Clinical and Translational Radiation Oncology 48 (2024) 100820

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

Validity test of small cell lung cancer (SCLC) graded prognostic assessment and proposal of a new index for patients with brain metastases from SCLC☆

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ARTICLE INFO

Keywords:
Brain metastases
Small cell lung cancer
Radiosurgery
Prognostic grade

ABSTRACT

Background and purpose: We performed a validity test of a recently-reported, small cell lung cancer (SCLC) graded prognostic assessment (GPA) system for SCLC patients with brain metastases (BMs). Thereafter, we created a new prognostic index, the SCLC Grade, for such patients.
Materials and methods: We studied 508 SCLC patients selected from among nearly 7000 consecutive patients undergoing gamma knife SRS for BMs since 1998.
Results: In the SCLC GPA, there were no median survival time (MST) differences among pairs of the neighboring subgroups. Therefore, the 508 patients were randomly divided into the two series, i.e., a test (340 patients) and a validity (168) series. In the test series, five factors were identified by univariable analyses as favoring longer survival (rounded lower 95 % CI of the HR was at least 1.3): Sex, Karnofsky Performance Status, tumor numbers, primary tumor status and extracerebral metastases. This new index is the sum of scores (0 and 1) of these five factors: SCLC-Grade 4–6 (score of 4, 5 or 6), 2–3 (2 or 3), and 0–1 (0 or 1). This new system showed highly statistically significant MST differences among subclasses. Next, this SCLC-Grade was applied to the verification series. Consistent results were obtained, i.e., there were highly statistically significant MST differences among subclasses.
Conclusions: Our validity test results for the SCLC GPA demonstrated this system to not precisely reflect the outcomes of SCLC patients with BMs. Our results suggest the herein-proposed SCLC-Grade to have superior prognostic value.

Introduction

In 2002, Serizawa et al reported stereotactic radiosurgery (SRS) to apparently be as effective for treating brain metastases (BMs) from small cell lung cancer (SCLC) as for those from non-small cell lung cancer [1]. Several studies supporting SRS for SCLC patients with BMs were subsequently published [2–5]. However, until the second decade of the 21st century, whole brain radiotherapy (WBRT) remained the standard treatment for patients with BMs from SCLC. After Rusthoven et al published an international cooperative study in which, based on 710 SCLC patients with BMs receiving first line SRS without WBRT, the primary trade-offs associated with SRS without WBRT were found to be similar to those observed in settings in which SRS had already become established [6,7]. Furthermore, Bernhardt et al recently performed a single-center prospective, randomized, two-arm Phase II study, of SCLC patients who underwent either WBRT or stereotactic radiotherapy (SRT) [8]. In their study, the primary endpoint was neurocognition after cerebral irradiation in SCLC patients. SCLC patients in the WBRT group were shown to be at a greater risk for a significant decline in neurocognitive function 3 months after determination of baseline status, as compared

☆ The Institutional Review Board of Southern Tohoku Hospital (No. 2024-00) gave approval for the present study.

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https://doi.org/10.1016/j.ctro.2024.100820
Received 27 June 2024; Received in revised form 13 July 2024; Accepted 18 July 2024
Available online 24 July 2024

Table 1
Clinical characteristics of 508 small cell lung cancer patients with brain metastases

Characteristics		Total*	Test series*	Verification series*	p=
No. of patients		508	340	168	
Gender	Female	92 (18.1)	64 (18.8)	28 (16.7)	0.62
	Male	416 (81.9)	276 (81.2)	140 (83.3)	
Age	<65 years	152 (29.9)	98 (28.8)	54 (32.1)	0.47
	≥65 year	356 (70.1)	242 (71.2)	114 (66.9)	
Karnofsky performance status	≥80 %	418 (82.3)	276 (81,2)	142 (84.5)	0.39
	≤70 %	90 (17.7)	64 (18.8)	26 (15.5)	
Neurological symptoms	No	360 (70.9)	240 (70.6)	120 (71.4)	0.92
	Yes	148 (29.1)	100 (29.4)	48 (28.6)	
Presentation	Metachronous	385 (75.8)	252 (74.1)	133 (79.2)	0.22
	Synchronous	123 (24.2)	88 (25.9)	35 (20.8)	
Primary cancer status	Controlled	92 (18.1)	65 (19.1)	27 (16.1)	0.46
	Not Controlled	416 (81.9)	275 (80.9)	141 (83.9)	
Extra-cerebral metastases	No	281 (55.3)	180 (52.9)	101 (60.1)	0.13
	Yes	227 (44.7)	160 (47.1)	67 (39.9)	
Tumor number	Solitary	120 (23.6)	78 (22.9)	42 (25.0)	0.22
	Multiple	388 (76.4)	262 (77.1)	126 (75.0)	
Cumulative tumor volume	<10 cc	356 (70.1)	239 (70.3)	117 (69.6)	0.91
	≥10 cc	152 (29.9)	101 (29.7)	51 (30.4)	
Largest tumor volume	<5.0 cc	332 (65.4)	219 (64.4)	113 (67.3)	0.55
	≥5.0 cc	176 (34.6)	121 (35.6)	55 (32.7)	

*No. of patients (%).

with the SRT group. They concluded that SRT should be among the standard regimens for patients with BMs from SCLC. Therefore, the National Comprehensive Cancer Network Guideline Version 3.2023 SCLC stated that while BMs have conventionally been treated with WBRT, selected patients with SCLC might be appropriately treated with SRT/SRS [9]. WBRT use continues to decline and implementation of SRS/SRT alone continues to rise.

Numerous factors in BM patients have an impact on outcomes. Furthermore, as yet there is little data available *clarifying* the roles and benefits of various treatment modalities, i.e., WBRT, surgery, SRS or SRT, anti-cancer agent administration, or combinations. Thus, clinicians are often uncertain as to the optimal treatment selection. An improved prognostic index might resolve a degree of the uncertainty encountered in making treatment decisions as well as guiding future research efforts. Sperduto et al recently proposed a new prognostic index, named the SCLC-Graded Prognostic Assessment (GPA) [10]. We validity tested this system using our dataset and found the SCLC-GPA to have little prognostic utility for managing SCLC patients with BMs. Therefore, we endeavored to create a new prognostic grading system for such patients.

Methods

Patient population

This retrospective cohort study was performed employing our prospectively accumulated database comprised of 7355 consecutive patients who had undergone gamma knife (GK) SRS for BMs during the 20-year-period spanning 1998 through 2018. Among these 7355 patients, 695 had SCLC. Excluding 187 patients who had undergone surgery and/or WBRT prior to SRS, 508 were selected for this study. Clinical characteristics are presented in Table 1. Among the 508 patients, 262 were treated by the first author (MY) and the other 246 by the second author (TS). The Institutional Review Board of Southern Tohoku Hospital provided approval for this study (No. 675).

Prior to being referred to us for SRS, the majority of these patients had been advised to receive SRS by their primary physicians because our clinics specialize in GK SRS. It should be noted that the patient selection criteria may well have differed among the referring physicians. Therefore, one of the first two authors (either MY or TS) decided whether or not a referred patient was a suitable candidate for SRS. We did not perform SRS on patients with low Karnofsky Performance Status (KPS) scores (<70 %) due to systemic diseases, a non-cooperative state associated with poor neurocognitive function, diffuse meningeal dissemination, or if a physician who treated the original cancer had reported that the anticipated survival period was no more than three months. Each patient, along with at least one adult relative, was given a detailed explanation of our treatment strategies. Written informed consent was thereby obtained from each patient by one of the two main treating neurosurgeons (either MY or TS) prior to all SRS procedures.

Radiosurgical techniques

Our radiosurgical techniques were described in detail in our previous publication and are thus not repeated herein [11,12]. Briefly, we performed standard, single-session GK SRS with frame placement. Selected doses delivered to the tumor periphery ranged from 12.00 Gy to 25.00 Gy (mean; 20.48 Gy, median; 20.00 Gy, inter-quartile range [IQR]; 20.00–22.00 Gy). However, in 25 patients, a two-/three-stage treatment protocol was selected because there was only one, or at most a few, relatively large BMs [13,14]. Among these 25 patients, 8 underwent two-stage treatment; peripheral doses of 14–15 Gy were delivered at a three-week interval, while the other 17 received a 3-stage treatment protocol; peripheral doses of 9–10 Gy were administered at a two-week interval.

Before June of 2003, in the Yamamoto series, SRS was performed using a Leksell GK Model B unit (1988–2003, Elekta, Sweden), later a Leksell GK Model C unit (2003–2013, Elekta, Sweden) was employed. Thereafter, a Leksell GK Perfexion unit (Elekta, Sweden) was used. In the Serizawa series, the switch from the GK Model B to C was in 2003 and from the Model C to Perfexion in 2011.

Post-SRS, all patients were routinely managed by their referring physicians. All were advised to undergo clinical and neuro-imaging examinations at an interval of approximately 2–3 months. However, 68 (13.4 %) of the 508 patients could not receive neuro-imaging follow-up due to early post-SRS death or severe deterioration of their general conditions.

Statistical analysis

For the clinical characteristics of the two series, summary statistics were constructed employing frequencies and proportions for categorical data. We compared patient characteristics using the chi-square test for categorical outcomes. For time-to-event outcomes, overall survival (OS) time was compared using the log-rank test, while the Kaplan-Meier method was used to estimate the absolute risk of each event for each factor, and hazard ratios and 95 % confidence intervals (CIs) were

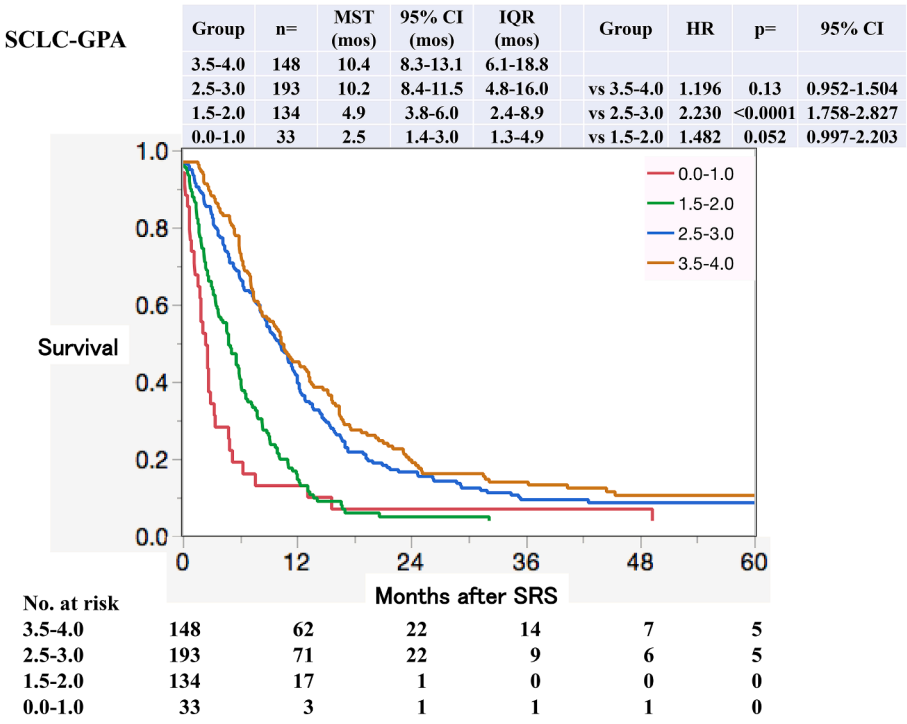


Fig. 1. Overall survivals based on small cell lung cancer (SCLC) graded prognostic assessment (GPA) [10] MST; median survival time, CI; confidence interval, IQR; inter-quartile range, HR; hazard ratio, SRS; stereotactic radiosurgery.

estimated by the Cox proportional hazards model. The reliability of the six reported prognostic indexes, i.e., Recursive Partitioning Analysis (RPA) [15], Score Index for Radiosurgery (SIR) [16], Basic Score for Brain Metastases (BSBM) [17], Modified-RPA (M−RPA) [18], SCLC-Graded Prognostic Assessment (GPA) [10] and our herein-reported SCLC-Grade, were compared using Receiver Operating Characteristics (ROCs). A larger area under the curve (AUC) indicates greater prognostic value. The 95 % CI of AUC was calculated with 2000 stratified bootstrap replicates.

Results

Validity test of the SCLC-GPA

The median post-SRS follow-up period for 50 censored observations (9.8 %) was 10.1 (IQR; 2.3–36.7) months, with 458 patients (90.2 %) having died as of the end of June 2020. The overall MST after SRS was 7.7 (95 % confidence interval [CI]; 6.5–8.5) months. The respective actuarial post-SRS survival proportions were 32.5 % (No. at risk; 154), 10.6 % (46), 5.5 % (24), 4.9 % (14) and 4.0 % (19) at the 12th, 24th, 36th, 48th and 60th post-SRS months, respectively.

Fig. 1 shows survival plots according to the SCLC-GPA. There was no MST difference between groups 1.5–2.0 and 2.5–3.0, i.e., the survival periods were 10.4 and 10.2 months (hazard ratio [HR]; 1.196, 95 % CI; 0.952–1.504, p = 0.13]), respectively. Likewise, there was no statistically significant MST difference between the two groups, 0.0–1.0 vs 1.5–2.5, i.e., 2.5 vs 4.9 months (HR; 1.482, 95 % CI; 0.997–2.203, p = 0.052), while a statistically significant MST difference was demonstrated between groups 1.5–2.0 and 2.5–3.5 (1.2 vs 4.9 months, HR; 2.230, 95 % CI; 1.758–2.827), p < 0.0001).

New grading system, SCLC-Grade

The 508 patients were randomly divided into two series for testing and validation: 340 patients in the test series and 168 patients in the validation series. Clinical characteristics were well balanced between these two series (Table 1). As shown in Table 2, in the test series, five factors were identified by univariable analyses as favoring longer survival (rounded lower 95 % CI of the HR was at least 1.3): Sex (female vs male), Karnofsky Performance Status (KPS, 80 % or better vs 70 % or

Table 2
Clinical factors relating to overall survival: Uni-variable analyses

Categories	Category 1	Category 2	HR	95 % CI	p=
Sex	Male	Female	1.940	1.431–2.631	<.0001
Age	≥65 years	<65 years	1.399	1.090–1.797	0.0085
Presentation	Synchronous	Metachronous	1.054	0.811–1.371	0.69
Neurology	Symptomatic	Asymptomatic	1.431	1.116–1.835	0.0047
KPS	70 % or worse	80 % or better	2.344	1.755–3.132	<.0001
Tumor number	Multiple	Solitary	1.755	1.320–2.332	<.0001
Cumulative tumor volume	≥10.0 cc	<10.0 cc	1.532	1.197–1.960	0.0007
Largest tumor volume	≥5.0 cc	<5.0 cc	1.246	0.985–1.576	0.066
Peripheral dose	<20.00 Gy	20. 00 Gy	1.420	1.078–1.869	0.013
Maximum dose	<36.00 Gy	≥36.00 Gy	1.034	0.826–1.296	0.77
Original tumor status	Not controlled	Controlled	2.107	1.549–2.865	<.0001
Extra-cerebral METs	Yes	No	1.628	1.297–2.042	<.0001

HR; hazard ratio, 95 % CI; 95 % confidence interval, KPS; Karnofsky performance status, METs; metastases.

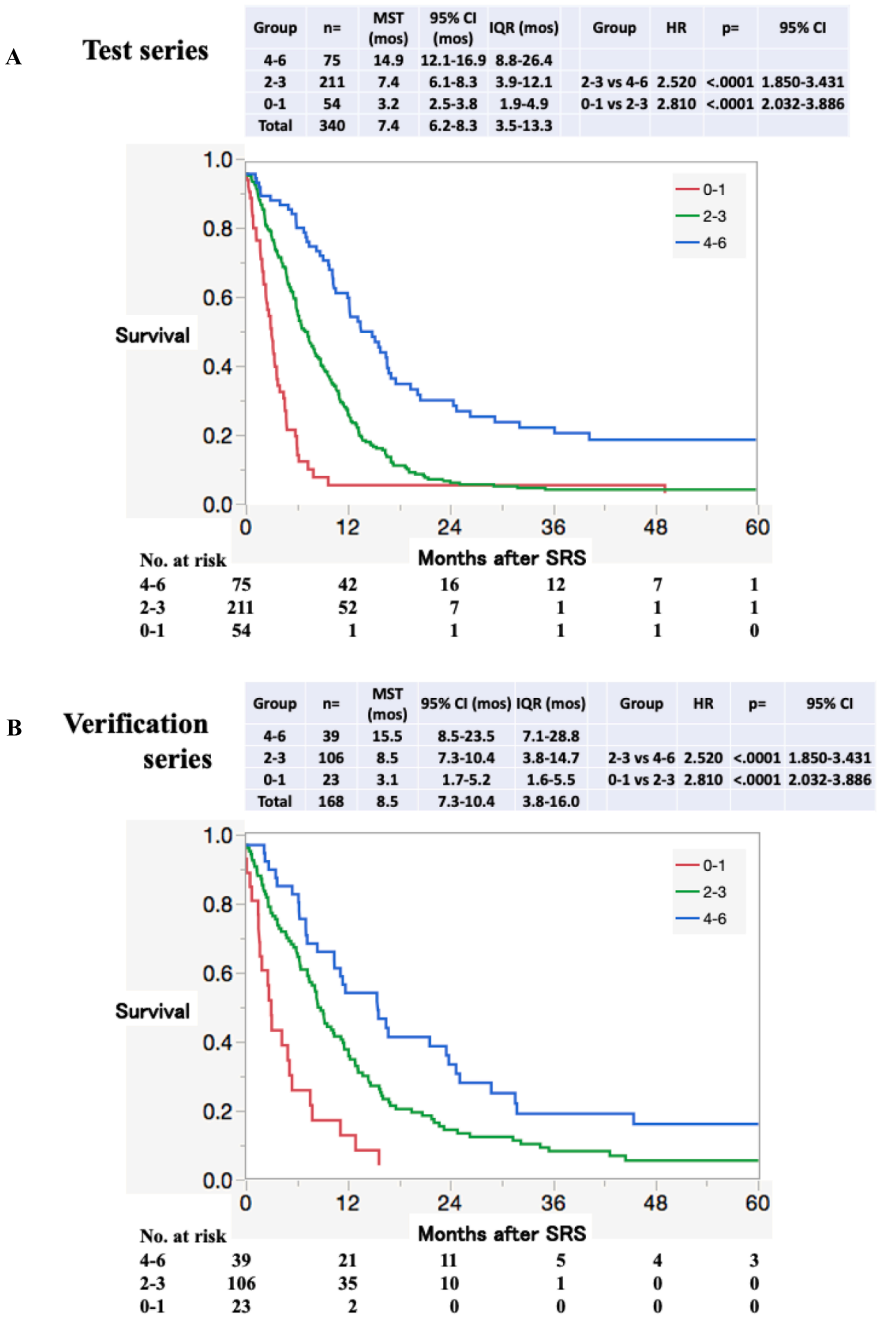


Fig. 2. Overall survival based on small cell lung cancer (SCLC) grade in the two series, i.e., test (A) and verification (B) series. MST; median survival time, CI; confidence interval, IQR; inter-quartile range, HR; hazard ratio, SRS; stereotactic radiosurgery.

worse), tumor numbers (solitary vs. multiple), primary tumor status (controlled vs. not controlled) and extracerebral METs (no vs. yes). This new index is the sum of scores (0 and 1) of these five factors: SCLC Grade 4–6; score of 4, 5 or 6, SCLC Grade 2–3; score of 2 or 3, and SCLC Grade 0–1; score of 0 or 1. Highly statistically significant MST differences among subclasses, as shown in Fig. 2-A, were demonstrated employing this new system.

Next, this SCLC Grade was applied to the verification series. As shown in Fig. 2-B, consistent results were obtained, i.e., there were highly statistically significant MST differences among subclasses.

Discussion

As an accurate contemporary prognostic index for SCLC patients with BMs was lacking before Sperduto et al reported their SCLC GPA in 2022 [10], we began the present study by performing a validity test of this system. However, with the SCLC GPA, no MST differences were detected among some of the neighboring subgroups. It should be noted that our patient group differed markedly from that studied by Sperduto et al, i.e., our patients all received upfront SRS while the Sperduto subjects were treated mostly with WBRT. Needer et al. reported a validity test of the SCLC GPA (15). Although the stratified p-value was < 0.001 for MSTs for their four subgroups, there was no significant survival difference between patients with scores of 3.5–4 versus 2.5–3 points.

Therefore, we next created a novel grading system for SCLC patients with BMs, the SCLC Grade. As noted above, this system showed highly statistically significant MST differences among subclasses in the test

Table 3
Median survival time (MST) differences among subgroups in recursive partitioning analysis (RPA) [16], Score Index for Radiosurgery (SIR) [17], Basic Score for Brain Metastases (BSBM) [18], Modified-RPA (M−RPA) [19], small cell lung cancer (SCLC) Graded Prognostic Assessment (GPA) [10]

RPA	n=	MST (mos)	95 % CI (mos)	IQR (mos)	RPA	HR	p=	95 % CI
1	21	16.5	10.3–27.7	10.3–25.1				
2	456	7.9	6.9–8.9	3.7–13.8	2 vs 1	1.934	0.0064	1.204–3.107
3	28	2.7	1.8–5.0	1.7–5.7	3 vs 2	2.797	<0.0001	1.873–4.177
SIR	n=	MST (mos)	95% CI (mos)	IQR (mos)	SIR	HR	p=	95% CI
8–10	27	16.9	10.7–22.1	8.9–23.8				
4–7	386	8.5	7.5–9.6	4.5–14.7	4–7 vs 8–10	1.959	0.0023	1.201–3.020
0–3	95	3.6	2.8–4.9	1.9–7.7	0–3 vs 4–7	2.001	<0.0001	1.590–2.539
BSBM	n=	MST (mos)	95% CI (mos)	IQR (mos)	BSBM	HR	p=	95% CI
3	66	15.6	11.4–17.7	9.2–24.8				
2	188	9.7	8.0–11.5	5.5–15.9	2 vs 3	1.568	0.0043	1.151–2.135
1	213	6.1	5.2–7.4	3.3–11.2	1 vs 2	1.619	<0.0001	1.314–1.994
0	41	2.0	1.6–2.8	1.0–3.6	0 vs 1	2.883	0<.0.0001	2.024–4.108
M-RPA	n=	MST (mos)	95% CI (mos)	IQR (mos)	M−RPA	HR	p=	95% CI
1+2a	95	15.1	11.0–16.8	7.3–24.8				
2b	164	10.5	8.5–12.3	6.2–16.6	2b vs 1+2a	1.534	0.0028	1.158–2.031
2c+3	249	4.9	4.3–5.5	2.4–9.3	2c+3 vs 2b	2.208	<0.0001	1.788–2.728
SCLC-GPA	n=	MST (mos)	95% CI (mos)	IQR (mos)	SCLC-GPA	HR	p=	95% CI
3.5–4.0	148	10.4	8.3–13.1	6.1–18.8				
2.5–3.0	193	10.2	8.4–11.5	4.8–16.0	2.5–3.0 vs 3.5–4.0	1.196	0.13	0.952–1.504
1.5–2.0	134	4.9	3.8–6.0	2.4–8.9	1.5–2.0 vs 2.5–3.0	2.230	<0.0001	1.758–2.827
0.0–1.0	33	2.5	1.4–3.0	1.3–4.9	0.0–1.0 vs 1.5–2.0	1.482	0.52	0.997–2.203
SCLC Grade	n=	MST (mos)	95% CI (mos)	IQR (mos)	SCLC Grade	HR	p=	95% CI
4–6	114	15.3	11.8–16.7	7.6–26.4				
2–3	317	7.9	6.6–8.7	3.9–13.0	2–3 vs 4–6	2.282	<0.0001	1.786–2.917
0–1	77	3.2	2.5–3.7	1.84–5.0	0–1 vs 2–3	2.750	<0.0001	2.107–3.588

MST; median survival time, CI; confidence interval, IQR; Interquartile range, HR: hazard ratio.

Table 4
Receiver Operating Characteristics were used to compare the reliability of the six reported prognostic grading systems.

Reported prognostic systems*	Area under the curve	95 % confidence interval	p-value (vs SCLC-Grade)
SCLC Grade	0.6519	0.5722–0.7315	reference
Modified-RPA	0.6437	0.5666–0.7207	0.77
BSBM	0.6326	0.5548–0.7103	0.53
SCLC GPA	0.5686	0.4943–0.643	0.042
SIR	0.5668	0.5084–0.6253	0.012
RPA	0.5178	0.4737–0.5619	0.0005

*The area under the line; from largest to smallest.
SCLC: small cell lung cancer, Modified RPA: Modified Recursive Partitioning Analysis (RPA) [1p], BSBM: Basic Score for Brain Metastases [18], SCLC GPA; SCLC Graded Prognostic Assessment [10], SIR: Score Index for Radiosurgery [17], RPA [16].

series. These results were validated employing the verification series, i.e., our results suggest that the herein-proposed SCLC Grade has the highest prognostic value. Therefore, this system is recommended for making the clinical judgements required to select the most appropriate treatment modalities, i.e., more aggressive treatment or an essentially palliative management approach, as well as a future clinical trials.

Since Gaspar et al reported their prognostic grading system for BM patients, RPA [16], four other indexes have been proposed: (1) SIR [17], (2) BSBM [18], (3) Modified RPA (19) and (4) GPA [20]. The GPA system was upgraded to the Diagnostic-Specific (DS) GPA [21]. When the three systems were reported, SRS for SCLC patients was not generalized. Thus, only a small number of SCLC patients were included in the three reports. Even DS GPA and a further modified system [22] were aimed at NSCLC, not SCLC, patients. With the RPA system, large patient number discrepancies among the three classes might reflect clinical factors. Survival periods vary markedly within Class II. This prompted us to develop a subclassification of RPA Class II patients, with division into three subclasses, the M−RPA system which we have already reported [11,19]. In the present investigation, approximately 10 % of patients had SCLC. We endeavored to apply these four indexes for the 508 herein-reported SCLC patients. As shown in Table 3, there were statistically significant MST differences among the three/four subgroups. The four previously reported systems were also shown to be highly applicable to SCLC patients.

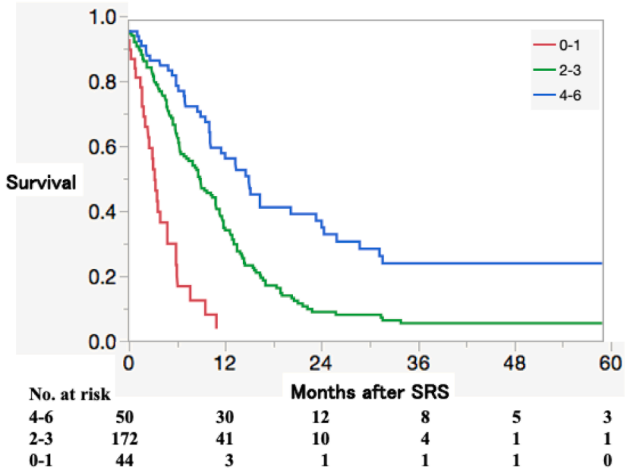
The next question involves which system is optimal for predicting patient outcome. The ROC was applied for the four previously reported systems and the two more recently developed systems, i.e., SCLC GPA and our SCLC Grade. As shown in Table 4, the AUC of the SCLC Grade was largest, followed by those of the M−RPA and BSBM. The AUCs of the other three systems were relatively small and there were statistically significant differences between the SCLC Grade and each of the other three, i.e., SCLC GPA, SIR and RPA.

The major weakness of our study would be the retrospective design. Another possible weakness is that all patients had been referred by other clinics for SRS. Thus, patients who had undergone neither WBRT nor surgical intervention were included in the present study. Furthermore, administration of systemic anti-cancer agent treatments, which are regarded as correlating with survival, was not included in the information in our database. Another possible weakness is that the study period was 20 years (from 1998 through 2018). During this 20-year period, remarkable advances were achieved in the treatment of cancer patients. In the present study, MSTs actually differed significantly between the earlier and the most recent 10-year periods (7.2 vs 9.3 months, $p = 0.0038$). Nevertheless, our two databases had been contemporaneously accumulated such that the long-term study period is considered to have had little impact on the study results. As shown Fig. 3, the herein-reported SCLC Grade was shown to be applicable to both the study periods, i.e., earlier and most recent. However, prospective randomized studies will test these conclusions and may provide more robust support for this hypothesis.

A

Earlier 10 years

Group	n=	MST (mos)	95% CI (mos)	IQR (mos)	Group	HR	p=	95% CI
4-6	50	14.5	10.7-16.9	7.6-23.5				
2-3	172	7.3	6.0-8.1	3.3-11.5	2-3 vs 4-6	2.186	<.0001	1.564-3.057
0-1	44	2.9	2.0-3.9	1.7-4.8	0-1 vs 2-3	2.306	<.0001	1.642-3.239
Total	266	7.2	6.0-7.9	3.1-12.4				

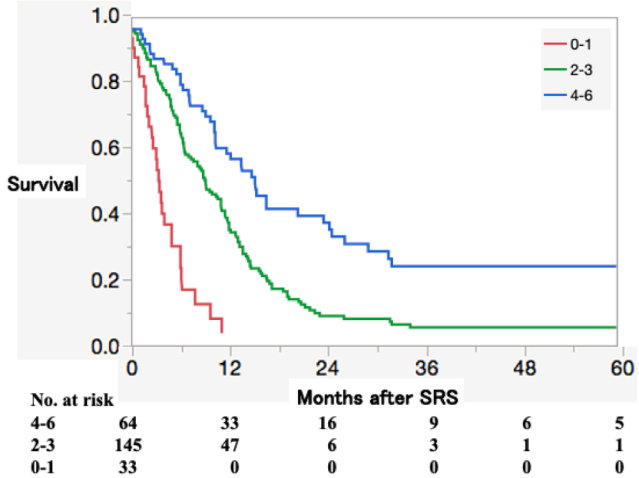


No. at risk						
4-6	50	30	12	8	5	3
2-3	172	41	10	4	1	1
0-1	44	3	1	1	1	0

B

Recent 10 years

Group	n=	MST (mos)	95% CI (mos)	IQR (mos)	Group	HR	p=	95% CI
4-6	64	15.3	10.3-23.8	7.3-31.8				
2-3	145	9.2	6.7-11.2	4.9-14.4	2-3 vs 4-6	2.321	<.0001	1.616-3.332
0-1	33	3.5	2.2-5.0	1.8-6.1	0-1 vs 2-3	3.683	<.0001	2.371-5.721
Total	242	9.3	7.4-11.1	4.8-15.8				



No. at risk						
4-6	64	33	16	9	6	5
2-3	145	47	6	3	1	1
0-1	33	0	0	0	0	0

Fig. 3. Overall survival based on small cell lung cancer (SCLC) grade in the two series, i.e., the earlier (A, before June 2008) and the most recent (B, after July 2008) series. MST; median survival time, CI; confidence interval, IQR; inter-quartile range, HR; hazard ration, SRS; stereotactic radiosurgery.

Conclusion

Our validity test results for the SCLC GPA demonstrated that this system did not precisely reflect the outcomes of SCLC patients with BMs. As described above, it should be noted that our patient group differed markedly from those studied by Sperduto and colleagues in that all of our patients received upfront SRS while the cohort of Sperduto et al were mostly given WBRT. Therefore, we created a new prognostic index, the SCLC Grade. As compared with already reported indexes, our system had the highest prognostic value, followed by M−RPA and BSBM, for managing SCLC patients with BMs.

Roles of authors

Study design: MY, TS, YS and YH.
Statistical analyses: YS and YH.
Gamma knife treatment and patient follow-up: MY, TS, YK and SS.
Manuscript writing: MY.
Manuscript reviewing: TS, YS, YH, YK and SS.

Financial support

None.
For this type of study, formal consent is not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are very grateful to Bierta E. Barfod, M.D., M.P.H., who was an

employee of the Katsuta Hospital Mito GammaHouse until the end of 2019 and currently resides in Seattle, USA, for her help with the language editing of this manuscript.

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