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Original Article

Comprehensive summary and retrospective evaluation of prognostic scores for patients with newly diagnosed brain metastases treated with upfront radiosurgery in a modern patient collective

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ABSTRACT

Background: Numerous prognostic scores (PS) for patients with brain metastases (BM) have been developed. Recently, PS based on laboratory parameters were introduced to better predict overall survival (OS). A comprehensive comparison of the wide range of scores in a modern patient collective is still missing.
Materials and methods: Twelve PS considering clinical parameters only at the time of BM diagnosis were calculated for 470 patients receiving upfront SRS between January 2014 and March 2020. In a subcohort of 310 patients where a full laboratory dataset was available five additional prognostic scores were compared. Restricted mean survival time (RMST), partial likelihood and c-index were calculated as metrics for performance evaluation. Univariable and multivariable analysis were used to identify prognostic factors for OS.
Results: The median OS of the whole cohort was 15.8 months (95% C.I.: 13.4–20.1). All prognostic scores performed well in separating patients into different prognostic groups. RPA achieved the highest c-index, whereas GGS achieved highest partial likelihood with evaluation in the total cohort. With incorporation of the laboratory scores the recently suggested EC-GPA achieved highest c-index and highest partial likelihood. A prognostic score solely based on the assessment of performance status achieved considerable high performance as either 3- or 4-tiered score. Multivariable analysis revealed performance status, systemic disease status and laboratory parameters to be significantly associated with OS among variates included in prognostic scores.
Conclusion: Although recent PS incorporating laboratory parameters show convincing performance in predicting overall survival, older scores relying on clinical parameters only are still valid and appealing as they are easier to calculate, and as overall performance is almost equal. Moreover, a score just based on performance status is not significantly inferior and should at least be assessed for informed decision making.

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Around 20–40% of all adult cancer patients suffer from brain metastases (BM) as the most common intracranial malignancy, predominantly developing from solid cancers like non-small-cell lung cancer (NSCLC), melanoma, and breast cancer [1,2]. The incidence of BM has been steadily increasing over the last years and their occurrence is considered a substantial cause of morbidity and mortality [3,4]. Improved extracranial cancer control and prolonged survival through improved systemic therapy is associated with an increasing risk of developing BM during the course of the disease [5–7]. Patients developing BM represent a highly heterogeneous population. Individualized decision making in regard to systemic therapy and aggressiveness of the local treatment of BM or distant metastases is of paramount importance [8]. However, the management of BM has become increasingly complex in recent years with the introduction of highly effective intracranial systemic therapy (targeted therapies and immunotherapies) and due to paradigm shifts in radiation therapy in general by moving away from WBRT in multiple brain metas-

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tases [9–12]. The challenge ahead will be to select the right treatments – or combinations thereof – at the right time for the right patient, or to avoid treatment entirely, since it has been shown that some patients do not benefit from brain-directed therapy at all [13]. A wide range of prognostic scores has been developed over the last decades to improve overall survival (OS) estimation and to provide decision support for choosing the right treatment for the right patient [14–20]. Recursive partitioning analysis (RPA), introduced in 1997 by Gaspar et al., was one of the first prognostic tools for the prediction of OS, and was based on three Radiation Therapy Oncology Group (RTOG) trials [21]. About a decade later, a different score named graded prognostic assessment (GPA) [22] was proposed by Sperduto et al. and was further adjusted over time to account for underlying differences in histology and at molecular levels [5,23,24]. In recent years, scores have been developed that additionally consider laboratory parameters: Extracranial Score [25], LabBM [26], LabPS [27], and EC-GPA [28]. In addition, another laboratory score, the modified Glasgow Prognostic Score (mGPS), was initially developed for gastro-intestinal malignancies and was also proposed for its applicability in patients with BM [29–31]. Nevertheless, the most popular and established scores remain RPA and GPA, which are used to varying degrees in daily clinical practice [32,33].

The main goal of our study was to provide a comprehensive overview and comparison of all existing scores in a contemporary cohort of patients with BM. We considered it therefore highly relevant to investigate to what extent prognostic scores still allow for accurate survival estimations, since prognostic scores were mainly developed on cohorts from previous oncological eras, where the treatment of cancer and radiotherapeutic approaches significantly differ from current guideline-based recommendations.

Material and methods

Patient cohort and data collection

A total of 470 patients treated at our department from January 2014 to March 2020 with upfront stereotactic radiosurgery (SRS) for newly diagnosed BM were included in this study. Radiotherapy was performed after decision by a multidisciplinary tumor board and mostly initiated within a few weeks after diagnosis. The study was approved by the Local Ethics Committee (BASEC-Nr. 2018-01794) and consent for retrospective analysis was obtained.

Patients' medical records were reviewed and clinical data including information on general patient demographics, treatment and survival, histology of primary tumor, number and volume of brain metastases, systemic disease status, use of steroids (parallel to radiotherapy), as well as laboratory data were collected to calculate all available prognostic scores. Routinely acquired laboratory values (hemoglobin, platelet count, albumin, CRP, and LDH) were retrieved for the calculation of scores only if they were analyzed 14 days before or after diagnosis.

We focused our analysis on the period from 2014 to 2020, since a comparison with two in-house patient cohorts comprising 601 patients treated between 2002 and 2007 and between 2008 and 2013 showed a significant difference in OS (Fig. S1).

Prognostic scores

A literature research was performed in order to enumerate all scores developed since the introduction of the RPA (Table 1). All patients were classified using RPA [21], GPA [22], Rotterdam Score [15], Score Index For Radiosurgery (SIR) [16], Basic Score for Brain Metastases (BSBM) [17], Golden Grading System (GGS) [18] and Rades Score for WBRT [19]. Patients for whom laboratory parameters were also available, from now on referred to as the lab-subcohort, were also classified using Extracranial Score (ECS) [25], LabBM [26], LabPS [27], EC-GPA [28], and mGPS [30,34]. For patients with BM from NSCLC or melanoma, the Disease Specific Graded Prognostic Assessment (dsGPA) [23] and the updated Graded Prognostic Assessment for molecular markers (lungmolGPA and melanomamolGPA) [5,24] were added. The Rades score for SRS [20], which was developed in 2015, was excluded from further analysis as it was the only score with two risk groups and a reasonable comparison to other scores, consisting of either three or four risk groups, was therefore not possible. On the other hand, the earlier developed Rades score was incorporated into our comparison, although developed for WBRT [19]. The variable "Time to WBRT" was adjusted to "Time to SRS". The Rotterdam score was not incorporated into the final comparison, since calculation was only possible in patients treated simultaneously with corticosteroids and where information on following clinical response to steroid use was available [15].

Most scores were developed using the "time from start of treatment to death", except Rotterdam Score and GGS considering "time from diagnosis to death". For final analysis and comparison of the scores, OS was defined as "time from start of treatment to death" for all scores, and patients still alive at the last follow-up were considered right-censored.

Performance status was the only parameter which all prognostic scores have in common as either Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group performance status (ECOG). Therefore, we additionally evaluated a new score exclusively based on the assessment of the performance status, hereinafter referred to as the "Performance Score".

The calculation of the 3- or 4-tiered scores is possible either with ECOG or KPS. For example, the best group in both scores contains ECOG 0 or KPS 100, while the worst group contains ECOG 4 or KPS 60 and worse. The exact subgroup classification based on ECOG or KPS values can be found in the Appendix (Table S1).

Performance evaluation metrics

All statistics were performed in R (version 4.0.2) [35]. The proportional hazards assumption was tested for each Cox model using the *cox.zph* function of the *survival* package [36], which tests whether there is a significant relationship between the Schoenfeld residuals and time. We observed that for the majority of scores the proportional hazards assumption does not hold. Conventional evaluation metrics for discrete risk scores such as the concordance probability estimate and the hazard ratio are not valid when the proportional hazards assumption is violated [37]. Since the c-index is well-known and easy to interpret, we have calculated the weighted c-index using the *c-index* function of the *pec* package and reported it for the overall comparison of the scores [38,39]. Furthermore, to avoid estimating the time-varying effects in the Cox model and the resulting challenging comparison between scores, we decided to report the partial likelihoods [40]. This was calculated using the *logLik* function. The value of the partial likelihood is not easily interpreted, but the higher the value, the better the model fits the data. Finally, as an alternative to the hazard ratio, we calculated the ratios of the restricted mean survival times (RMST), which allows for a clinically relevant interpretation of the survival difference between risk groups [41–43]. The RMST is simply the area under the Kaplan-Meier (KM) curve, and was calculated at 2-years of follow-up using the *rmst2* function of the *survRM2* package [44].

We deliberately refrained from ranking the scores, as this would not yield a clear result due to the different performance metrics, the different stratification levels (3-tiered vs. 4-tiered), and the underlying cohort (total cohort vs. lab-subcohort).

Table 1
Overview of prognostic scores.

Factors	RPA	GPA	Rotterdam	SIR	BSBM	GGS	Rades (WBRT)	Rades (SRS)	ds-GPA	Lung- molGPA	Melanoma-molGPA	ECS	Lab BM	EC-ds-GPA	Lab PS	Modified Glasgow PS
Age	–	✓	–	✓	–	✓	✓	✓	✓	✓	✓	–	–	✓	–	–
KPS	✓	✓	–	✓	✓	✓	–	–	✓	✓	✓	–	–	✓	–	–
ECOG	–	–	✓	–	–	–	–	✓	–	–	–	–	–	–	✓	–
Control of primary	✓	–	✓	✓	✓	–	✓	–	–	–	–	–	–	–	–	–
Systemic disease	✓	✓	✓	✓	✓	✓	–	–	✓	✓	✓	–	–	✓	–	–
Response to Steroids	–	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
Volume of BM	–	–	–	✓	–	–	–	✓	–	–	–	–	–	–	–	–
Number of BM	–	✓	–	✓	–	–	–	–	✓	✓	✓	–	–	✓	–	–
Number of extracranial metastatic organs	–	–	–	–	–	–	–	–	–	–	–	✓	–	✓	–	–
Gene status	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	–	–
Time to Treatment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hemoglobin	–	–	–	–	–	–	–	–	–	–	–	–	✓	–	✓	–
Platelet count	–	–	–	–	–	–	–	–	–	–	–	–	✓	–	✓	–
Albumin	–	–	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	✓
Lactate dehydrogenase (LDH)	–	–	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–
C-reactive protein (CRP)	–	–	–	–	–	–	–	–	–	–	–	–	✓	–	✓	✓
Introduction	1997	2008	1999	2000	2004	2008	2008	2015	2012	2016	2017	2014	2017	2019	2021	2021
Validation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	–
Number of patients	1200	1960	1292	65	110	479	1085	214	3940	2186	823	139	1200	141	212	340
Therapy of the cohort based on which the Prognostic Score was developed.	WBRT	WBRT, SRS, surgery	WBRT, SRS, surgery, steroid only	SRS	SRS	SRS ± WBRT	WBRT	SRS	WBRT, SRS, surgery, or combination	WBRT, SRS, surgery, or combination	WBRT, SRS, surgery, or combination	WBRT	WBRT, SRS, surgery	WBRT, SRS, surgery	WBRT, SRS	SRS

Univariable analysis

Univariable analyses were performed including all available parameters in our dataset: age, KPS, Charlson Comorbidity Index (CCI), primary tumor control (yes/no), extracranial metastases (no/yes, controlled/yes, non-controlled), number of BM, volume of largest BM, total BM volume, number of involved organs, time from diagnosis to treatment, time from first extracranial metastasis to BM, synchronous disease (yes/no), symptomatic disease (yes/no), first metastasis in bone, brain, liver, lung or lymph nodes, extensive systemic tumor activity (yes/no, with "yes" being progressive primary tumor growth and systemic metastases), actionable driver mutation (yes/no), response to steroids (yes/no), hemoglobin level, platelet count, white blood cell count, albumin level, creatinine level, lactate dehydrogenase (LDH) level, and C-reactive protein level. The parameters with a category in brackets were the categorical variables, while all others were included as continuous variables in the Cox proportional hazards model. The univariable analyses were repeated for the NSCLC-subcohort and the melanoma-subcohort.

Multivariable analysis

The multivariable analysis was performed on the lab-subcohort for which information on actionable driver mutation was available (n = 280). All parameters were used as input for the multivariable modeling, with the exception of 'response to steroids', since it was only available for 187 patients. Although it was not the purpose of this work to develop a model or a new prognostic score, we investigated which parameters are selected in a final model using a commonly used regression analysis method: least-absolute shrinkage and selection operator (LASSO). LASSO was performed using the repeated 10-fold cross-validation with the *glmnet* package [45].

Results

Median [interquartile range] OS for the evaluated cohort was 16.8 months [6.0–74.2]. The median [interquartile range] follow-up time, calculated using reversed Kaplan-Meier, was 42.3 months [28.0–60.9].

In total, we were able to calculate prognostic scores based on clinical parameters for 470 patients. The laboratory data with values for hemoglobin, platelet count, albumin, LDH, and C-reactive protein were available for 310 patients. NSCLC was the most frequent underlying primary tumor in our cohort (n = 245), followed by malignant melanoma (n = 120). Median KPS was 90, median age at diagnosis of BM was 62.5 years, and the median number of BM with newly diagnosed metastatic spread to the central nervous system was 2. In our patient population, 139 patients received targeted therapy and 202 received immunotherapy at some point in the course of their disease. See Table 2 for patient characteristics.

Table 3 summarizes the values for c-index, partial likelihood, and RMST of the 3- and 4-tiered prognostic scores for all patients (n = 470) and for the lab-subcohort (n = 310). The results for the histological subgroups (NSCLC and melanoma) with the inclusion of the dsGPA, lungmolGPA, and melanomamolGPA are presented in the supplement (Tables S3 and S4).

Prognostic power among scores varied depending on the chosen performance metric, but differences were marginal. Among the 3-tiered scores, RPA yielded the highest c-index and the Performance Score yielded the highest partial-likelihood in the entire cohort, while in the lab-subcohort these were RPA and LabBM, respectively. For the 4-tiered scores, BSBM and the Rades Score achieved the highest c-index and GGS the highest partial-likelihood, whereas in the lab-subcohort the EC-GPA achieved the highest c-index and partial likelihood. The 3- and 4-tiered Performance

Table 2
Patient Characteristics.

No. of patients	470	
Gender		
male	271	58%
female	199	42%
Median age at BM diagnosis (range)	63 (16–89)	
No. of BM		
Median No. of BM at diagnosis (range)	2 (1–21)	
Single Metastasis	188	40%
Multiple Metastases	282	60%
2	100	21%
3	49	10%
≥4	133	28%
Volume of BM (in cc)		
Median cumulative Volume of BM at diagnosis (range)	2.5 (0.01–68)	
Median Volume of largest BM at diagnosis (range)	2 (0.01–68)	
Histology		
NSCLC	245	52%
KRAS	62	25%
EGFR	28	11%
ALK	11	4%
Melanoma	120	26%
Mut_Melanoma	100	83%
BRAF	64	53%
NRAS	30	25%
Breast cancer	44	10%
Gastrointestinal Cancer	22	5%
Others	39	8%
KPS		
90–100	244	52%
70–80	172	37%
<70	54	11%
No. of Patients with steroids	216	46%
Steroid response		
Good response	111	60%
Intermediate response	44	24%
Little response	32	16%
Control of primary tumor at BM diagnosis		
Primary controlled	291	62%
Primary not controlled	179	38%
Extracranial metastases at BM diagnosis		
Yes	373	79%
No	97	21%
No. of Patients with **systemic therapy** (somewhen during the course of metastatic brain disease)	423	90%
Immunotherapy	202	43%
Targeted therapy	139	30%
Chemotherapy	284	60%

Scores achieved high values for both c-index and partial likelihood, achieving comparable performance as RPA and GPA. A table showing which prognostic scores achieved the highest values for different metrics can be found in the supplement (Table S2).

The KM curves for all clinical scores are shown in Fig. 1, and for all laboratory scores in Fig. 2.

At two years follow-up, mGPS achieved the best discrimination of the group with the best prognosis in the lab-subcohort. On the other hand, the Performance Score achieved the best discrimination of the group with the worst prognosis (cf. Table 3 and Fig. 3). Differences in RMST varied over time (Fig. 3).

Univariable analysis show that age, KPS, primary tumor control (yes/no), extracranial metastases (no/yes, non-controlled), number of BM, number of involved organs, time from first extracranial metastasis to BM, first metastasis in bone, first metastasis in brain, hemoglobin level, albumin level, and C-reactive protein level were significant in predicting OS (Table 4).

Variables selected using LASSO were KPS, extracranial metastases, first metastasis in bone, first metastasis in brain, hemoglobin, albumin, and C-reactive protein (shown in bold in Table 4). In the NSCLC-subcohort the same variables were selected except for KPS (Supplementary Table S5). In the melanoma-subcohort first metastasis in bone, albumin, and C-reactive protein were selected (Supplementary Table S6).

Discussion

The provided study gives a comprehensive comparison of all previously published relevant prognostic scores for patients with newly diagnosed BM. To the best of our knowledge, there is no comparable work that provides such a broad overview over prognostic scores being used for survival estimation in patients with BM.

Previous work included fewer scores or combined patient data from a longer time span with the possibility of confounded OS due to differing therapies [22,46–51]. In addition, we provide the first independent external validation for the recently published LabPS [27].

The median OS of our patients (treated between 2014 and 2020) was 16.8 months which is much longer than the median OS of the cohort used for the development of RPA (4.4 months) or dsGPA (7.1 months), and also longer than a previous patient cohort from our institution (2002–2013 with median 10.7 months) [21,22]. With this remarkable difference in OS, in addition to the lack of a comprehensive comparison of prognostic scores, we saw further justification in the assessment of the value of prognostic scores in a modern cohort. The large difference in OS may have been caused by the paradigm shift in systemic therapy in recent years reflected by a substantial proportion of patients which have received any form of targeted therapy or immunotherapy in addition to SRS [52–54].

The performance evaluation with RMST, partial likelihood, and c-index resulted in comparable values for all prognostic scores. However, all scores shared the limitation of unbalanced proportions of patients among the different prognostic classes, with the middle groups generally encompassing the majority of patients. These intermediate risk groups seem to be very heterogeneous and it seems difficult to further disaggregate them based on the factors included in the prognostic scores.

While evaluating the RMST over time (Fig. 3), it becomes evident that the discriminative power of the scores is not equally distributed over the different risk groups. Prognostic scores may have varying strengths and provide a good or poor discriminative quality depending on the underlying question to be answered. For example, mGPS was able to best determine the group with the best prognosis within the 3-tiered scores, but performed worse than others in discriminating the worst group. However, looking at all prognostic scores together we can conclude that the difference in the overall performance among all listed scores is marginal and most scores are still suitable as prognostic instruments.

The restriction to specific histologies (dsGPA) and the inclusion of molecular information (molecular GPA) have been suggested to improve performance of prognostic scores [5,23,24]. Our results show that despite all molecular and targeted advances, KPS and systemic disease status still seem to be among the most relevant parameters driving OS. In our NSCLC-subcohort, the frequency of activating mutations in the EGFR gene or the number of ALK translocations was comparable to other data collected in Europe or the United States. Within this cohort, the lungmolGPA (the most developed score in the GPA line) did not stand out against other 4-tiered scores or the RPA, which is still valid and convenient 25 years after its recommendation [55]. Moreover, it is remarkable that a score simply based on performance status achieves good discrimination andcan even outperform prominent 3- and 4-tiered scores. Therefore, our proposed Performance Score may be an attractive

Table 3
Performance evaluation of prognostic scores. Partial likelihood, c-index and RMST values of 3- and 4-tiered scores for all patients (n = 470) and the lab-subcohort (n = 310). RMST: Restricted mean survival time.

		Total cohort (n = 470)			"lab-subcohort" (n = 310)		
	Score	Partial likelihood	c-Index	Ratio RMST (t = 2 yr)	Partial likelihood	c-Index	Ratio RMST (t = 2 yr)
3-tiered Prognostic Scores	*RPA*	−1691.57	0,76	1 vs. 2: 1.33 [95% C.I.: 1.19–1.49] 2 vs. 3: 1.81 [95% C.I.: 1.37–2.39]	−990.38	0,76	1 vs. 2: 1.32 [95% C.I.: 1.13–1.53] 2 vs. 3: 1.84 [95% C.I.: 1.31–2.57]
	SIR	−1697.67	0,73	1 vs. 2: 1.34 [95% C.I.: 1.19–1.51] 2 vs. 3: 1.79 [95% C.I.: 1.28–2.50]	−993.99	0,70	1 vs. 2: 1.33 [95% C.I.: 1.14–1.55] 2 vs. 3: 1.57 [95% C.I.: 1.08–2.29]
	Performance Status Score	−1690.22	0,74	1 vs. 2: 1.26 [95% C.I.: 1.11–1.42] 2 vs. 3: 1.96 [95% C.I.: 1.47–2.63]	−986.39	0,74	1 vs. 2: 1.24 [95% C.I.: 1.06–1.44] 2 vs. 3: 2.26 [95% C.I.: 1.54–3.33]
	LabBM	–	–	–	−982.84	0,72	1 vs. 2: 1.27 [95% C.I.: 1.10–1.45] 2 vs. 3: 1.64 [95% C.I.: 1.22–2.19]
	mGPS	–	–	–	−984.05	0,75	1 vs. 2: 1.38 [95% C.I.: 1.21–1.56] 2 vs. 3: 1.59 [95% C.I.: 1.19–2.11]
	LabPS	–	–	–	−990.95	0,69	1 vs. 2: 1.21 [95% C.I.: 1.05–1.41] 2 vs. 3: 1.35 [95% C.I.: 1.11–1.65]
4-tiered Prognostic Scores	*GPA*	−1694.45	0,71	1 vs. 2: 1.10 [95% C.I.: 0.95–1.27] 2 vs. 3: 1.36 [95% C.I.: 1.18–1.56] 3 vs. 4: 1.43 [95% C.I.: 1.22–1.69]	−991.91	0,69	1 vs. 2: 1.05 [95% C.I.: 0.88–1.25] 2 vs. 3: 1.37 [95% C.I.: 1.18–1.59] 3 vs. 4: 1.33 [95% C.I.: 1.09–1.62]
	GGS	−1677.07	0,72	1 vs. 2: 1.24 [95% C.I.: 1.10–1.39] 2 vs. 3: 1.36 [95% C.I.: 1.18–1.56] 3 vs. 4: 2.20 [95% C.I.: 1.50–3.21]	−980.29	0,71	1 vs. 2: 1.23 [95% C.I.: 1.06–1.43] 2 vs. 3: 1.34 [95% C.I.: 1.13–1.59] 3 vs. 4: 2.15 [95% C.I.: 1.32–3.51]
	BSBM	−1678.62	0,73	1 vs. 2: 1.23 [95% C.I.: 1.09–1.39] 2 vs. 3: 1.30 [95% C.I.: 1.13–1.49] 3 vs. 4: 2.55 [95% C.I.: 1.84–3.54]	−976.44	0,73	1 vs. 2: 1.22 [95% C.I.: 1.05–1.43] 2 vs. 3: 1.31 [95% C.I.: 1.10–1.55] 3 vs. 4: 2.71 [95% C.I.: 1.82–4.02]
	Rades	−1678.69	0,73	1 vs. 2: 1.30 [95% C.I.: 1.17–1.46] 2 vs. 3: 1.26 [95% C.I.: 1.03–1.54] 3 vs. 4: 2.33 [95% C.I.: 1.56–3.47]	−979.67	0,73	1 vs. 2: 1.29 [95% C.I.: 1.11–1.49] 2 vs. 3: 1.24 [95% C.I.: 0.98–1.56] 3 vs. 4: 2.60 [95% C.I.: 1.60–4.23]
	Performance Status Score	−1687.22	0.72	1 vs. 2: 1.22 [95% C.I.: 1.08–1.38] 2 vs. 3: 1.40 [95% C.I.: 1.08–1.80] 3 vs. 4: 1.52 [95% C.I.: 1.13–2.05]	−984.78	0,72	1 vs. 2: 1.20 [95% C.I.: 1.03–1.40] 2 vs. 3: 1.37 [95% C.I.: 1.01–1.86] 3 vs. 4: 1.70 [95% C.I.: 1.05–2.74]
	EC-GPA	–	–	–	−973.39	0,76	1 vs. 2: 1.03 [95% C.I.: 0.88–1.20] 2 vs. 3: 1.43 [95% C.I.: 1.24–1.65] 3 vs. 4: 2.22 [95% C.I.: 1.37–3.60]
	ECS	–	–	–	−982.55	0,69	1 vs. 2: 1.09 [95% C.I.: 0.82–1.45] 2 vs. 3: 1.23 [95% C.I.: 1.06–1.42] 3 vs. 4: 2.28 [95% C.I.: 1.40–3.72]

alternative for physicians who would like to avoid time-consuming scoring. Furthermore, the Performance Score seems to reliably identify patients with a poor prognosis.

Even though laboratory parameters like hemoglobine, albumin, and c-reactive protein were significant in the multivariable analysis, the calculation of laboratory scores in clinical practice is considerably more complex and time-consuming than the calculation of clinical scores. Several recent patterns-of-care studies have already shown that prognostic scores are generally used rather rarely [32,33]. Thus, it is doubtful that more complex models will be used more frequently.

Since 2014, all patients treated at our center who received upfront radiosurgery, have been systematically documented in a database with extensive assessment of clinical parameters before treatment and at prespecified follow-up timepoints. The collection of laboratory parameters was performed subsequently. The incompleteness of laboratory data for 160 patients is a limitation of our analysis. A further limitation is the limited number of patients with histologies other than NSCLC and malignant melanoma, such that additional histology-specific scores could not be addressed in our study [56–61]. Nevertheless, we can provide a larger dataset compared to other studies that developed new scores which include laboratory parameters [25,27,28].

The homogeneous treatment present in our data may represent an advantage over cohorts on which prognostic scores were developed (Table 1). We implemented an SRS program in our department starting in 2014 to gradually eliminate WBRT as an upfront local treatment for all patients presenting with newly diagnosed BM. We therefore consider the possibility of selection bias due to the application of different treatment options to be rather low, as all received the same local therapy, namely SRS or SRT. Prognostic scores have not been implemented in our clinic to guide treatment decisions. However, we cannot exclude a selection bias with regards to (a) the patients presented at our hospital and (b) the omission of some patients relevant to this analysis in the transition phase where WBRT was still used in cases of multiple (n > 10) BM. As the data was recorded retrospectively from medical records, the single-center retrospective design of our study has to be mentioned as a limitation.

Score performance was evaluated in our entire cohort and additionally in a smaller lab-cohort with inclusion of laboratory scores where a full laboratory dataset was available. To exclude a possible systematic selection bias of the underlying lab-cohort, we compared some characteristics of the entire cohort and the lab-subcohort (not shown). According to this, patients in the lab-subcohort received immunotherapy more often, whereas patients outside this subcohort received chemotherapy more often. In addition, primary tumor control was achieved more often in patients outside the lab-subcohort than within at the time of BM diagnosis. Although there were only minor differences in performances of prognostic scores between the entire cohort and the lab-subcohort, we cannot fully exclude a possible selection bias.

Comparing the full range of different scores is a major challenge, since some of the scores include different numbers of prognostic tiers, survival time periods have not been defined consistently across all scores, and some scores have been developed on very heterogeneous patient cohorts. Nevertheless, we present a robust comparison and overview of the most common prognostic scores. We decided against ranking scores, since their performances are quite similar and a clear winner or best score

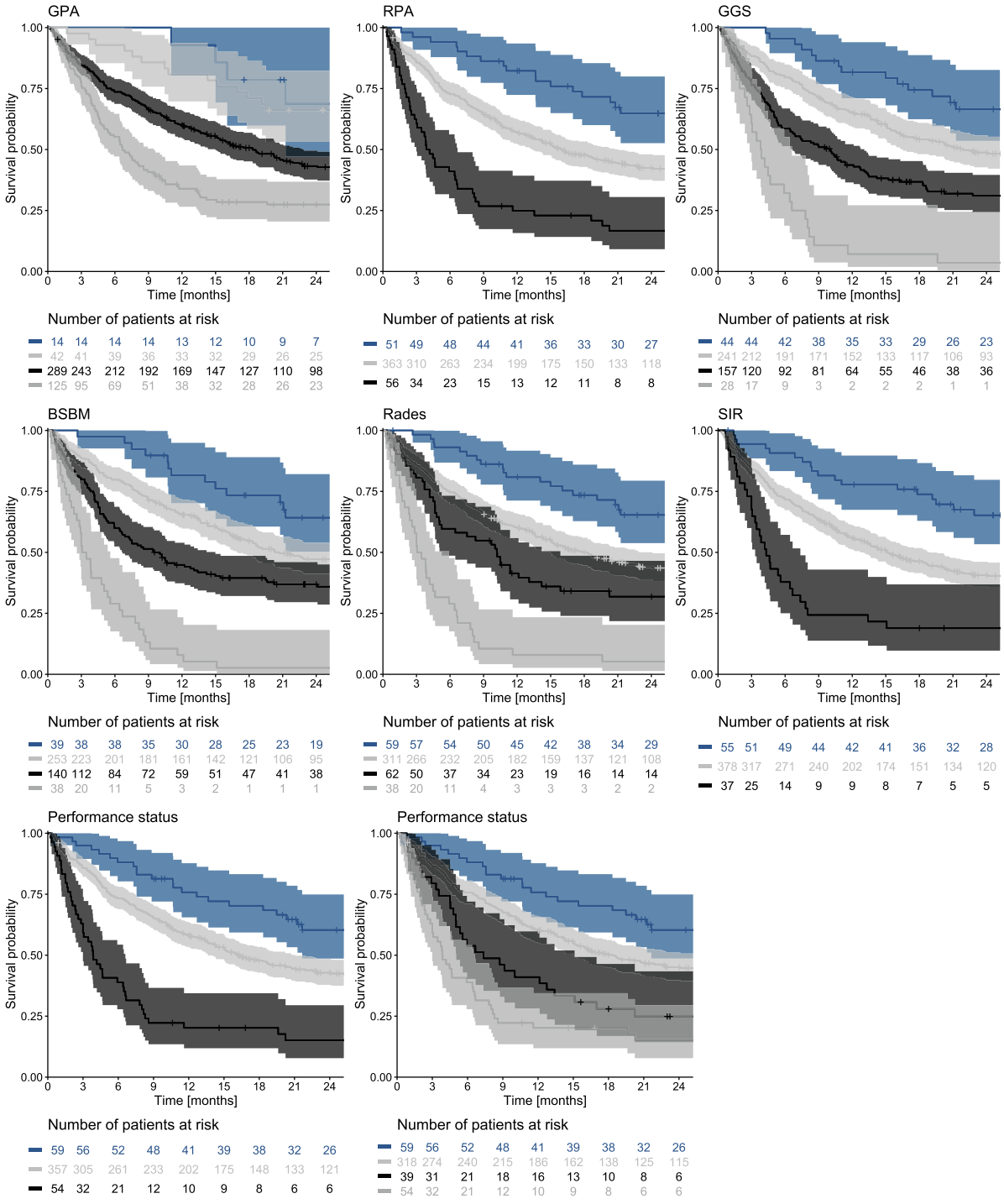

Fig. 1. Kaplan-Meier curves of all clinical scores (all patients).

cannot be proclaimed. Even though we can apply different statistical metrics to evaluate score performance, defining one best score isn't possible as the best statistical performance might not be clinically relevant while there is no prospective validation regarding treatment decisions.

The oncological community has many efficient prognostic scores at its disposal to better select patients for different therapies. The crucial problem of scores still lies in the lack of evidence for deriving therapeutic consequences for different subgroups or to make score-based treatment decisions which may also explain the poor application of prognostic scores in clinical practice. Although the question regarding the right treatment for the right patient is beyond the work presented here, clinical treatment decisions are in principle limited to 3 real-world scenarios: (1) Administer all treatment options and maximum therapy for patients with excellent prognosis, i.e., combine aggressive systemic therapy and radiotherapy for BM and distant metastases. (2) Discuss therapeutic options for patients with intermediate prognosis, e.g., delay of radiotherapy for patients with targetable driver mutations or administration of targeted therapies or immunotherapy. (3) Pro-

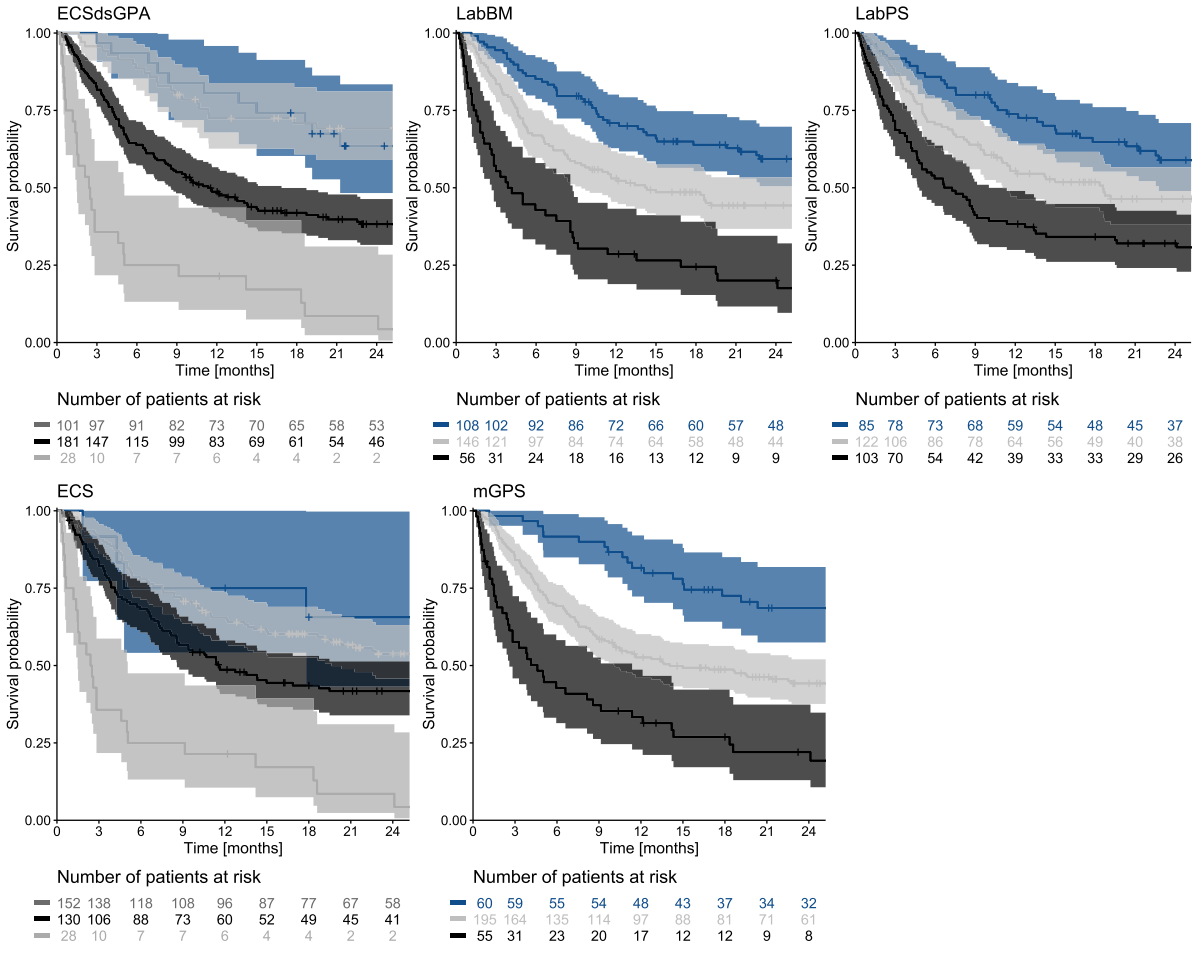

Fig. 2. Kaplan-Meier curves of all laboratory scores (lab-subcohort).

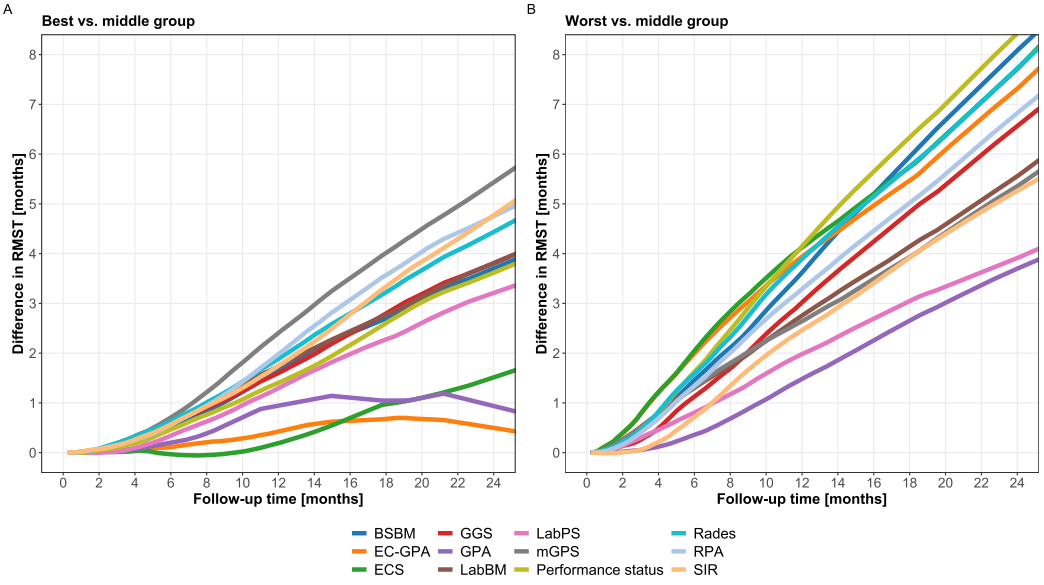

Fig. 3. Difference in restricted mean survival time (RMST) between two risk groups calculated over the time interval 0–24 months for the lab-subcohort.

Table 4
Results of univariable analysis. The variables that are selected by LASSO regression are indicated in bold. HR = Hazard Ratio, CI = Confidence Interval, PH = Proportional Hazards, CCI = Charlson Comorbidity Index, LDH = Lactate Dehydrogenase.

	beta	HR (95% CI for HR)	p-value
Age [continuous, per 1 yr]	0.0191	1.02 (1.01–1.03)	0.0001
KPS [continuous, per 10]	**−0.291**	**0.75 (0.69–0.81)**	**<0.0001**
CCI [categorical, >6]	−0.18	0.84 (0.67–1.05)	0.1170
Primary controlled yes	−0.234	0.79 (0.63–1.00)	0.0458
Extracranial mets: yes, controlled	0.337	1.40 (0.95–2.07)	0.0914
Extracranial mets: yes, non-controlled	**0.881**	**2.41 (1.75–3.34)**	**<0.0001**
# of brainmets [continuous]	0.04	1.04 (1.01–1.07)	0.0116
Volume largest brain metastasis [continuous]	0.00222	1.00 (0.99–1.02)	0.7390
Total brainmets volume [continuous]	0.00118	1.00 (0.99–1.01)	0.8440
# of involved organs [continuous]	0.199	1.22 (1.12–1.33)	<0.0001
Time from diagnosis to treatment [continuous, per 10]	0.00101	1.00 (0.99–1.02)	0.8970
Time from first met to brain met [continuous, per 100]	1.5	4.47 (1.18–16.9)	0.0275
Synchronous disease: yes	−0.218	0.80 (0.63–1.03)	0.0810
Symptomatic disease: yes	0.106	1.11 (0.89–1.39)	0.3560
First metastasis in bone: yes	**0.443**	**1.56 (1.19–2.05)**	**0.0014**
First metastasis in brain: yes	**−0.492**	**0.61 (0.49–0.77)**	**<0.0001**
First metastasis in liver: yes	0.493	1.64 (1.19–2.26)	0.0025
First metastasis in lung: yes	0.198	1.22 (0.96–1.55)	0.1100
First metastasis in lymph nodes: yes	0.127	1.14 (0.90–1.44)	0.2920
Systemic tumor activity: extensive	0.48	1.62 (1.27–2.05)	0.0001
Actionable driver mutation: yes (n = 379)	−0.164	0.85 (0.65–1.11)	0.2230
Response to steroids (n = 187)	−0.781	0.46 (0.33–0.65)	<0.0001
Hemoglobin (n = 418)	**−0.194**	**0.82 (0.77–0.88)**	**<0.0001**
Platelet count [continuous, per 100] (n = 418)	0.0296	1.03 (0.90–1.17)	0.6570
White blood cells (n = 419)	0.0199	1.02 (0.99–1.05)	0.1920
Albumin (n = 386)	**−0.0828**	**0.92 (0.90–0.94)**	**<0.0001**
Creatinine [continuous, per 10] (n = 420)	0.0223	1.02 (0.97–1.08)	0.4190
LDH [continuous, per 100] (n = 352)	0.0819	1.09 (1.06–1.11)	<0.0001
C-reactive protein (n = 412)	**0.0168**	**1.02 (1.01–1.02)**	**<0.0001**

vide best supportive care rather than active treatment for patients with very limited prognosis. Nevertheless, such scenarios need to be validated prospectively. Furthermore, it is also recommended that centers with a sufficiently high number of patients validate prognostic scores based on their own cohorts to reveal possible internal characteristics.

As patients with BM are still excluded from clinical studies, prognostic scores could serve as a tool to consider patients for clinical trials. The recently suggested 'trial eligibility quotient' indicates patients' individual eligibility for clinical trials when the estimated survival probability is at least 50% for one additional year [62]. The trial eligibility quotient has been proposed for use with GPA, but can in principle be applied to any score.

In conclusion, inspection of the currently available and recently published prognostic scores together with our performance analysis, shows that an improvement in predictive power was only marginal. Therefore, efforts to develop better scores without incorporating finer grained tumor characterization or novel biomarkers may not seem justified. Rather, one can argue for the selection of an easy to use and widely accepted score together with a consistent and stringent clinical application thereof. Ideally this would happen in a prospective fashion to gain evidence for deriving treatment decisions for different prognostic subgroups. If no score is ultimately used for prognostic assessment, performance status offers a simple yet powerful tool to estimate patient survival and should be minimally assessed for informed decision making.

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Conflict of interest

Dr. Weller reports grants and personal fees from Apogenix, grants and personal fees from MSD, grants and personal fees from Merck (EMD), grants from Quercis, grants and personal fees from Philogen, personal fees from Adastra, personal fees from BMS, personal fees from Medac, personal fees from Nerviano, personal fees from Novartis, personal fees from Orbus, personal fees from yMabs, outside the submitted work.

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Dr. Tanadini-Lang reports outside the submitted work that her husband is an employee of Varian, a Siemens Healthineer company.

All other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.04.024.

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