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Original Article

Predicting Survival with Brain Metastases in the Stereotactic Radiosurgery Era: are Existing Prognostic Scores Still Relevant? Or Can we do Better?

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Abstract

Predicting survival is essential to tailoring treatment for patients diagnosed with brain metastases. We have evaluated the performance of widely used, validated prognostic scoring systems (Graded Prognostic Assessment and diagnosis-specific Graded Prognostic Assessment) in over 1000 'real-world' patients treated with stereotactic radiosurgery to the brain, selected according to National Health Service commissioning criteria. Survival outcomes from our dataset were consistent with those predicted by the prognostic systems, but with certain cancer subtypes showing a significantly better survival than predicted. Although performance status remains the simplest tool for prediction, total brain tumour volume emerges as an independent prognostic factor, and a new, improved, prognostic scoring system incorporating this has been developed.

Key words: Brain metastases; prognostic score; radiosurgery; stereotactic; survival

Introduction

The incidence and prevalence of brain metastases are increasing due to improvements in imaging and extracranial disease control [1]. Outcomes vary widely, predominantly driven by underlying tumour biology. Options for treating brain metastases have improved, particularly with the development of targeted systemic therapies that penetrate the brain [2–4] and local therapies with reduced morbidity, such as radiosurgery [5]. Sadly, symptomatic care alone still remains an appropriate choice for some, so accurate prognostication is essential to guide the decision-making process and identify the treatment best suited for the individual patient.

Prognostic scoring systems have been developed and validated using clinical trial data and earlier systems, such as the Recursive Partitioning Analysis [6,7] and subsequently the Graded Prognostic Assessment (GPA) [8,9], were agnostic of cancer types. More recently, a plethora of more tumour type-specific prognostic scores have been developed, reflecting the impact of histological subtype and newer available therapies on outcome. Most notably, the GPA system has been updated and validated to the diagnosis-specific GPA (DS-GPA), which incorporates newly identified prognostic factors, such as molecular markers [10–18].

Other published prognostic indices, developed in the radiosurgery era, include the Score Index for Radiosurgery (SIR) [19], the Basic Score for Brain Metastases [20] and the Golden Grading System [21], using a combination of age, Karnofsky Performance Status (KPS), extracranial disease assessment, brain metastases number and, for SIR, brain metastases volume. The dose-fractionation schedules used in the studies to design these scoring systems were not specifically available. Unlike DS-GPA, these systems do not take histology into account, and were designed using data from patients treated prior to immunotherapy and targeted systemic therapies. More recently, the Comprehensive Prognostic Index (CPI) [22]

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found KPS, brain metastases number, the volume of the largest brain metastasis and the presence/absence of extracranial metastases to be significant prognostic factors, but the results were based on a small study and have not yet been validated. As such, GPA and DS-GPA have been chosen for comparison in our study.

Stereotactic radiosurgery (SRS) describes the delivery of high-dose, highly conformal radiotherapy, delivered in a single or a few (three to five) fractions, with rapid dose fall-off outside the target. SRS has been delivered at our institution according to National Health Service (NHS) England commissioning criteria (volume of intracranial disease <20 cm^3, controlled or controllable extracranial disease and a prognosis of more than 6 months) since 2016 [23]. We set out to explore the performance of GPA and DS-GPA, the most widely used, established, validated and relevant prognostic scoring systems, in our patients treated within the NHS. In addition, we evaluated the prognostic impact of the size and number of brain metastases as well as age and KPS from this large single-institution series.

Using the results, we devised a new prognostic scoring system, appropriate for patients treated with SRS in the 2020s.

Materials and Methods

Approval and Patient Recruitment

Institutional review board approval was obtained prior to data analysis. Patients with brain metastases treated with SRS at our institution between 1 May 2016 and 31 June 2021, according to national commissioning guidelines, and using Cyberknife or Linac platforms were included. Patients who had received prior SRS were excluded but those who had received prior whole-brain radiotherapy or neurosurgery were eligible for inclusion.

Data Collection

Demographic and clinical data were collected prospectively at the time of referral for SRS. The date of diagnosis of brain metastases was defined as the date of definitive imaging confirming intracranial disease. Data regarding the number and volume of brain metastases were extracted from the radiotherapy planning system at the time of SRS planning. Survival data were retrieved from the NHS Spine database. To allow for delays in reporting, a censor date was set 3 months before the last data acquisition (11 May 2022) for those without a recorded date of death. Mortality status was verified manually with the primary care team for 50 cases, confirming 100% concordance.

Statistical Analysis

Data analysis was conducted in R (3.6.0) using the survival (3.2–13), finalfit (1.0.4), survminer (0.4.9) and survivalAnalysis (0.2.0) packages. Survival data were calculated using the Kaplan–Meier method and Log-rank tests, prior to univariate and multivariate analysis using the Cox proportional hazards model. To allow for multiple testing, covariates were analysed for multivariate analysis only if they met a significance threshold of <0.001 on univariate analysis. Age, tumour number and volume were statistically significant as continuous univariate variables. In order to simplify scoring they were then dichotomised by iterative optimisation. The full range of threshold values was evaluated at integer values for age/number of 0.1 cm^3 intervals for volume and the threshold value selected with the greatest hazard ratio and Log-rank significance for survival. Multivariate corrected hazard ratios were then used to construct new prognostic scores if they met a significant threshold of <0.01. Scores were attributed to each covariate proportional to the multivariate adjusted hazard ratio.

Results

After the introduction of NHS commissioned SRS at our institution in May 2016, 1037 patients received SRS for brain metastases prior to 30 June 2021 (Table 1). Radiosurgery fractionation was determined based on the size and location of the brain metastases. A single fraction was delivered in 610 (58.8%) patients, three fractions in 417 (40.2%) and five fractions in 10 (0.9%), although within fractionated courses, some smaller lesions may also have been treated in a single fraction. The median follow-up interval was 13.7 months (range 1–88.6 months). The median overall survival after diagnosis and SRS treatment for brain metastases was 15.1 months (95% confidence interval 14.1–16.5 months) and 12.2 months (95% confidence interval 11.0–13.4 months), respectively (Table 2).

Survival with Brain Metastases Exceeded Historic Expectations

GPA and DS-GPA, where appropriate, were calculated for all patients. Survival of our patients greatly exceeded those predicted from the original GPA risk groups (Table 2); the median survival of 11 months expected for the best prognostic GPA group, GPA 3.5–4, is consistent with the survival seen for the poorest prognostic group in our cohort, GPA score 0–1 (median 9.9 months, 95% confidence interval 8.5–12.3 months). This probably reflects the historic nature of the trial data used to design and validate the original GPA groups, the selected nature of patients who receive SRS and improvements in survival due to contemporary treatment. Nevertheless, our data show that GPA groups remain highly discriminating for survival (Log-rank, $P < 0.0001$, Figure 1a) and survival in our patients with GPA 3.5–4 (median 59.4 months; 95% confidence interval 33.2–NA) was significantly longer than for patients with GPA 0–1 (median 9.9 months; 95% confidence interval 8.5–12.3, Table 2).

For DS-GPA, survival outcomes in our dataset were consistent with those expected from published DS-GPA risk groups, which were derived from more contemporaneous data and analysed according to tumour types (Table 2, Figure 2). Metastatic melanoma was an exception, with

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Table 1
Baseline characteristics of patients and univariate and multivariate analysis of prognostic features and their relative weighting in our new prognostic score (RMH-SRS Survival Score)

	Categorical	*n* (%)	Hazard ratio (univariable)	Hazard ratio (multivariable)	Score (maximum 11)
Age (years)	≤70	775 (74.7)	–	–	1
Median 63 (range 21–89)	>70	262 (25.3)	1.47 (1.25–1.72, $P < 0.001$)	**1.41 (1.19–1.66, $P < 0.001$)**	0
Sex	Female	589 (56.8)	–	–	
	Male	448 (43.2)	1.21 (1.05–1.40, $P = 0.009$)	1.15 (0.97–1.37, $P = 0.114$)	
Karnofsky Performance Status	70	131 (12.6)	–	–	0
	80	262 (25.3)	0.63 (0.50–0.78, $P < 0.001$)	–	0
	90	481 (46.4)	0.43 (0.35–0.53, $P < 0.001$)	**0.63 (0.55–0.74, $P < 0.001$)**	2
	100	163 (15.7)	0.29 (0.22–0.38, $P < 0.001$)		2
Number of brain metastases	1	376 (36.3)	–	–	1
	2	196 (18.9)	1.26 (1.03–1.54, $P = 0.025$)		0
	3–5	235 (22.7)	1.49 (1.23–1.80, $P < 0.001$)	**1.35 (1.15–1.58, $P < 0.001$)**	0
	6–10	147 (14.2)	1.27 (1.01–1.59, $P = 0.039$)		0
	>10	83 (8.0)	1.25 (0.94–1.67, $P = 0.122$)		0
Brain disease volume (cm^3)	<1.5	257 (24.8)	–	–	1
	1.5–4.5	239 (23.0)	1.37 (1.11–1.70, $P = 0.004$)		0
	4.5–8.5	275 (26.5)	1.50 (1.22–1.84, $P < 0.001$)	**1.31 (1.09–1.56, $P = 0.004$)**	0
	>8.5	266 (25.7)	1.62 (1.32–1.99, $P < 0.001$)		0
Extracranial disease	Absent	142 (13.7)	–	–	2
	Present	895 (86.3)	1.67 (1.33–2.09, $P < 0.001$)	**1.59 (1.26–2.01, $P < 0.001$)**	0
Primary site	Breast	216 (20.8)	–	–	0
	Gastrointestinal tract	87 (8.4)	2.26 (1.72–2.97, $P < 0.001$)	1.25 (0.84–1.86, $P = 0.262$)	0
	Gynaecological	32 (3.1)	1.23 (0.81–1.86, $P = 0.338$)	0.65 (0.40–1.06, $P = 0.087$)	0
	NSCLC Adeno	342 (33.0)	1.24 (1.01–1.51, $P = 0.039$)	0.69 (0.49–0.98, $P = 0.038$)	0
	NSCLC Non-adeno	79 (7.6)	2.10 (1.57–2.81, $P < 0.001$)	1.10 (0.73–1.65, $P = 0.652$)	0
	SCLC	18 (1.7)	1.23 (0.71–2.13, $P = 0.459$)	0.90 (0.49–1.68, $P = 0.747$)	0
	Melanoma	147 (14.2)	0.81 (0.62–1.05, $P = 0.114$)	**0.53 (0.34–0.82, $P = 0.004$)**	2
	Other*	45 (4.3)	0.93 (0.63–1.37, $P = 0.710$)	**0.52 (0.32–0.85, $P = 0.009$)**	0
	Renal	71 (6.8)	1.12 (0.81–1.54, $P = 0.499$)	0.60 (0.39–0.94, $P = 0.024$)	0
Tartgetable mutation	NULL	702 (67.7)	–	–	0
	Breast_ER	57 (5.5)	0.82 (0.61–1.11, $P = 0.205$)	0.67 (0.44–1.02, $P = 0.063$)	0
	Breast_Her2	120 (11.6)	0.56 (0.44–0.72, $P < 0.001$)	**0.45 (0.31–0.65, $P < 0.001$)**	2
	Lung_EGFR	55 (5.3)	0.66 (0.47–0.93, $P = 0.016$)	0.73 (0.51–1.04, $P = 0.083$)	0
	Lung_ALK	28 (2.7)	0.49 (0.30–0.81, $P = 0.005$)	0.56 (0.34–0.94, $P = 0.027$)	0
	Melanoma_BRAF	75 (7.2)	0.47 (0.34–0.64, $P < 0.001$)	0.77 (0.51–1.17, $P = 0.217$)	0
Prior brain treatment (%)	Nil prior	740			
	Primary chemotherapy	114			
	Prior neurosurgery	162			
	Prior WBRT/partial	62			

Adeno, adenocarcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; WBRT, whole-brain radiotherapy; ER, Oestrogen receptor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; +/- her, human epidermal growth factor receptor.
* Urology (18), unknown primary (10), sarcoma (8), thyroid (5), head and neck (4).

survival substantially exceeding that expected by DS-GPA, possibly reflecting recent improvements in imaging surveillance and systemic therapies.

Intracranial Tumour Volume Independently Predicted Survival

Univariate analysis was conducted to identify prognostic factors predicting overall survival (Table 1, Figure 3). Further to the known prognostic factors (age, sex, performance status, number of brain metastases, presence of extracranial disease, primary tumour type and presence of driver mutations), the total volume of intracranial disease proved highly prognostic (Table 1, Figure 1b). We measured the total volume of intracranial disease as the gross tumour volume, without a margin, outlined on routinely available planning software.

Our analysis showed a significant difference in survival between those with a total treated volume <1.5 cm^3 and those with treated volumes >1.5 cm^3 (hazard ratio 1.31, $P = 0.004$). However, increasing total treated volume beyond 1.5 cm^3 did not appear to significantly impact survival (median survival <1.5 cm^3 group = 17.6 months, 1.5–4.5 cm^3 = 11.0 months, 4.5–8.5 cm^3 = 11.5 months, >8.5 cm^3 = 10.4 months). This relationship also held true for tumours lacking targetable drivers (Figure 4). This remained the case after multivariate correction and was independent of the number of brain metastases (Figure 1c).

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Table 2
Kaplan–Meier estimates of survival from diagnosis. Groups are separated by tumour type, Graded Prognostic Assessment (GPA) and diagnosis-specific GPA (DS-GPA) group, with published GPA/DS-GPA predicted survival shown for comparison

		n	Events	Median	0.95 LCL	0.95 UCL	GPA estimate
Total	All tumours	1037	762	15.1	14.1	16.5	
	Primary_Site = Breast	216	150	20.5	15.8	25.6	
	Primary_Site = GI	87	80	8.2	6.2	10.1	
	Primary_Site = Gynae	32	26	15.6	10.1	38.0	
	Primary_Site = L_Adeno	342	258	14.9	13.6	17.4	
	Primary_Site = L_NonAd	79	66	7.7	5.7	9.3	
	Primary_Site = L_SCLC	18	14	13.0	10.1	NA	
	Primary_Site = Melanoma	147	88	21.3	17.3	35.0	
	Primary_Site = Other	45	31	17.3	14.3	39.3	
	Primary_Site = Renal	71	49	15.8	9.8	24.0	
Overall	GPA = 0–1	287	234	9.9	8.5	12.3	2.6
	GPA = 1.5–2.5	642	470	15.6	14.4	17.7	3.8
	GPA = 3	76	45	33.6	20.2	54.9	6.9
	GPA = 3.5–4	32	13	59.5	33.2	NA	11
Breast	GPA_Cat = 0–1	14	12	10.9	3.9	NA	6
	GPA_Cat = 1.5–2	94	77	13.3	12.2	19.1	13
	GPA_Cat = 2.5–3	86	48	27.5	23.3	42.5	24
	GPA_Cat = 3.5–4	22	13	37.2	18.5	NA	36
GI	GPA_Cat = 0–1	16	16	6.8	3.6	13.2	3
	GPA_Cat = 1.5–2	26	24	7.5	5.4	15.8	7
	GPA_Cat = 2.5–3	33	32	6.6	6.0	11.5	11
	GPA_Cat = 3.5–4	12	8	15.3	9.3	NA	17
L_adeno	GPA_Cat = 0–1	75	60	8.6	5.4	15.0	7
	GPA_Cat = 1.5–2	174	142	14.3	11.9	17.7	13
	GPA_Cat = 2.5–3	83	51	24.7	17.2	39.3	25
	GPA_Cat = 3.5–4	10	5	44.5	17.4	NA	46
L_non-adeno	GPA_Cat = 0–1	27	26	5.5	4.4	7.9	5
	GPA_Cat = 1.5–2	38	29	8.4	5.9	16.6	10
	GPA_Cat = 2.5–3	14	11	11.6	7.9	NA	13
Melanoma	GPA_Cat = 0–1	17	13	10.2	6.5	NA	5
	GPA_Cat = 1.5–2	68	49	18.3	14.9	23.6	8
	GPA_Cat = 2.5–3	41	17	47.1	17.2	NA	16
	GPA_Cat = 3.5–4	21	9	46.6	33.2	NA	34
Renal	GPA_Cat = 0–1	10	9	8.3	3.7	NA	4
	GPA_Cat = 1.5–2	24	22	5.5	4.1	12.1	12
	GPA_Cat = 2.5–3	19	10	27.0	18.0	NA	17
	GPA_Cat = 3.5–4	18	8	33.8	18.5	NA	35

GI, gastrointestinal; Gynae, gynaecological; L_Adeno, lung adenocarcinoma; LCL, lower confidence limit; L_non-adeno, lung non-adenocarcinoma; L_SCLC, lung small cell lung cancer; UCL, upper confidence limit.

Patients were treated according to departmental protocols and according to usual standard practice with dose-fractionation protocols chosen according to clinical requirement. As this study was assessing the survival outcomes in routine clinical practice, the impact of variation in dose per fraction and fractionation schedule on survival was not evaluated in this study.

Creating a New Prognostic Score, Incorporating all Factors Significant on Multivariate Analysis

A new prognostic score, the Royal Marsden Hospital -SRS Survival Score (RMH-SSS), combines seven variables into a novel scoring system (Table 3). The score was not designed to be tissue specific, with histological subtypes embedded as a prognostic factor within the system. Nevertheless, in Supplementary Table S1, we present the scoring system divided by histology, to allow comparison with DS-GPA (Table 2). The scores add up to a maximum of 11 and a minimum of 0. These numerical values are converted to four prognostic groups (0–2, 3, 4–5 and ≥6) with corresponding increasing survival (median 8.6, 12.8, 20.7 and 45.8 months, respectively).

The RMH-SSS, by incorporating tumour volume into the overall prognostic score, was more discriminating than GPA, identifying groups with more prolonged survival and with less overlap of confidence intervals than in GPA (Figure 1a,d).

Survival by Primary Histology

Survival outcomes were markedly worse for patients with brain metastases from non-adenocarcinoma non-small cell lung cancer (NSCLC) and gastrointestinal primaries (Table 1, Figure 2), with a median survival of 7.7 and

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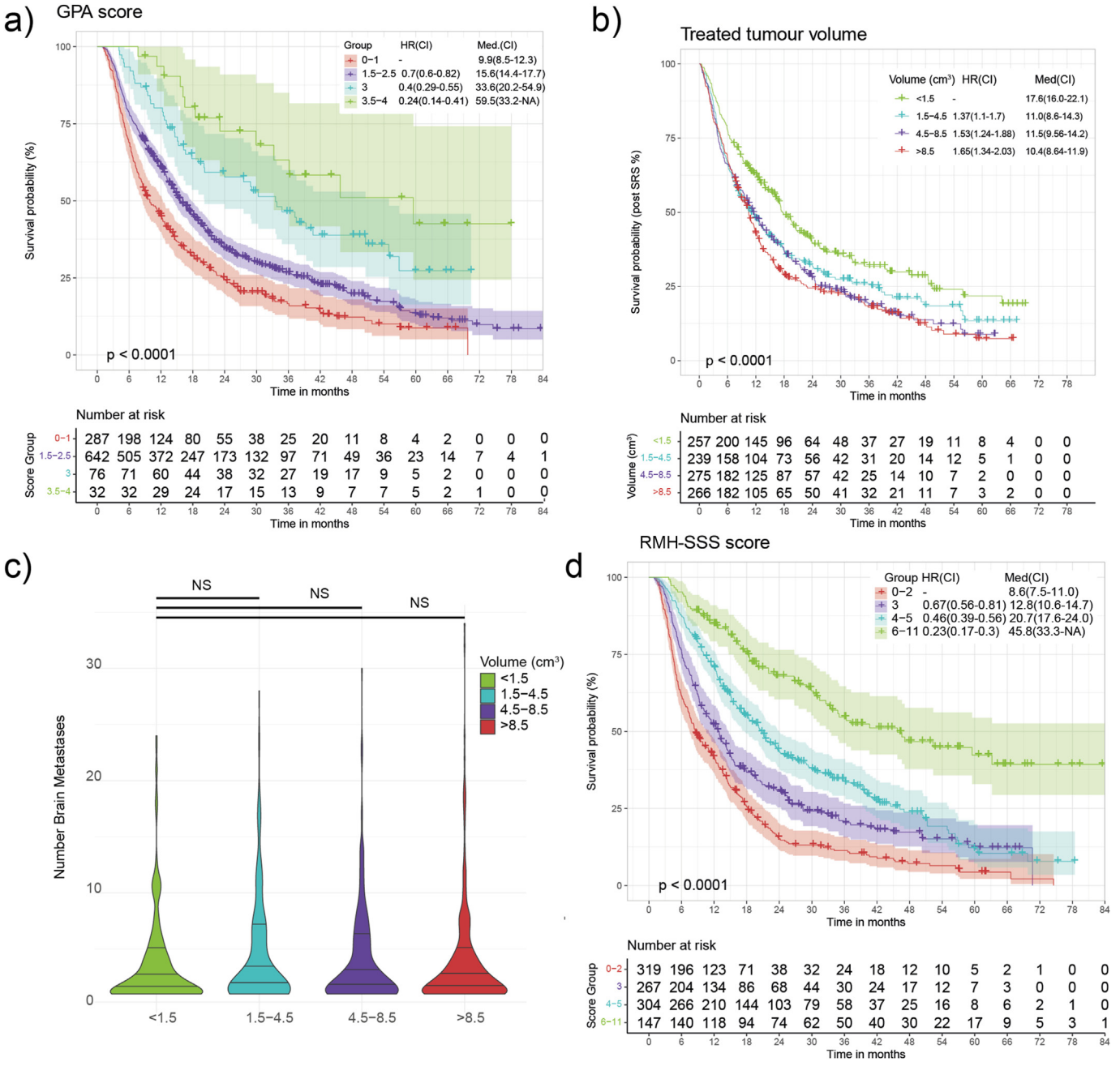

Fig 1. The prognostic enhancement provided by the measurement of intracranial disease volume. (a) Kaplan–Meier plots of overall survival by the original Graded Prognostic Assessment (GPA) groups. (b) Kaplan–Meier plots of overall survival after stereotactic radiosurgery (SRS) treatment for each quartile of patients by treated tumour volume. (c) Violin plots demonstrating the similar distribution of the number of brain metastases for the different quartiles of volume. Wilcoxon signed rank tests were non-significant between all groups. (d) Kaplan–Meier plots of overall survival for prognostic groups for the RMH–SRS Survival Score (RMH–SSS) derived from multivariate analysis (Table 1), including total brain tumour volume.

8.2 months, respectively. This is compared to the next lowest, 13.0 months for small cell lung cancer (SCLC), and the highest, 21.3 months for melanoma. Brain metastases in the context of gastrointestinal cancer are known to be a poor prognostic feature [24] and the shorter survival in this group is consistent with previous published findings. The poor survival in the non-adenomatous NSCLC patients may reflect extracranial disease control and should be the subject of further research.

Discussion

We report the largest series of outcome data from patients treated with SRS for brain metastases outside of a clinical trial setting. As these patients were all treated through a nationally commissioned routine service in a single institution, the findings provide real-world insights into survival outcomes using a uniform approach. Survival

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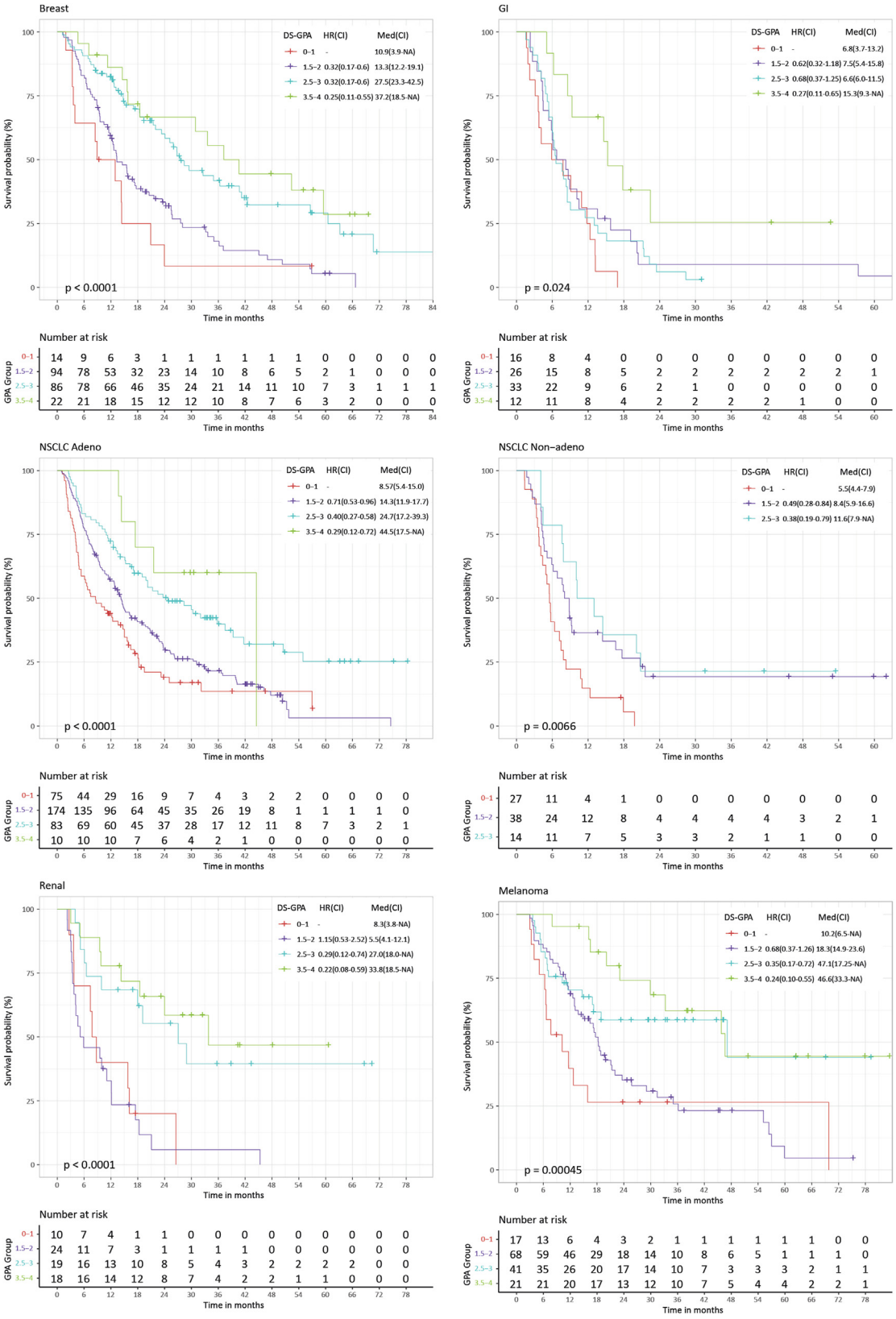

Fig 2. Diagnosis-specific Graded Prognostic Assessment (DS-GPA) Kaplan–Meier survival plots. Kaplan–Meier plots are shown for the DS-GPA categories for breast, gastrointestinal (GI), adenocarcinomas of the lung (NSCLC Adeno), non-adenocarcinoma non-small cell lung cancer (NSCLC Non-adeno), renal cancers and melanoma. Hazard ratios (HR) and median survival with 95% confidence intervals (CI) are shown in the legends for each plot.

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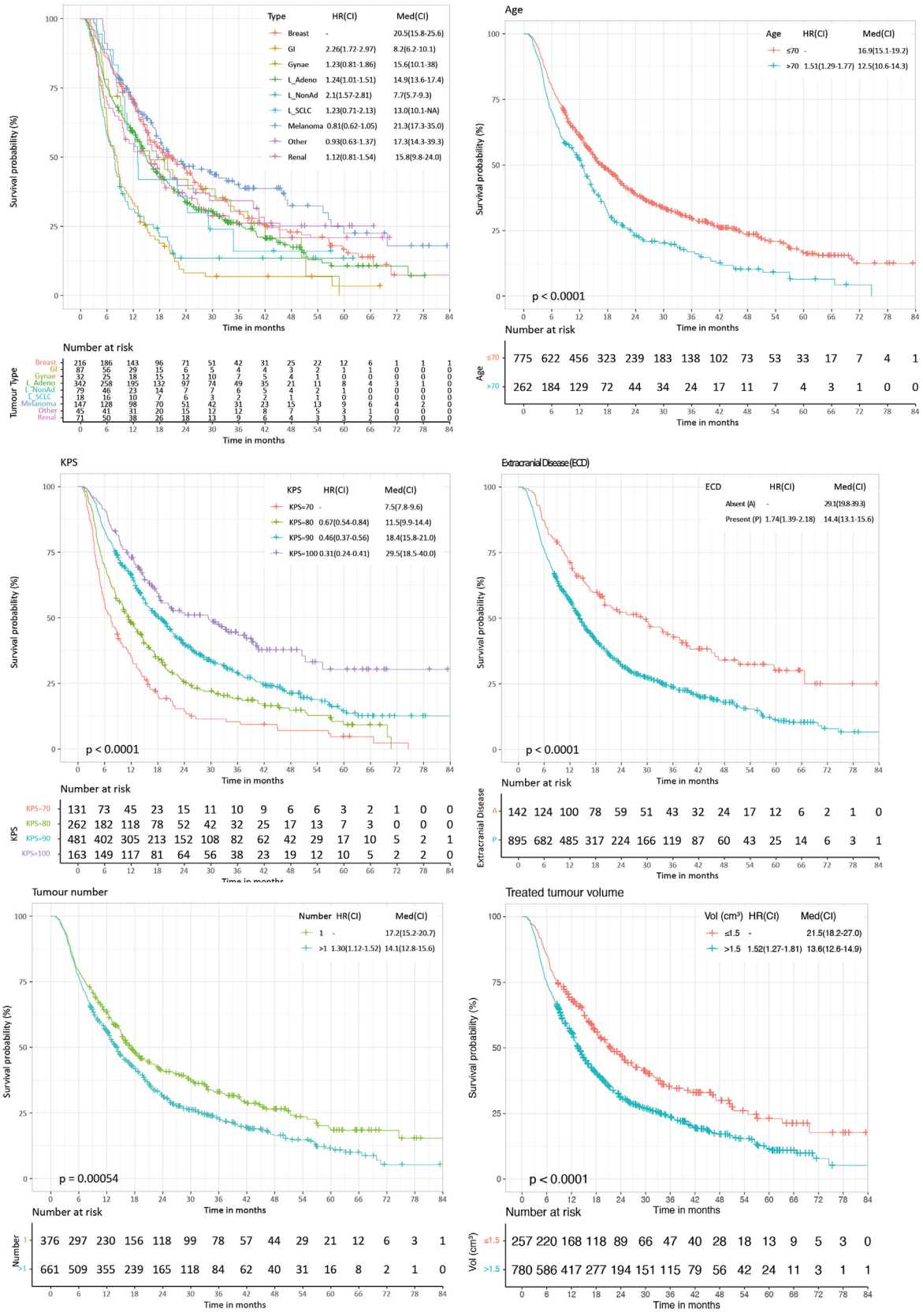

Fig 3. Kaplan–Meier survival plots by tumour type and selected prognostic categories. Kaplan–Meier plots are shown for the tumour types, age, Karnofsky Performance Status (KPS), the presence of extracranial disease (ECD), the number of brain metastases and the treated tumour volume. Hazard ratios (HR) and median survival with 95% confidence intervals (CI) are shown in the legends for each plot.

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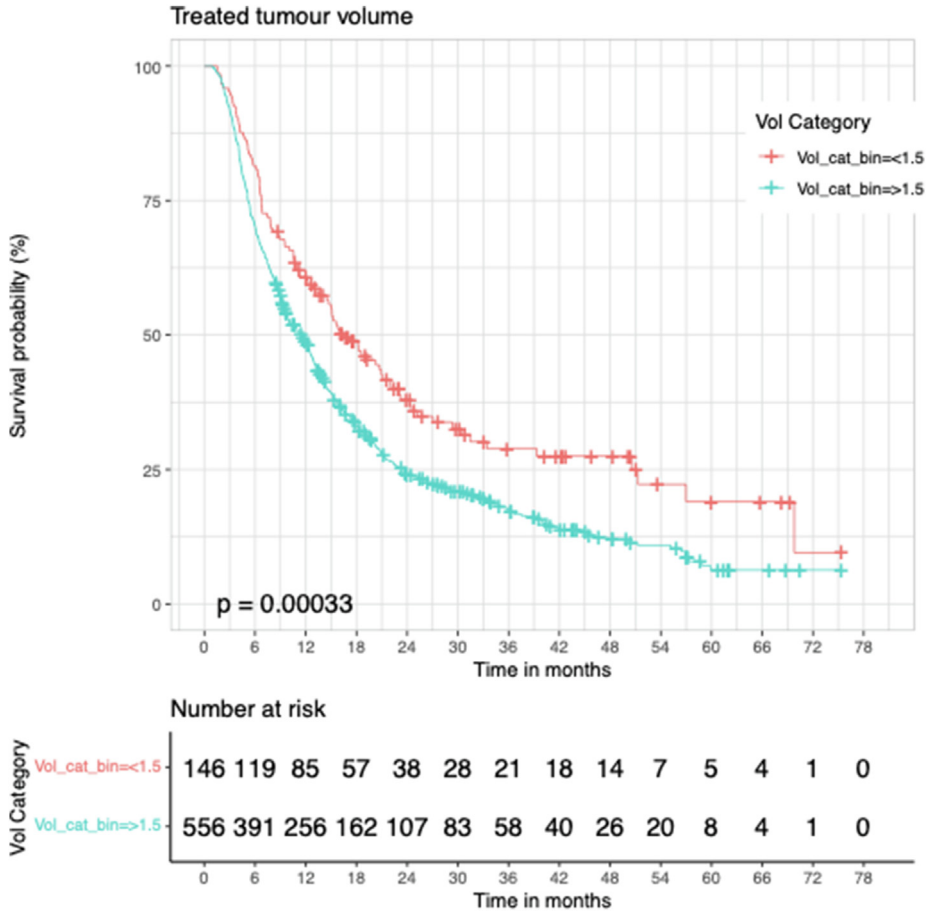

Fig 4. Kaplan–Meier survival plot by tumour volume, excluding all patients with driver mutations, across two groups: <1.5 cm^3 and >1.5 cm^3 tumour volume.

outcomes compared well with those predicted by the DS-GPA and far exceeded those from the older GPA series.

As would be expected, given the criteria used to select patients for SRS, no group could be identified that had a median survival of less than 6 months, indicating appropriate patient identification for treatment. Although the study included a large number of patients overall, some groups had relatively few patients when divided by histology and GPA, and the results from the smallest groups, such as SCLC, should be interpreted with caution, as the heterogeneity in terms of previous treatments received within this population may be considerable.

Table 3
RMH-SRS Survival Score. Patients are assigned a score of between 0 and 2 across seven variables that were deemed significant on multivariate analysis for survival. Minimum score = 0, maximum score = 11

Score	0	1	2
Age	≤70	>70	–
Karnofsky Performance Status	≤80	–	90–100
No. brain metastases	>1	1	–
Brain disease volume (cm^3)	≥1.5	<1.5	–
Extracranial disease	Present	–	Absent
Primary tumour	All others	–	Melanoma
Molecular subtype	All others	–	Her2+ breast cancer

Prognostic scores continue to be developed and refined over time, as diagnostic modalities and treatments improve. We have identified total brain tumour volume to be an independent prognostic factor. In deciding possible prognostic factors for assessment, we chose total brain tumour volume (rather than the volume of the largest brain metastasis, used in SIR and CPI scoring systems), as previous studies have suggested that total brain tumour volume has an impact on survival outcome and freedom from progression [25–30]. Among these, the results of Banfill *et al.* [25] were most relevant to our findings. They analysed their data as groups <5 cm^3, 5–10 cm^3 and >10 cm^3, with a statistically significant improvement in survival in the lower volume groups compared with the >10 cm^3 group [25]. Our findings, by comparison, showed a significant difference only between the <1.5 cm^3 group and the >1.5 cm^3 groups (Table 1, Figure 1b).

To our knowledge, total treated tumour volume does not form part of any widely used prognostic scoring system to date, but is increasingly relevant due to the better detection of metastases (including micrometastases) with modern

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magnetic resonance imaging scanners and volumetric sequence acquisition and can be measured in clinic using readily available imaging software. We acknowledge that treatment dose may be a confounding factor for the assessment of survival against tumour volume, as smaller tumours tend to be treated with higher radiation doses, which may affect clinical outcomes. Although further assessment is required, we note that in the CPI-derived population, 48.6% of patients received single-fraction treatment [22] but fractionation was not a predictor of survival. Whether or not dose is a confounding factor, we have shown that total brain tumour volume is strongly prognostic for survival. We have designed a novel prognostic score, RMH-SSS, which incorporates total brain tumour volume, and have shown that this may outperform existing, validated scoring systems.

Interestingly, our data demonstrate that patients with both the lowest tumour volume and the highest numbers of brain metastases (<1.5 cm^3 and >10 metastases) have the longest median survival (26.8 months, 95% confidence interval 17.25—NA, $P = 19$). For some of these patients, the improved survival probably reflects a difference in underlying tumour biology and behaviour — 13/19 patients with more than 10 brain metastases with a small total volume (<1.5 cm^3) had targetable tumour driver mutations, known to be associated with improved survival compared with similar patients without driver mutations. However, even when excluding patients with targetable driver mutations, there remained a statistically significant difference in survival between the <1.5 cm^3 and >1.5 cm^3 groups (median survival 16 months versus 11 months, $P = 0.00033$), supporting our primary findings of an independent relationship between total brain metastasis volume and survival (Figure 4).

The number and complexity of prognostic scores for brain metastases is increasing [31]. In the SRS era, our data show that performance status continues to be a simple and effective measure for prognostication (Figure 3). It requires no molecular or imaging analysis, and its survival predictions, based on our data, are easily memorable, with each 10-point increase in the KPS approximately equating to an additional 5, 7 and 9 months of survival from diagnosis (KPS 70: 7.5 months; 80: 11.5 months; 90: 18.4 months; 100: 29.5 months). KPS is universally incorporated into scoring systems as one variable among many [22], but even used alone, is independently associated with survival [19].

The new, refined RMH-SSS includes seven variables, whereas other prognostic scores typically have between three and six variables. This may contribute to better, more personalised prognostication for an individual patient but may seem more cumbersome for use in a busy clinic. However, in the era of web- and app-based normograms and scoring systems, if validated, an easy-to-use program could be built using the RMH-SSS algorithm.

RMH-SSS now requires validation in an independent cohort, and this is currently underway. In addition, we propose future work in the following areas: (i) Further exploration of the impact of the number of metastases on survival. Our analysis in this paper has shown that although those with one metastasis live longer than those with more than one metastasis, the relationship does not appear to be linear; (ii) Investigation of the patterns of disease relapse (i.e. local, regional or distant), alongside overall survival, progression-free survival and time to reirradiation. Brain metastasis velocity [32], described as the number of new metastases developing since first SRS, expressed as a rate (new brain metastases/year) allows prognostication for survival after distant brain failure. Evaluation of brain metastasis velocity according to initial brain metastases number and brain metastases volume, and according to prognostic group using the RMH-SSS and a standardised follow-up imaging protocol would be interesting.

Conclusion

Our research shows that prognostic scores continue to be relevant and reliable in predicting survival in patients with brain metastases treated with SRS, selected according to NHS England criteria. We identify a further significant prognostic parameter — total tumour volume — which independently predicts survival. We present a novel prognostic scoring system — the RMH-SSS, which incorporates total tumour volume, which offers more personalised, superior survival prognostication compared with existing scores and compares favourably with GPA in terms of group discrimination.

Author Contributions

MWF and NR are the guarantors of integrity of the entire study. MWF, MB and NR were responsible for study concepts and design. MWF, JdeB and NR carried out the literature research. MWF, MB, LK, AB, JK carried out the experimental studies/data analysis. MWF was responsible for the statistical analysis. MWF, MB, JdeB and NR prepared the manuscript. MWF, MB, JdeB, HT, FS, FS, AC, LW and NR edited the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2024.01.037.

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