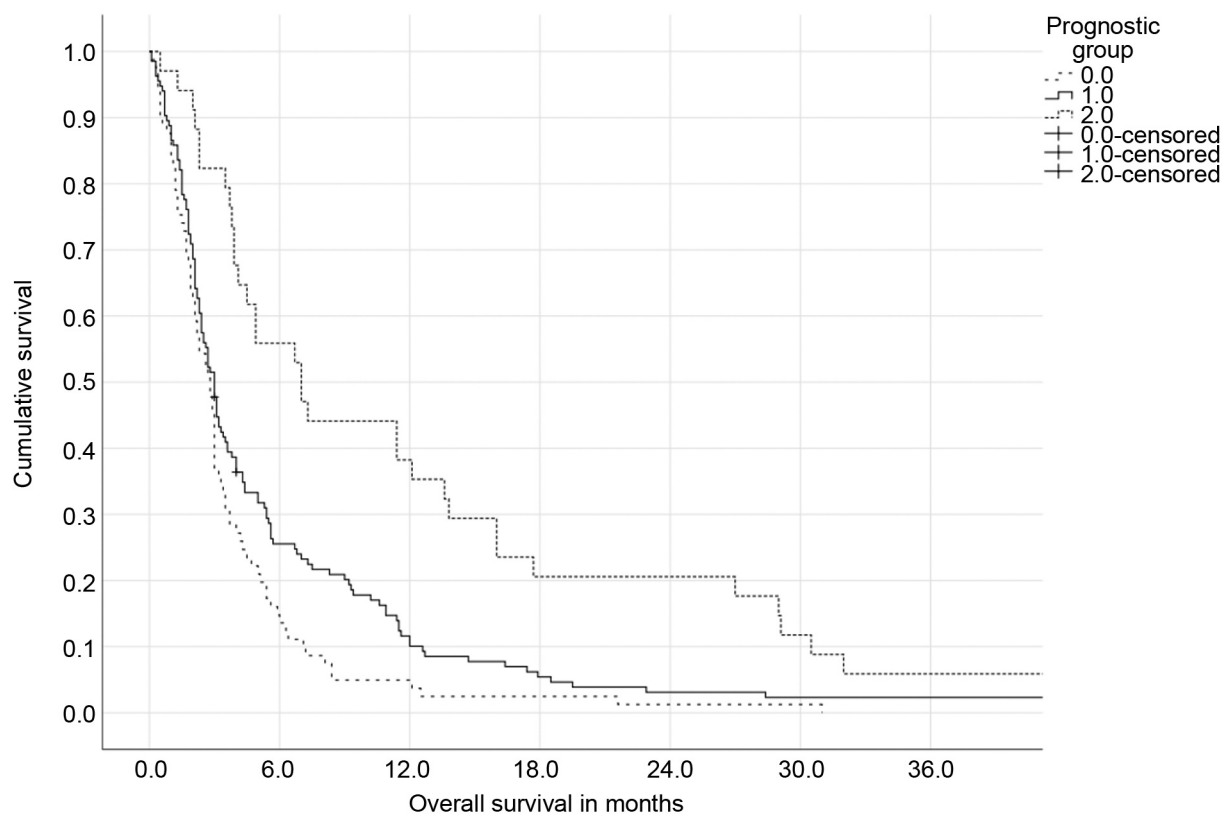


Figure 1. Actuarial overall survival stratified by the sum score ($p=0.0001$ pooled over all strata). Eighty-one patients had 0-9 points (median survival 2.8 months, 3-year rate 0%). The largest group ($n=134$) had 10-19 points (median survival 3.0 months, 3-year rate 2%). Thirty-four patients had 20-29 points (median survival 7.0 months, 3-year rate 6%). Mean survival was 3.7, 7.3 and 14.3 months, respectively. The study did not include patients with 30-36 points. Pairwise comparison resulted in p -values of 0.025 (0 vs. 1), 0.00001 (0 vs. 2) and 0.001 (1 vs. 2), respectively.

Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. CN, BM and RY conceived the study and drafted the article. All Authors read and approved the final article.

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