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Missing data in cross-sectional networks - An extensive comparison of missing data treatment methods

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Original Article

Comparing survival predicted by the diagnosis-specific Graded Prognostic Assessment (DS-GPA) to actual survival in patients with 1–10 brain metastases treated with stereotactic radiosurgery

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ABSTRACT

Background and purpose: Multiple prognostic models for predicting survival after treatment for brain metastases have been developed. One of them, the diagnosis-specific Graded Prognostic Assessment (DS-GPA), has been developed to predict the median survival for brain metastases from the most frequent primary sites: lung carcinoma, breast cancer, melanoma, renal cell cancer and gastrointestinal tumours. In this study we aim to compare the survival predicted by the DS-GPA to actual survival, and to assess this models performance on both population and individual levels.

Methods: We identified a consecutive cohort of patients treated with SRS for brain metastases in our institute. DS-GPA scores were calculated for each patient, and the median survival for each DS-GPA group was calculated. Differences in survival between DS-GPA groups were tested with Wilcoxon Signed Rank tests and log-rank tests.

Results: In total 367 patients were included in the analysis. Median survival in our cohort is largely comparable to corresponding DS-GPA cohorts, but some notable differences are present. There was a significantly shorter median survival (15.4 months, compared to 26.5 months) in the adenocarcinoma NSCLC subgroup with a GPA score of 2.3–3. We confirmed the significant differences in survival time for most cancer-specific subgroups.

Conclusion: DS-GPA seems to be a reliable tool to classify patients with brain metastases treated with SRS into prognostic subgroups. However, we found some aberrations from predicted median survival times, which may be due to specific characteristics of the populations of patients treated with SRS versus other patients.

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Of all patients diagnosed with cancer, 8–10% will develop brain metastases (BM) [1]. This incidence is expected to increase with more effective treatments for the primary tumours, thereby improving survival and thus increasing the time for possible dissemination of tumour to the brain [1,2]. Brain metastases most frequently originate from lung cancer, breast cancer and melanoma [1–5], but in up to 14% of patients, the metastases are of unknown origin [3–5].

The expected survival is an important factor in selecting the most optimal treatment. To aid this process, several scores have been developed to predict survival of patients with brain metastases. One of them, the diagnosis-specific Graded Prognostic Assessment (DS-GPA), has a specific predictive model for the five

most prevalent primary sites: lung cancer, breast cancer, melanoma, renal cell carcinoma (RCC) and gastro-intestinal (GI) cancer [6]. Each model gives the estimated median survival and its IQR based on several criteria, among which Karnofsky Performance Status (KPS), age, number of brain metastases, presence of extracranial metastases and disease-specific tumour markers. These predictive models are constantly being updated with the newest findings and additional patient data. The scores for lung cancer and melanoma now feature the molecular subtypes of the tumour, and the model for RCC has recently been updated to include haemoglobin count (Hb) at baseline [7–9]. The most recent models are freely available on brainmetgpa.com [10], and can be used by physicians and patients alike.

Over the last few years, an increasing proportion of BM's is being treated with stereotactic radiosurgery (SRS). In the Netherlands, the current guidelines suggest treating patients with 1–3 BM's with SRS

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[11], but observational studies in which patients with four or more lesions were treated suggest that SRS is also a valid treatment for these patients [12,13]. There are even centres where patients with ≥ 10 or ≥ 15 BM's are treated with SRS only [14,15].

This change in treatment protocols may lead to a different survival, and so may lead to inaccurate estimations of the median survival with the DS-GPA. Therefore, we retrospectively computed the DS-GPA for patients with brain metastases who were treated with SRS in our centre, in order to compare the predicted survival to actual survival. The aim of this study is twofold: (1) testing to what extent the DS-GPA is able to stratify our patient cohort into groups with different survival, and (2) how well the DS-GPA is able to predict the survival for individual patients.

Methods

Patient selection

We retrospectively identified a cohort of consecutive patients treated with SRS for brain metastases in the University Medical Center in Utrecht, the Netherlands between January 2012 and July 2017. Patients were eligible if they were treated with SRS for newly discovered brain metastases within that period, and when their primary tumour was one of the following: non-small cell lung carcinoma (NSCLC), breast cancer, melanoma, RCC or GI cancer. Even though the lung-specific GPA model still applies to SCLC patients according to the brainmetgpa.com website [10], no SCLC cases were included in this study. The lung-molGPA was based solely on NSCLC patients, therefore only these patients were used to assess this model [8].

As this retrospective study only involves patient files, the need for informed consent was waived. We obtained permission from the Ethics Board of our institution to conduct this study. This study was done according to the Code of Conduct for Medical Research as set up by the Dutch Federation of Biomedical Scientific Societies.

Data collection

Baseline data were collected from patient records. Collected data consisted of patient demographics, primary tumour and metastasis characteristics and survival. Additionally, data needed for DS-GPA calculation were collected: KPS, BRAF gene status (for melanoma), EGFR and ALK gene status (for NSCLC), Hb (converted from mmol/l to g/dL, for RCC) and Her2, ER and PR receptor status (for breast cancer).

Outcome

For calculation of the DS-GPA, the most current scoring method and predicted median survival were used (see Box 1). For NSCLC and melanoma, the scores that incorporated molecular markers (Lung-molGPA and Melanoma-molGPA) were used [8,9]. For breast cancer and GI tumours, the DS-GPA scoring was taken from the latest summary on DS-GPA [6]. The newest model for calculating DS-GPA for RCC was taken from a recent update, which incorporates Hb at baseline as a criterion [7]. In order to avoid confusion, all the aforementioned scores will be called "DS-GPA" in this publication.

Box 1. DS-GPA scores for each tumour subtype

NSCLC	0	0.5	1		
Age	≥ 70	< 70	–		
KPS	< 70	80	90–100		
ECM	Present	–	Absent		
BM number	≥ 5	1–4	–		
Gene status	EGFR neg/unk and ALK neg/unk	–	EGFR pos or ALK pos		
Breast cancer	0	0.5	1	1.5	2
Age	≥ 60	< 60	–	–	–
KPS	≤ 50	60	70–80	90–100	–
Subtype*	Basal	–	LumA	HER2	LumB
Melanoma	0	0.5	1		
Age	≥ 70	< 70	–		
KPS	≤ 70	80	90–100		
ECM	Present	–	Absent		
BM number	≥ 5	2–4	1		
BRAF gene status	Neg/unk	Pos	–		
RCC	0	0.5	1	2	
KPS	≤ 70	–	80	90–100	
ECM	Present	Absent	–	–	
Hb (g/dL)	≤ 11.1	11.2–12.5 or unk	≥ 12.6	–	
BM number	≥ 5	1–4	–	–	
GI tumours	0	1	2	3	4
KPS	≤ 60	70	80	90	100

*Subtype definitions: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive. ALK = Anaplastic lymphoma kinase, BM = brain metastasis, ECM = extracranial metastases, EGFR = Epidermal growth factor receptor, ER = estrogen receptor, Hb = haemoglobin, HER2 = human epidermal growth factor receptor 2, KPS = Karnofsky Performance Score, Neg = negative, NSCLC = non-small cell lung carcinoma, Pos = positive, PR = progesterone receptor, Unk = unknown.

For each patient, the disease-specific GPA score was calculated with the collected clinical data. In case of any missing data crucial for DS-GPA (i.e. where “unknown” was not in the scoring model), no DS-GPA was calculated. These patients were not excluded from further analysis, in order to give an accurate portrayal of our patient cohort.

Survival was defined as the time between first treatment for brain metastasis and death, or the time between first treatment and date of censoring in case patients were still alive. This definition was also used in creating the DS-GPA [6–9]. Patients without recorded death in our patient files were checked in the Municipal Personal Records Database (*Gemeentelijke Basisadministratie, GBA*) on July 17th 2018, in order to verify whether they were still alive.

Statistical analysis

Descriptive baseline data were calculated. The mean survival with its interquartile range (IQR) was calculated, stratified per tumour type and DS-GPA score. A one-sample Wilcoxon Signed Rank test was performed to test for significant differences in actual and predicted median survival. We used the Bonferroni correction to correct for multiple testing with an adjusted p-value threshold of 0.002 (0.05/21). Additionally, survival was marked as being within or outside the predicted IQR, in order to test whether half of the survival was within this range. Kaplan-Meier curves were created for each disease group stratified by DS-GPA score, with use of the log-rank test to test for significant differences between the groups. The significance threshold was set at 0.05.

All analyses were performed with SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

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All analyses were performed with SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Participants

In total, 401 patients who were treated with SRS for newly discovered brain metastasis were identified. Of them, 367 had either NSCLC, melanoma, breast cancer, RCC or GI tumour as primary malignancy, and were included in further analysis. Baseline characteristics of these patients are presented in Table 1. In accordance with Dutch national guidelines, SRS was considered first-choice treatment in patients with no more than 3 brain metastases. On an individual basis, the tumour board advised SRS for patients with more brain metastases (mostly 4–6), depending on their DS-GPA

Table 1
Baseline characteristics.

		NSCLC n = 212	Breast cancer n = 41	Melanoma n = 31	RCC n = 26	GI tumours n = 57
Mean age (SD)	Years	63.7 (9.9)	55.9 (9.9)	57.9 (9.3)	64.4 (11.6)	64.9 (9.1)
Sex	Male	109 (51.4%)	0	18 (58.1%)	14 (53.8%)	42 (73.7%)
	Female	103 (48.6%)	41 (100%)	13 (41.9%)	12 (46.2%)	15 (26.3%)
Number of BM's	1	109 (51.4%)	15 (36.6%)	13 (41.9%)	13 (50.0%)	33 (57.9%)
	2	53 (25.0%)	9 (22.0%)	8 (25.8%)	6 (23.1%)	7 (12.3%)
	3	34 (16.5%)	10 (24.4%)	5 (16.1%)	5 (19.2%)	11 (19.3%)
	≥4	15 (7.1%)	7 (17.1%)	5 (16.1%)	2 (7.7%)	6 (10.5%)
Extracranial metastases	Yes	86 (40.6%)	29 (70.7%)	20 (64.5%)	20 (76.9%)	50 (87.7%)
	No	126 (59.4%)	12 (29.3%)	11 (35.5%)	6 (23.1%)	7 (12.3%)
KPS	≤70	72 (34.0%)	11 (26.8%)	6 (19.4%)	6 (23.1%)	22 (39.0%)
	80	74 (34.9%)	22 (53.7%)	14 (45.2%)	12 (46.2%)	22 (38.6%)
	90–100	66 (31.1%)	8 (19.5%)	11 (35.5%)	8 (30.8%)	13 (22.8%)
WBRT before SRS	Yes	10 (4.7%)	2 (4.9%)	2 (6.5%)	1 (3.8%)	2 (3.5%)
	No	202 (95.3%)	39 (95.1%)	29 (93.5%)	25 (96.2%)	55 (96.5%)
Resection of new BM	Yes	53 (25.0%)	17 (41.5%)	14 (45.2%)	5 (19.2%)	14 (24.6%)
	No	159 (75.0%)	24 (58.5%)	17 (54.8%)	21 (80.8%)	43 (75.4%)
Mean time between diagnosis and first treatment (SD)	Months	1.5 (2.1)	0.7 (0.3)	1.1 (1.0)	1.1 (0.5)	1.2 (1.5)
EGFR	Positive	11 (5.2%)	–	–	–	–
	Negative	47 (22.2%)	–	–	–	–
	Missing	154 (72.6%)	–	–	–	–
ALK	Positive	5 (2.4%)	–	–	–	–
	Negative	25 (11.8%)	–	–	–	–
	Missing	182 (85.8%)	–	–	–	–
ER/PR	Positive	–	22 (53.7%)	–	–	–
	Negative	–	19 (46.3%)	–	–	–
	Missing	–	0	–	–	–
HER2	Positive	–	17 (41.5%)	–	–	–
	Negative	–	23 (56.1%)	–	–	–
	Missing	–	1 (2.4%)	–	–	–
BRAF	Positive	–	–	16 (51.6%)	–	–
	Negative	–	–	14 (45.2%)	–	–
	Missing	–	–	1 (3.2%)	–	–

ALK = Anaplastic lymphoma kinase, BM = brain metastasis, EGFR = Epidermal growth factor receptor, ER = estrogen receptor, GI = gastrointestinal, HER2 = human epidermal growth factor receptor 2, IQR = interquartile range, KPS = Karnofsky Performance Scale, NSCLC = non-small cell lung carcinoma, PR = progesterone receptor, RCC = renal cell carcinoma, WBRT = whole-brain radiation therapy.

life expectancy of more than 3 months and systemic therapy options. The dose of SRS is according to Dutch national guidelines (<1cc 24 Gy, 1–10 cc 21 Gy, 10–20 cc 18 Gy, 20–65 cc 15 Gy).

DS-GPA scores

Calculated DS-GPA scores per tumour group are presented in [Supplementary Table 1](#). DS-GPA could not be calculated for one breast cancer patient (0.3% of all patients) due to missing receptor status.

Survival

Overall, the median survival was 10.5 months, with a predicted median survival of 13.5 months. Median survival per tumour group and DS-GPA score is presented in [Table 2](#), together with the predicted median survival and the results of the Wilcoxon Signed rank test. In the NSCLC subgroups, 24 patients could not be included in median survival testing due to missing NSCLC tumour type. After correcting for multiple testing, a significant difference was only found the 2.5–3.0 DS-GPA strata in the adenocarcinoma NSCLC subgroup, in which the median survival in our cohort was 10.5 months shorter than predicted (15.4 months, compared to 26.5 months).

In the entire patient cohort, 55.6% of survival times were within the predicted IQR. Survival below Q1 was seen in 26.6%, and 17.8% lived longer than the predicted third quartile. Similarly, 42.9% of patients lived longer than the predicted median survival.

Waterfall plots showing the difference between the predicted median and the actual survival on a per patient basis, stratified by number of BM's are shown in [Fig. 1](#).

Kaplan-Meier curves per tumour group and DS-GPA score are shown in [Fig. 2](#). A significant difference in survival between

patients with different DS-GPA scores was seen in the adenocarcinoma NSCLC, non-adenoma NSCLC, melanoma and RCC subgroups. In the patients with breast cancer and GI cancer, no significant differences were found.

In 30 patients (8.2%), the interval between MRI diagnosis and first intracranial treatment exceeded 2 months. Mostly administration of systemic therapy caused this planned delay (as concurrent systemic therapy and RT is discouraged in our guidelines [11]), although for some patients a “wait-and-scan” protocol was decided on. As these patients were excluded in Sperduto's patient cohorts used for creating the scoring models, a post-hoc analysis was performed with these patients excluded from analysis. The differences with the original analysis were minor: a new significant difference in median survival was seen for the RCC subgroup with DS-GPA scores of 2.5–3.0 (median survival 30.2 months, vs 17 months predicted, $p = 0.018$ by Wilcoxon Signed Rank test). Inversely, the log-rank test lost significance in the non-adenocarcinoma NSCLC group.

Discussion

There are two ways a scoring method such as the DS-GPA can be interpreted. Firstly, its prediction can be seen as an estimate of the expected survival on an individual level, which aids the physician to give an accurate estimation of prognosis to the patient. Secondly, it is used as a tool to stratify the patient population into groups with a more or less favourable survival, which may help to decide on the most suitable treatment and intensity of follow-up. We have noticed that the two ways of interpreting the DS-GPA results are used in clinical practice, while only the latter one is the formal intention of the model. Therefore, we have tested the performance of the DS-GPA for these two applications in patients with brain metastases who were treated with SRS.

Table 2
DS-GPA scores and median survival in our patient cohort, compared to survival as predicted by DS-GPA.

Primary tumour type	DS-GPA score	n	Median survival in our patient cohort (IQR)	Median survival as predicted by DS-GPA (IQR)	p
NSCLC Adenocarcinoma*	0–1	21	7.7 (2.6–18.3)	6.9 (2.6–15.3)	0.114
	1.5–2	71	11.2 (5.3–18.3)	13.7 (5.5–24.6)	0.112
	2.5–3	43	15.4 (9.3–27.4)	26.5 (10.7–53.8)	0.001 ^{††}
	3.5–4	3	29.5 (25.6–35.6)	46.8 (25.8–)	0.068
NSCLC Non-adenocarcinoma*	0–1	7	2.6 (1.4–3.4)	5.3 (1.9–11.1)	0.237
	1.5–2	24	6.1 (2.1–7.3)	9.8 (3.9–20.3)	0.011
	2.5–3	18	8.9 (5.2–18.5)	12.8 (7.0–30.1)	0.586
Breast cancer	0–1	2	11.4 (2.0–)	3.4 (1.4–7.3)	0.655
	1.5–2	16	7.1 (4.3–38.8)	7.7 (3.0–15.2)	0.234
	2.5–3	16	18.5 (10.9–27.7)	15.1 (5.9–27.4)	0.134
	3.5–4	6	16.3 (13.9–23.7)	25.3 (12.8–45.8)	0.345
	No GPA**	1	6.0	–	
Melanoma	0–1	2	11.5 (1.9–)	4.9 (2.3–10.7)	0.655
	1.5–2	15	7.8 (4.2–15.5)	8.3 (3.9–18.2)	0.496
	2.5–3	8	22.9 (16.9–34.9)	15.8 (8.2–49.3)	0.069
	3.5–4	6	24.0 (12.4–51.7)	34.1 (15.1–)	0.600
RCC	0–1	3	4.4 (1.9–)	4 (2–8)	0.593
	1.5–2	8	11.8 (3.0–22.1)	12 (5–24)	1.000
	2.5–3	10	27.6 (14.8–47.7)	17 (8–36)	0.059
	3.5–4	5	8.7 (5.0–17.3)	35 (13–61)	0.043
GI tumour	0–1	22	4.3 (1.8–8.6)	3.1 (1.8–6.2)	0.039
	1.5–2	22	7.5 (1.7–11.9)	4.4 (2.4–10.4)	0.020
	2.5–3	8	11.7 (3.6–17.1)	6.9 (4.1–15.2)	0.161
	3.5–4	5	7.6 (4.1–26.9)	13.5 (9.9–27.1)	0.686

[†] Bold values signify those under the unadjusted significance threshold of 0.05.

DS-GPA = disease-specific Graded Prognostic Assessment, GI = gastrointestinal, IQR = interquartile range, NSCLC = non-small cell lung carcinoma, RCC = renal cell carcinoma.

* NSCLC subtype unknown for 24 patients.

** No GPA calculable due to missing tumour receptor status.

^{††} Value under adjusted significance threshold of 0.002.

Fig. 1. Waterfall plots showing the differences between the predicted and the actual survival on an individual level, stratified by the number of brain metastases.

For the first application, the DS-GPA seems to be a valuable tool. Although the waterfall plots reveal some large differences between the actual and predicted median survival, especially in patients with longer survival, we found that around half of the patients reached the predicted median survival. Similarly, more than half of the patients' survival fell within the predicted IQR. This means that the median survival (and the IQR) from the DS-GPA model is an accurate prediction of the actual survival in our cohort from clinical practice. It also confirms that the DS-GPA does not provide a point prediction of survival on an individual level.

On a group basis, our results prove to be less conclusive. Although most DS-GPA strata in the disease subgroups showed no significant difference in median survival, one stratum of patients with adenocarcinoma NSCLC had a 10 month shorter median survival than predicted, which remained significant even after correcting for multiple comparisons. Kaplan-Meier curves revealed that DS-GPA was useful for dividing the NSCLC, melanoma and RCC subgroups into strata with significantly different survival times. The other disease subgroups showed no significant difference in survival between the DS-GPA strata, although this may be due to insufficient power in these smaller subgroups.

There are several possible explanations for any of the differences found between predicted and actual survival. Firstly, this

cohort only included patients treated with SRS, whereas Sperduto et al.'s patient populations underwent a variety of treatments (WBRT, SRS, surgery, or a combination of the three) [6–9]. In the databases used to create the models for RCC, breast and GI tumours, 34–61% of patients did not receive SRS, but received only WBRT and/or surgery instead. In the melanoma and lung databases, these proportions are 15% and 5%, respectively. According to the current Dutch guidelines, only patients with certain characteristics (≤ 3 BM's and KPS ≥ 70) should be considered for SRS, which means this cohort consists of a subset of patients that does not represent the entirety of the BM patient population. Although our analysis, comparing DS-GPA-strata, automatically corrects for some of these baseline differences, some residual differences between cohorts may exist.

Another possible problem with a prediction model is misclassification of patients. This problem is unlikely to occur as a result of objectively measured criteria, which the DS-GPA criteria are with the exception of KPS. Interobserver concordance rates of KPS have been reported to range between 38% and 75% [16,17], with the highest variability seen when dealing with patients with low performance scores [18]. As all the DS-GPA scores have critical KPS cut-off points at 60 and 70, giving a lower or higher score around these values assigns patients a different DS-GPA score. However,

Fig. 2. Survival curves per DS-GPA-subgroup for each cancer type. P-values from log-rank tests are given, revealing significant differences between the DS-GPA strata in four disease subgroups. In these subgroups, the DS-GPA works for stratifying by survival.

in creating the DS-GPA scores, Sperduto et al. also used KPS as reported in a clinical setting [6–9], which underscores the predictive value of KPS despite its imperfect inter-observer-reliability. Furthermore, scoring models in which KPS categories are very broad (e.g. ≥ 70 or < 70 for melanoma) are less susceptible to inter-observer variability.

There are several limitations to this study. First of all, this is a retrospective cohort, meaning that all clinical information had to be extracted from patient files. Not all information had been recorded in the files, including tumour subtype and molecular markers. Although the DS-GPA could be calculated for all but 1 patient due to missing breast tumour receptor status, there was missing data in other tumour markers as well. For the NSCLC and melanoma groups, an “unknown” marker status option is included in the scoring model. This means that patients with missing mar-

ker status can still be assigned a GPA-score. However, this score does not reflect their true marker status, and thus misclassification can occur in these patients. This is especially likely in the NSCLC patients, as the majority of these patients had missing marker status. Aside for tumour markers, this potential misclassification also applies to the RCC patients and their Hb levels.

Similarly, no DS-GPA could be calculated for lung cancer patients with missing pathological data, because information about tumour histology (NSCLC or SCLC) is needed to decide whether or not the lung-specific GPA is applicable. This is because the most recent lung-specific GPA scoring model, the lung-molGPA, is based solely on NSCLC patients. Please note that selecting SCLC is still an option on the brainmetgpa.com website, despite the fact that the subsequently used scoring model is not based on SCLC data.

Additionally, 24 NSCLC patients could not be included in the analysis of predicted and actual survival, due to missing information on tumour subtype (adenocarcinoma or non-adenocarcinoma).

As mentioned above, there were low numbers of patients in the DS-GPA groups, especially the lowest and highest ones, which reduces the power to show significant differences in median survival and in the Kaplan-Meier analysis.

Another limitation regards one of the applications of the DS-GPA score, which is to select the desired treatment based on expected survival. As completed SRS treatment was needed for inclusion in our cohort, we do not have data on all patients who were eligible for treatment, regardless of actually receiving it. We therefore cannot assess the performance of the DS-GPA in patients who did not receive SRS, which means we cannot address the aforementioned application of the DS-GPA. Similarly, we don't have enough data to reflect on the effect of newer targeted therapies on the performance of the DS-GPA model.

Lastly, in 30 patients (8.2%), the interval between diagnosis and first treatment exceeded 2 months. These patients were excluded in Sperduto's patient cohorts used for creating the scoring models. We decided to include them, in order to reflect daily practice. In a post-hoc test without these patients, no major differences were seen with the original analysis.

These limitations warrant further research within a larger prospective cohort, preferably from multiple centres. Should differences in survival persist, these pooled clinical data could be used for creating a SRS-specific prediction model, which best fits the patient population treated with radiosurgery. Recent observational data and an on-going randomized trial on the effect of SRS in patients with up to 15 brain metastases may aid in developing a model, in such a way as to reflect all patients eligible for SRS treatment [15,19].

The way in which physicians and other health professionals discuss the results of the DS-GPA score is important. The fact that it results in a median survival and not a predicted survival is an important distinction. We have noticed that the result of the DS-GPA model is sometimes interpreted as a point prediction of survival, but this is beyond its scope. Patients should not be told that the DS-GPA gives a precise prediction of the expected survival. Instead, a patient needs to be informed that around half of the patients with similar clinical characteristics reach the median survival time, but that the other half dies before that time. We were able to replicate most of these median survival times, with some notable exceptions, as mentioned above. Additionally, the window of survival that applies to half of the patients, i.e. the interquartile range, is probably the most important message for patients, since it reflects the variation in survival more accurately than the median. We were also able to confirm the validity of the published interquartile ranges from the DS-GPA-models.

In our cohort of patients undergoing SRS for brain metastases of lung cancer, melanoma, renal cell carcinoma, breast cancer or gastrointestinal cancer, we were able to confirm the predictive value of the DS-GPA for median survival, with one notable exception. One subgroup, the intermediate-prognosis adeno-NSCLC patients, had a significantly shorter median survival than predicted by their DS-GPA score. Our findings confirm the value of the DS-GPA as a useful prognostic tool for the counselling of individual patients with brain metastases before undergoing SRS; while it does not provide a survival that is accurate for every patient, the predicted median and IQR could be reproduced on a group level. Additionally, it proved useful for accurately stratifying patients with both types of NSCLC, RCC and melanoma into prognostic subgroups. The

limited number of patients within each subgroup and stratum of our cohort warrants replication in larger-scale prospective cohorts.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.06.033>.

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