External validation of a prognostic score for patients with brain metastases: extended diagnosis-specific graded prognostic assessment

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Abstract

Purpose: The aim of our study was the external validation of an extended variant of the four-tiered diagnosis-specific graded prognostic assessment (DS-GPA) that includes more information about extracranial disease burden and blood test results, and predicts survival of patients with brain metastases. The extracranial DS-GPA (EC-GPA) includes serum albumin, lactate dehydrogenase (LDH) and number of extracranial organs involved. Originally, the score was developed in Germany.

Methods/Patients: A retrospective analysis of 236 patients with brain metastases treated with primary whole-brain radiotherapy in North-Norway was performed (independent external validation cohort).

Results: The four-tiered EC-GPA score showed good discrimination between all prognostic groups (log-rank test $p<0.05$ for all pairwise comparisons). One-year survival was 0, 11, 30 and 100%, respectively. Median survival was 0.7 months (95% CI 0.5-0.9) in the worst prognostic group, with a hazard ratio for death of 44.31 (95% CI 5.78-339.50) compared to the best group. In the German database, the corresponding HR was 31.64 (median survival 0.4 months). The remaining hazard ratios in this validation study were 7.13 and 12.10, compared with 4.84 and 9.26 in the score development study.

Conclusions: This study provides an independent validation of the EC-GPA, which was the best prognostic model for defining patients who did not benefit from radiation therapy of brain metastases in terms of overall survival in the original German study. The proposed modification of the established DS-GPA should undergo further validation in multi-institutional databases.

Introduction

The current treatment options for patients with brain metastases include much more efficacious approaches than those available 10 or 20 years ago, including but not limited to high-precision focal radiotherapy and newly approved medications [1-5]. Fortunately, many patients benefit from these treatments, both in terms of symptom control or prevention, radiological disease control and overall survival. However, a subset of patients is at risk of early death just few weeks after brain metastases were diagnosed [6-9]. It is therefore of utmost importance to assess each patient's prognosis at the time of diagnosis of brain metastases, in order to provide guidance and to avoid an obvious mismatch between intensity of therapeutic measures and outcome.

The tools available to support clinicians who care for these patients have recently undergone substantial refinement [10, 11]. Nevertheless, statistically significant differences between a set of actuarial survival curves in commonly used three- and four-tiered models, such as recursive partitioning analysis (RPA) [12] or diagnosis-specific graded prognostic assessment (DS-GPA) [13, 14], do not imply the complete absence of long-term survivors in the groups with unfavorable prognosis. The same is true for groups with better prognosis (some patients die shortly after initiation of treatment). Our previous efforts to improve survival prediction have resulted in a model that incorporates extended assessment of extracranial disease activity [15]. Rather than dichotomizing presence or absence of extracranial metastases, we relied on number of involved organs as well as surrogate markers of activity, such as serum lactate dehydrogenase (LDH) and albumin. This four-tiered model (extracranial score, EC-S) had a promising clinical impact, especially in terms of defining a poor-prognosis group that was devoid of long-term survivors. Potentially, the model may allow for a reduction in overtreatment in patients unlikely to derive any benefit.

Independent validation of the EC-S has confirmed the promising results obtained in the original study [16]. Furthermore, we discovered that it might be recommendable to combine

the EC-S and DS-GPA scores in order to obtain four groups with optimally distinct survival curves. The hazard ratios (HR) of the newly proposed EC-GPA classes 1, 2 and 3 compared to class 0 were 4.84 (95% CI 1.42-16.46), 9.26 (2.83-29.97) and 31.64 (8.36-119.76) [16]. However, there were only 141 patients in the German database for whom we could calculate the new EC-GPA combination. Therefore (and for external validation purposes), we evaluated the EC-GPA in an independent, larger cohort of patients.

Materials and Methods

We extracted all available patient records from our prospectively maintained brain metastases database at the Department of Oncology at Nordland Hospital Bodø, Norway, as already described [17]. Data from treatments conducted between June 2007 and June 2018 were available. In order to avoid selection bias caused by treatment assignment (more aggressive approaches in better patients), we limited the inclusion to patients who received upfront whole-brain radiotherapy (WBRT). After WBRT, further treatment was individualized (different systemic regimens, focal salvage radiotherapy, second WBRT etc.). Prognostic scores for each patient were determined as originally described [14-16]. The EC-S was calculated as follows: one point was counted for each of three risk factors, 1) LDH higher than institutional upper limit of normal, 2) albumin lower than institutional lower limit of normal, and 3) more than one extracranial site of metastatic involvement (for example liver and adrenal gland(s)). The final score ranged from 0 to 3 (0: normal LDH and albumin, extracranial metastases absent or one organ only, e.g. lung(s)).

All LDH and albumin measurements were performed within 2 weeks before the first fraction of WBRT. Elevated LDH was defined as above 254 U/l, and decreased albumin was defined as below 34 g/l. An overview of all relevant patient characteristics is given in Table 1.

Actuarial survival from the first day of WBRT was calculated using the Kaplan-Meier method and compared between different groups with the log-rank test. To determine the HR in multivariable analysis, backward stepwise Cox regression was used. Statistical analysis was performed with IBM-SPSS-25©. At the time of data extraction, six of 236 patients were alive (censored observations after a median follow-up of 38.5 months). Our previous EC-S study [15] included 189 of the current patients, while the others were added to the database in the last few years.

Results

Most patients in this cohort had more than three brain metastases (52%) and additional extracranial metastases (85%), commonly to more than one organ (49%). Non-small cell lung cancer (NSCLC, 39%) and breast cancer (22%) were the dominant primary diagnoses. The median Karnofsky performance status (KPS) was 70, range 30-100. According to the DS-GPA [14], most patients had an unfavorable prognosis (57% in the lowest class). Only 3% belonged to the best DS-GPA class. However, the EC-S assigned only 7% to the poor-prognosis group, while 27% had a favorable prognosis (Table 1). The median survival outcomes (months) were as follows, DS-GPA: 2.4 (95% CI 1.9-2.9), 3.8 (95% CI 3.3-4.3), 5.4 (95% CI 3.9-6.9) and 16.4 (6.3-26.5), $p<0.0001$ (pooled over all four strata). The corresponding figures for the EC-S were 0.7 months (0.5-0.9), 2.3 months (1.7-2.9), 3.7 months (3.1-4.3) and 6.7 months (3.7-9.7), $p<0.0001$ (pooled over all four strata).

As described previously [16], we combined the DS-GPA and EC-S, resulting in the EC-GPA (Table 2). The four Kaplan-Meier survival curves are displayed in Figure 1 ($p<0.0001$, pooled over all strata). One-year survival was 0, 11, 30 and 100%, respectively. Statistically significant survival differences between all groups were seen (Table 2). The HR of the EC-

GPA classes 1, 2 and 3 compared to class 0 were 7.13 (95% CI 0.97-52.58), 12.10 (1.68-87.25) and 44.31 (5.78-339.50), respectively. With only three patients in the best prognostic group and 184 patients (78%) in third group, the validation results are difficult to compare to those obtained in the German development cohort. However, agreement was excellent for the three prognostic groups containing at least 16 patients, as displayed in Table 3. For example, the one-year survival rates were 0, 11 and 30% in both datasets.

Finally, an unplanned secondary analysis was performed, which aimed at better understanding of the largest prognostic group, i.e. the EC-GPA 2 with 184 patients. The Kaplan-Meier analyses of univariate prognostic factors in this large group included the parameters shown in Table 1. These analyses revealed that KPS, LDH, albumin, more than one extracranial site of metastatic involvement, and primary tumor type (breast/lung cancer vs. non-breast or lung cancer) significantly influenced survival. All five parameters were analyzed by Cox regression analysis with the following results: primary tumor type breast or lung cancer HR 0.56, p=0.001; better KPS (in steps of 10) HR 0.97, p=0.0001; high LDH HR 1.53, p=0.007; low albumin HR 2.22, p=0.004. More than one extracranial metastatic site was not significant (HR 1.17, p=0.5).

Discussion

Proper patient and/or therapy selection continues to play an important role in the current era of personalized medicine. Some previous studies of treatment intensification after diagnosis of brain metastases provided discouraging results [18, 19]. Afterwards, several strategies were pursued to create prognostic tools for discrimination of patient populations benefiting from more aggressive treatment (summarized in [10, 11]). The well-known problem of these scoring systems is their limited ability to predict an individual patient’s

prognosis. Even the most recent scores, such as the lung and melanoma molGPA [20, 21], which integrate molecular features, include several long-term survivors in the group with unfavorable prognosis, and early deaths in the two more favorable groups.

The role of extracranial factors such as KPS, presence and extent of extracranial metastases or control of the primary tumor provided some further valuable information about prognosis [13, 14, 22]. A further refinement of survival prediction for the group of patients with very limited survival was possible after inclusion of such widely available and inexpensive surrogate parameters of advanced-tumor-related processes such as LDH and albumin [15]. The role of blood test results, including but not limited to LDH and albumin, has also been confirmed by Berghoff et al. [23]. Indirect evidence for the important influence of extracranial disease extent comes from studies that examined the risk of neurological death. These studies reported non-neurological death as the prevailing cause of death after effective local management of brain metastases, e.g. by radiosurgery [24].

The validity of the EC-S score (LDH, albumin, number of involved organs) has recently been confirmed in an independent database [16]. In the validation study, the EC-S performed better than the RPA and DS-GPA in separating the group of patients with very poor prognosis. This was also true after adjusting for treatment modality as a confounding covariate (not all patients were managed with initial WBRT, in contrast to the Norwegian dataset). Both the DS-GPA and EC-S were (together with treatment modality) prognostically relevant in the multivariate model. Due to these findings, we pursued the idea of combining these two scores. Application of the new combined score (EC-GPA) resulted in a clear separation of the survival curves and yielded much better discrimination between all prognostic groups than either the DS-GPA or EC-S alone, although the uncertainties in the HRs (95% CI) were large due to the small sample size.

The present study validates the proposed EC-GPA in a larger and more homogeneous database (primary WBRT in all 236 patients; LDH and albumin were part of the department's

standard work-up (no missing data)). As shown in Tables 2 and 3, good agreement between the results of the development and the validation study was observed. Despite the larger database, two prognostic strata still contained less than 20 patients each. Especially the group with best prognosis (n=3) was too small to draw meaningful conclusions. The majority of 78% was included in the EC-GPA 2 group, which has a relatively unfavorable, yet not uniformly poor prognosis. As result of the group sizes, the 95% CI of the HRs were large also in the validation study. Most likely, the fact that so many patients belonged to the same prognostic group can be explained by the oncologists' decision to treat with WBRT. Patients with better prognostic characteristics were often considered for surgical resection or radiosurgery. Furthermore, our study has limitations due to its retrospective nature.

The unplanned exploratory analysis of the EC-GPA 2 group provided interesting insights. It suggests that the parameter "more than one extracranial site of metastatic involvement" is less important than the others, and that the primary tumor type may contribute relevant prognostic information. Patients with lung or breast cancer survived significantly longer than those with other malignancies. Therefore, it might be possible to split the EC-GPA 2 group into subgroups with different outcomes. The presently available cohorts from Würzburg and Bodø are too small to pursue this strategy in a convincing way.

The randomized QUARTZ trial has provided data suggesting that in preselected patients with NSCLC the use of very hypofractionated WBRT (5 fractions of 4 Gy) has limited effect on overall survival and quality of life, when compared to optimal supportive care [6]. A subgroup of younger patients included in the QUARTZ trial experienced significantly improved survival after WBRT. It would be interesting to stratify the trial results by EC-GPA to address the unresolved issue of patient selection (when to recommend supportive care rather than radiotherapy?). Primary tumors other than NSCLC have to be studied in separate trials, because of different treatment options and biological behavior.

The following aspects are important in clinical practice, 1) selection of patients who have a chance to derive any profit from antitumor treatment, 2) selection of patients who can derive worthwhile benefit from aggressive local antitumor treatment, and 3) reduction of futile treatment for those who have a very limited survival prognosis [25]. Fifteen of 16 patients (94%) in the most unfavorable EC-GPA group had died within three months from the start of WBRT (Figure 1). Therefore, this new prognostic score may add value to the assessment of patients with brain metastases, and to stratification in future prospective studies. Ideally, additional and even larger validation studies should be performed to strengthen the arguments for clinical implementation of the EC-GPA.

Conclusions

In conclusion, our study provides the first independent validation of the prognostic EC-GPA score, which was developed from a database at a tertiary German center. Further validation of the EC-GPA score will be pursued in an ongoing analysis of combined patient cohorts from different tertiary care centers with already established research cooperation. Given that a valid score is of interest also outside of tertiary care centers (where many patients are treated in routine practice and the same challenges apply), the score's performance in this setting should be monitored, e.g. by institutions which participate in clinical research projects and/or record the survival outcomes of their patients on a regular basis. This post-validation quality assurance strategy would strengthen the acceptance of the score across the spectrum of care providers.

Statements

Acknowledgements

None.

Ethical Statement

As a retrospective quality of care analysis, no approval from the Regional Committee for Medical and Health Research Ethics (REK Nord) was necessary. This research project was carried out according to our institutions' guidelines and with permission to access the patients' data.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Author contributions

CN, SH and VL participated in the design of the study and performed the statistical analysis. CN collected patient data. CN and VL conceived of the study and drafted the manuscript. All authors read and approved the final manuscript.

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Table 1. Patient characteristics (n=236)

Parameter	Number (%)
Female gender	128 (54)
Male gender	108 (46)
Non-small cell lung cancer	93 (39)
Small cell lung cancer	21 (9)
Breast cancer	52 (22)
Malignant melanoma	33 (14)
Gastrointestinal primary tumors	21 (9)
Kidney cancer	16 (7)
Extracranial metastases present	200 (85)
More than one organ involved*	115 (49)
Controlled primary tumor	154 (65)
Single brain metastasis	34 (14)
Two or three brain metastases	80 (34)
Four or more brain metastases	122 (52)
Albumin below 34 g/l	35 (15)

Lactate dehydrogenase above 254 U/l	118 (50)
Extracranial score (EC-S) 0	64 (27)
EC-S 1	89 (38)
EC-S 2	67 (28)
EC-S 3	16 (7)
Diagnosis-specific (DS)-GPA 3	6 (3)
DS-GPA 2	32 (14)
DS-GPA 1	64 (27)
DS-GPA 0	134 (57)
Median Karnofsky performance status	70 (range 30-100)
Median age (years)	64 (range 24-93)

* for example bone(s) and lung(s)

GPA: graded prognostic assessment

Table 2. Results of the EC-GPA validation in 236 patients (p-values from pairwise log-rank test comparisons are shown on the right hand side of the table)

EC-GPA	Number of patients	Mean OS	Median OS	95% CI	DS-GPA	EC-GPA	0	1	2	3
0	3	61.0	n/a	n/a	0			0.02	0.002	0.003
1	33	10.7	5.9	4.1-7.7	1		0.02		0.005	0.000
2	184	6.2	3.0	2.7-3.3	2		0.002	0.005		0.000
3	16	1.7	0.7	0.5-0.9	3		0.003	0.000	0.000	

DS-GPA: diagnosis-specific graded prognostic assessment; EC-GPA: extracranial graded prognostic assessment (3: same three criteria as in EC-S (high lactate dehydrogenase, low albumin, more than one extracranial organ involved, 2: max. two of these criteria present + DS-GPA 0 or 1, 1: max two of these criteria present + DS-GPA 2 or two of these criteria present + DS-GPA 3, 0: max. one of these criteria present + DS-GPA 3 (best DS-GPA class)); OS: actuarial overall survival in months

Table 3. Comparisons of the EC-S and EC-GPA results in two different cohorts (Bodø and Würzburg)

	EC-S0				EC-S*0				EC-GPA0				EC-GPA*0			
		1	2	3		1	2	3		1	2	3		1	2	3
Median survival in months	9.5	4.1	2.9	0.7	7.8	8.8	1.9	0.6	27.0	7.8	2.9	0.4	n/a	5.9	3.0	0.7
% 6-months survival	55	24	17	0	47	57	23	8	90	43	30	10	100	48	25	6
% 1-year survival	31	13	12	0	13	29	8	0	50	30	11	0	100	30	11	0

EC-S: extracranial score (published 2014, 189 patients, 3: serum LDH above upper limit of normal + albumin below lower limit of normal + extracranial metastases to two or more organs, e.g. lung(s) and bone(s), 2: two of the criteria present, 1: one of these criteria present, 0: none of these criteria present); EC-S*: extracranial score validation (published 2019, 157 patients); EC-GPA: extracranial graded prognostic assessment (published 2019, 134 patients, 3: same three criteria as above, 2: max. two of these criteria present + DS-GPA 0 or 1, 1: max two of these criteria present + DS-GPA 2 or two of these criteria present + DS-GPA 3, 0: max. one of these criteria present + DS-GPA 3 (best DS-GPA class)); EC-GPA*: extracranial graded prognostic assessment validation (present study, 236 patients)

Fig 1. Actuarial Kaplan-Meier survival plot for all 236 patients stratified by EC-GPA class (log-rank test, $p<0.0001$).