Robustness of the neurological prognostic score in brain metastasis patients treated with Gamma Knife radiosurgery

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OBJECTIVE The neurological prognostic score (NPS) was recently proposed as a means for predicting neurological outcomes, such as the preservation of neurological function and the prevention of neurological death, in brain metastasis patients treated with Gamma Knife radiosurgery (GKRS). NPS consists of 2 groups: Group A patients were expected to have better neurological outcomes, and Group B patients were expected to have poorer outcomes. NPS robustness was tested in various situations.

METHODS In total, 3040 patients with brain metastases that were treated with GKRS were analyzed. The cumulative incidence of the loss of neurological function independence (i.e., neurological deterioration) was estimated using competing risk analysis, and NPS was compared between Groups A and B by employing Gray's model. NPS was tested to determine if it can be applied to 5 cancer categories—non–small cell lung cancer, small cell lung cancer, gastrointestinal tract cancer, breast cancer, and other cancers—as well as if it can be incorporated into the 5 major grading systems: recursive partitioning analysis (RPA), score index for stereotactic radiosurgery (SIR), basic score for brain metastases (BSBM), graded prognostic assessment (GPA), and modified-RPA (M-RPA).

RESULTS There were 2263 patients in NPS Group A and 777 patients in Group B. Neurological deterioration was observed in 586 patients (19.2%). The cumulative incidences of neurological deterioration were 9.5% versus 21.0%, 14.1% versus 25.4%, and 17.6% versus 27.8% in NPS Groups A and B at 1, 2, and 5 years, respectively. Significant differences were detected between the NPS groups in all cancer categories. There were significant differences between NPS Groups A and B for all classes in terms of the BSBM, GPA, and M-RPA systems, but the differences failed to reach statistical significance in terms of RPA Class I and SIR Class 0 to 3.

CONCLUSIONS The NPS was verified as being highly applicable to all cancer categories and almost all classes for the 5 grading systems in terms of neurological function independence. This NPS system appears to be quite robust in various situations for brain metastasis patients treated with GKRS.

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KEY WORDS neurological prognostic score; neurological function independence; neurological deterioration; qualitative survival; Gamma Knife radiosurgery; brain metastases; oncology; stereotactic radiosurgery

NEUROLOGICAL outcomes, such as the preservation of neurological function (qualitative survival) and the prevention of neurological death (neurological survival), are regarded as the ideal end points for evaluating the treatment results of patients with brain metastases, as

well as overall survival.^{8,9} In a previous study, we proposed using the neurological prognostic score (NPS) as a means of predicting both qualitative and neurological survival in brain metastasis patients treated with Gamma Knife radiosurgery (GKRS).⁹ This NPS system consists of 4 intracra-

ABBREVIATIONS BSBM = basic score for brain metastases; CITV = cumulative intracranial tumor volume; DS-GPA = diagnosis-specific graded prognostic assessment; GKRS = Gamma Knife radiosurgery; GPA = graded prognostic assessment; KPS = Karnofsky Performance Scale; M-RPA = modified recursive partitioning analysis; NPS = neurological prognostic score; RPA = recursive partitioning analysis; SIR = score index for stereotactic radiosurgery.

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nial disease factors: brain tumor number (≤ 10 vs > 10), cumulative intracranial tumor volume (CITV) (≤ 15 cm³ vs > 15 cm³), MRI findings of localized leptomeningeal dissemination (no vs yes), and neurological symptoms (no vs yes). For each of these intracranial disease factors, a score of 0 indicates a poor prognosis, and a score of 1 indicates a good neurological prognosis. According to the sum of these NPS values, we classified Group A as having a score of 3 or 4 and Group B as a score of 0, 1, or 2. Thus, better neurological outcomes can be expected in NPS Group A and poorer outcomes in Group B. In this study, we tested the robustness of this NPS system in various situations with a focus on neurological function independence.

Methods

A total of 3040 consecutive cases that were treated with GKRS by the first author (T.S.) were analyzed. The database consisted of 2 cohorts that were studied retrospectively after institutional review board approval: the Chiba series (1716 patients treated between January 1998 and March 2008) plus the Tokyo series (1324 patients treated between April 2008 and December 2014). During this 17-year period, all patients were treated according to the same indications and protocol, as reported previously.^{10,12} Our major inclusion criteria for GKRS are a tumor number up to 25, maximum tumor diameter less than 4 cm, no MRI findings of diffuse leptomeningeal dissemination, and a Karnofsky Performance Scale (KPS) score of 70 or better. However, we applied these indications with flexibility, especially for patients with special circumstances such as contraindications for whole-brain radiotherapy and craniotomy or the expectation of a good response to small molecular targeting agents.⁶ Patients with KPS scores less than 70 due to focal neurological signs and symptoms and whose performance status was expected to improve after GKRS were included. Furthermore, patients with functional independence before their cancer diagnosis—e.g., patients with cerebral palsy, polio infection, or spinal cord injuries—were also considered to be suitable candidates for GKRS. None of the cases in this series had diffuse leptomeningeal dissemination, which is widely regarded as a contraindication for GKRS. Leptomeningeal dissemination always indicates localized disease, meaning that the tumor margin is in contact with cerebrospinal fluid spaces. Our GKRS-alone treatment protocol is as follows: large tumors (> 3 cm in diameter) were surgically removed or irradiated with staged GKRS,^{3,17} and all other smaller tumors were irradiated with GKRS. We do not perform upfront whole-brain radiotherapy. New distant lesions, as detected with follow-up MRI, were appropriately irradiated with GKRS.

In this study, we focused on neurological functional independence. We defined functional independence as a KPS score of 70 or better. We divided the loss of functional independence into “neurological deterioration” due to intracranial disease progression and “systemic deterioration” due to extracranial disease progression. Thus, neurological deterioration was defined as a KPS score that decreased to less than 70 due to intracranial disease progression.^{9–11} The interval from the date of GKRS until the

date of loss of functional independence was calculated. We categorized functional independence as “censored,” neurological deterioration as “failure,” and systemic deterioration as a “competing risk.” For patients with an initial KPS score lower than 70 and who never achieved a KPS score of at least 70 after GKRS, we substituted the surrogate end point of a 20-point decrease in KPS score as a representation of functional dependence. Thus, we estimated the cumulative incidence of neurological deterioration by employing the competing risk analysis model.² We divided the cases into 5 cancer categories: non–small cell lung cancer, small cell lung cancer, gastrointestinal tract cancer, breast cancer, and other cancers. We also examined 5 major grading systems: recursive partitioning analysis (RPA),¹ score index for stereotactic radiosurgery (SIR),¹⁵ basic score for brain metastases (BSBM),⁵ graded prognostic assessment (GPA),¹³ and modified RPA (M-RPA).¹⁶ The cumulative neurological deterioration incidences were compared between the 2 NPS groups and among the 5 cancer categories and 5 major grading systems by employing Gray’s test.⁷ A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichii Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing).⁴ More precisely, it is a modified version of the R commander that is designed to add statistical functions frequently used in biostatistics.⁴

Results

Table 1 summarizes the patient backgrounds. At the end of December 2015, 222 (7.3%) patients were still alive and the remaining 2818 (92.7%) patients were confirmed to have died. The median survival time was 8.0 months. Among 2829 patients with loss of function independence, neurological deterioration was observed in 593 patients and systemic deterioration was observed in 2236 patients. Figure 1 shows the cumulative incidences of systemic and neurological deterioration. The cumulative incidences of loss of function independence were 65.6% (12.4% for neurological deterioration vs 53.4% for systemic deterioration), 83.2% (17.0% vs 66.2%), 90.4% (18.6% vs 71.8%), 93.9% (19.6% vs 74.3%), and 95.7% (20.2% vs 75.5%) at 1, 2, 3, 4, and 5 years, respectively. The causes of neurological deterioration were leptomeningeal dissemination progression in 184 patients (31.2%), GKRS-treated lesion regrowth in 140 (23.6%) patients, cerebral dissemination in 51 (8.6%) patients, the growth of untreated lesions in 46 (7.6%) patients, and unknown or other causes in 172 (29.0%) patients. The crude incidences of neurological deterioration were 16.7% (378 patients) in NPS Group A and 26.8% (208 patients) in Group B. Figure 2 shows neurological deterioration, which allowed the NPS groups to be compared. The cumulative neurological deterioration incidences were 9.5% versus 21.0%, 14.1% versus 25.4%, 15.9% versus 26.3%, 17.1% versus 27.0%, and 17.6% versus 27.8% in NPS Groups A and B at 1, 2, 3, 4, and 5 years, respectively. The differences were highly significant ($p < 0.0001$).

Figure 3 shows neurological deterioration, which allowed comparison of the NPS groups for each of the 5 cancer categories. There were significant differences between

TABLE 1. Characteristics of 3040 brain metastasis patients

Variable	Value*
Age	
Median (IQR), yrs	65 (58–72)
≥65	1606 (52.3)
<65	1434 (47.1)
Sex	
Male	1798 (59.1)
Female	1242 (40.9)
KPS score	
80–100	2327 (76.5)
50–70	713 (23.5)
Controlled primary cancer	
Yes	948 (31.2)
No	2092 (68.8)
Extracranial metastasis	
Yes	1951 (64.2)
No	1089 (35.8)
Primary cancer	
Non–small cell lung	1730 (56.9)
Small cell lung	282 (9.3)
Gastrointestinal tract	375 (12.4)
Breast	329 (10.8)
Other	324 (10.7)
Diagnostic lag btwn primary cancer & brain metastases	
Synchronous	1074 (35.3)
Metachronous	1966 (64.7)
Prior craniotomy	404 (13.3)
Prior whole-brain radiotherapy	233 (7.7)
No. of brain tumors	
Median (IQR)	3 (1–7)
Single	855 (28.1)
2–4	1001 (32.9)
5–10	667 (21.9)
>10	517 (17.0)
Maximum tumor diameter	
Median (IQR), mm	20.8 (13.5–29.5)
≥25 mm	1106 (36.4)
<25 mm	1934 (63.6)
Cumulative intracranial tumor vol	
Median (IQR), cm ³	4.4 (1.4–11.1)
>15	545 (17.9)
≤15	2495 (82.1)
MRI findings of localized leptomeningeal dissemination	
Yes	331 (10.9)
No	2709 (89.1)
Neurological symptoms	
Yes	1446 (47.6)
No	1594 (52.4)

IQR = interquartile range.

* Values are presented as number of patients (%) unless otherwise indicated.

NPS Groups A and B in all cancer categories ($p = 0.0002$ for non–small cell lung cancer, $p = 0.0235$ for small cell lung cancer, $p = 0.0439$ for gastrointestinal tract cancer, $p = 0.0042$ for breast cancer, and $p = 0.0011$ for other cancers).

Table 2 summarizes the comparisons of the cumulative neurological deterioration incidences between NPS Groups A and B for each class of RPA, SIR, BSBM, GPA, and M-RPA. For RPA, there were significant differences in Class II ($n = 2484$; $p < 0.0001$) and Class III ($n = 384$; $p = 0.0010$), but not Class I ($n = 172$; $p = 0.342$). For SIR, there were significant differences in SIR Class 4 to 7 ($n = 2340$; $p < 0.0001$) and SIR Class 8 to 10 ($n = 253$; $p < 0.0001$), but not SIR Class 0 to 3 ($n = 347$; $p = 0.0577$). For BSBM, there were significant differences in all classes. The p values were < 0.0001 for BSBM Class 0 ($n = 402$), < 0.0001 for BSBM Class 1 ($n = 1243$), 0.0004 for BSBM Class 2 ($n = 1064$), and 0.0002 for BSBM Class 3 ($n = 330$). For GPA, there were significant differences in all classes. The p values were 0.0001 for GPA Class 0 to 1 ($n = 1288$), < 0.0001 for GPA Class 1.5 to 2.5 ($n = 1535$), 0.0002 for GPA Class 3.0 ($n = 163$), and 0.0213 for GPA Class 3.5 to 4.0 ($n = 49$). For M-RPA, there were significant differences in all classes. The p values were $p < 0.0001$ for M-RPA Class I-IIa ($n = 564$), 0.0014 for M-RPA Class IIb ($n = 871$), and < 0.0001 for M-RPA Class IIc+III ($n = 1605$).

Discussion

We proposed using the NPS system for brain metastasis patients treated with GKRS as a means of predicting neurological outcomes such as qualitative and neurological survival.⁹ NPS consists of 4 intracranial disease factors: brain tumor number, CITV, an MRI finding of localized leptomeningeal dissemination, and neurological symptoms. We classified NPS Group A as those patients for which better neurological outcomes could be expected and Group B as those patients with poorer anticipated outcomes. The 5 major grading systems—RPA, SIR, BSBM, GPA, and M-RPA—can predict life expectancy but not neurological outcomes. Our NPS is unique because this is the only system that can predict neurological outcomes, the ideal end point for evaluating GKRS, as well as other radiation treatment results for patients with brain metastases. Furthermore, NPS can be incorporated into the 5 major grading systems, such that we can predict life expectancy and neurological outcomes independently.

In our previous study, we estimated qualitative and neurological survival by employing the Kaplan-Meier method.⁹ However, these cumulative incidences tended to be overestimates compared with the true values because the Kaplan-Meier method does not take competing risk into consideration.² For example, neurological deterioration cannot be observed if patients experience systemic deterioration and vice versa. Neurological and systemic deterioration are considered competing factors for each other. In this study, we applied competing risk analysis and estimated much more accurately the cumulative incidences of neurological deterioration.⁷ Furthermore, we tested if our NPS system can be applied to 5 primary cancer sites, as well as if it can be incorporated into 5 grading systems, in terms of evaluating neurological deterioration using Gray's test.

FIG. 1. Cumulative incidences of the loss of function independence due to systemic disease progression and neurological disease progression. The *red line* indicates systemic deterioration, and the *black line* indicates neurological deterioration. The cumulative incidences of the loss of function independence were 65.6% (12.4% for neurological deterioration vs 53.4% for systemic deterioration), 83.2% (17.0% vs 66.2%), 90.4% (18.6% vs 71.8%), 93.9% (19.6% vs 74.3%), and 95.7% (20.2% vs 75.5%) at 1, 2, 3, 4, and 5 years, respectively. CIF = cumulative incidence function; GKS = Gamma Knife (radio)surgery. Figure is available in color online only.

FIG. 2. Comparison of neurological deterioration between NPS Groups A and B. The *black line* indicates NPS Group A, and the *red line* indicates Group B. The cumulative incidences of neurological deterioration were 9.5% versus 21.0%, 14.1% versus 25.4%, 15.9% versus 26.3%, 17.1% versus 27.0%, and 17.6% versus 27.8% in NPS Groups A and B at 1, 2, 3, 4, and 5 years, respectively. The difference between the 2 NPS groups was highly significant ($p < 0.0001$). Figure is available in color online only.

FIG. 3. Cumulative incidences of neurological deterioration that allow comparison between the NPS groups for the 5 cancer categories. **A:** Non-small cell lung cancer. **B:** Small cell lung cancer. **C:** Gastrointestinal cancer. **D:** Breast cancer. **E:** Other cancers. The black line indicates NPS Group A, and the red line indicates Group B. There were significant differences between the 2 NPS groups for each cancer category ($p = 0.0002$ for non-small cell lung cancer, $p = 0.0235$ for small cell lung cancer, $p = 0.0439$ for gastrointestinal cancer, $p = 0.0042$ for breast cancer, and $p = 0.0011$ for other cancers). Figure is available in color online only.

First, we ascertained the validity of our NPS system according to 5 primary cancer types—non-small cell lung cancer, small cell lung cancer, gastrointestinal cancer,

breast cancer, and other cancers—and found statistically significant differences between NPS Groups A and B for all 5 categories. Thus, the NPS system was applicable to

TABLE 2. Comparison of the cumulative neurological deterioration incidences between NPS Groups A and B according to 5 major grading systems

Grading System	1 Yr	2 Yrs	5 Yrs	p Value
RPA				
Class I				0.3420
Group A	10.1	21.3	31.1	
Group B	18.2	28.0	37.8	
Class II				<0.0001
Group A	9.7	13.7	17.1	
Group B	20.8	25.8	28.4	
Class III				0.0010
Group A	10.7	11.8	11.8	
Group B	22.2	23.9	NA	
SIR				
Class 0–3				0.0577
Group A	11.9	14.3	NA	
Group B	20.0	21.2	BA	
Class 4–7				<0.0001
Group A	9.6	14.3	17.6	
Group B	21.6	27.1	30.2	
Class 8–10				<0.0001
Group A	6.3	12.3	19.9	
Group B	23.1	53.8	61.5	
BSBM				
Class 0				0.0031
Group A	9.6	9.6	NA	
Group B	20.3	20.3	21.9	
Class 1				<0.0001
Group A	9.4	12.2	12.9	
Group B	20.9	25.1	NA	
Class 2				0.0004
Group A	9.8	15.7	19.4	
Group B	19.7	26.9	30.5	
Class 3				0.0002
Group A	8.8	18.4	30.8	
Group B	34.3	45.7	57.1	
GPA				
Class 0–1.0				0.0001
Group A	11.2	14.2	16.0	
Group B	19.7	22.8	23.9	
Class 1.5–2.5				<0.0001
Group A	8.8	13.9	17.5	
Group B	22.6	29.1	33.3	
Class 3.0				0.0002
Group A	8.6	15.6	24.3	
Group B	45.5	56.8	68.2	
Class 3.5–4.0				0.0213
Group A	2.3	11.7	22.4	
Group B	40.0	40.0	60.0	

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TABLE 2. Comparison of the cumulative neurological deterioration incidences between NPS Groups A and B according to 5 major grading systems

Grading System	1 Yr	2 Yrs	5 Yrs	p Value
M-RPA				
Class I+IIa				<0.0001
Group A	7.4	14.8	23.9	
Group B	29.4	41.4	50.8	
Class IIb				0.0014
Group A	10.4	16.3	19.6	
Group B	20.6	27.9	31.3	
Class IIc+III				<0.0001
Group A	10.0	12.2	12.9	
Group B	20.4	23.4	25.1	

NA = not available.

Values are shown as percentages unless otherwise indicated.

all primary cancer types in our series. Next, we also tested the validity of the NPS system in each class of 5 grading systems: RPA,¹ SIR,¹⁵ BSBM,⁵ GPA,¹³ and M-RPA.¹⁶ These grading systems are highly applicable to patients treated with GKRS in terms of overall survival, as reported previously.⁸ We detected statistically significant differences in almost all classes of the aforementioned 5 grading systems. In RPA Class I and SIR Class 0 to 3, however, the differences did not reach statistical significance. We assume that this was due to the number of RPA Class I cases being too small ($n = 172$). SIR has 2 brain items (maximum tumor volume and tumor number) that are used for classification and can thus predict neurological outcomes such as qualitative survival, as reported previously.⁸ The NPS system has similar items: CITV and tumor number. For SIR, the number of tumors was classified as 1, 2, or ≥ 3 , whereas NPS uses ≤ 10 and > 10 . We assume that maximum tumor volume correlates very strongly with CITV. This overlapping may account for the lack of statistically significant differences in SIR Class 0 to 3 ($p = 0.0577$) despite the number of SIR Class 0 to 3 cases being relatively large ($n = 348$). Although GPA and M-RPA also use 1 brain factor (tumor number, which is classified as single or multiple) and the number of GPA cases (Class 3.0 and 3.5–4.0) was very small, there were highly statistically significant differences in all classes. Thus, our NPS system proved to be extremely robust in various situations.

We have highlighted the usefulness of incorporating NPS into established grading systems because this will provide very important information for selecting the optimal radiation treatment intensity when performing GKRS.⁹ What is the best grading system into which NPS can be incorporated? For statistical reasons, RPA and SIR are not recommended. Considering the overlapping of the evaluated items, GPA and M-RPA were not ideal. BSBM would thus be best. However, we found highly significant differences between NPS Groups A and B in all GPA and M-RPA classes. We conclude that BSBM, GPA, and M-RPA are the best grading systems for incorporation into NPS. Recently, Sperduto et al. modified their original

GPA system and developed a new index: diagnosis-specific GPA (DS-GPA).¹⁴ We plan to perform validity testing to determine if NPS can be incorporated into DS-GPA, but the number of cases in each class is still too small.

It should be noted that our NPS system has limitations. This was a two-institution, retrospective study. Furthermore, 2838 patients (93.4%) in the original NPS system report were among the 3040 patients included in this study. Validity testing on the other groups using patient selection criteria and practice patterns that are different from our series, especially those conducted outside of Japan, is needed. Clinical trials that assess the usefulness of our NPS system when incorporated into grading systems for predicting overall survival are also necessary. Finally, our NPS system can only be used at the completion of dose planning for radiosurgery because NPS scores can change between clinical diagnosis and GKRS due to an increase in the number of tumors, changes in neurological symptoms, the emergence of leptomeningeal dissemination, and/or increased CITV. However, our NPS system can predict neurological outcomes such as the deterioration of neurological function at the time of radiosurgery and provide important information as to whether GKRS alone would be sufficient treatment.

Conclusions

Our NPS system can predict the preservation of neurological function independence and was found to be extremely robust when applied to brain metastasis patients who were treated with GKRS in various situations.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Serizawa, Higuchi, Shibamoto. Acquisition of data: Serizawa, Nagano, Aoyagi, Matsuda. Analysis and interpretation of data: Serizawa, Higuchi, Nagano, Aoyagi, Matsuda. Drafting the article: Serizawa. Critically revising the article: Serizawa, Higuchi, Shibamoto. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Serizawa. Statistical analysis: Serizawa, Higuchi, Takemoto. Administrative/technical/material support: Serizawa, Higuchi. Study supervision: Serizawa, Saeki, Shibamoto.

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