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Original Article

Prognostic Models Predicting Survival of Patients with Brain Metastases: Integration of Lactate Dehydrogenase, Albumin and Extracranial Organ Involvement

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Abstract

Aims: To explore the role of expanded assessment of metastatic extracranial organ involvement, as well as albumin and lactate dehydrogenase (LDH), i.e. surrogates of disease extent, in survival prediction models for patients with brain metastases.
Materials and methods: A retrospective analysis of 189 patients treated with whole brain radiotherapy was carried out. Uni- and multivariate analyses included recursive partitioning analysis classes, basic score for brain metastases and diagnosis-specific graded prognostic assessment (DS-GPA).
Results: Elevated LDH correlated significantly with extracranial organ involvement, low albumin with primary tumour type and primary tumour control. Elevated LDH, low albumin and a combination of both correlated significantly with overall survival. LDH, albumin and the number of extracranial organs involved (none, one, two or more harbouring metastases) were independent prognostic factors in multivariate analyses (if added to the three established scores mentioned above and also if added to individual parameters such as age, performance status, etc.). A combination of these three new prognostic factors predicted very short survival (median 0.7 months if all three were present).
Conclusion: We have previously defined patient groups in whom foregoing radiotherapy was unlikely to compromise survival. These were patients with a DS-GPA score of 0–1.5 points and age ≥75 years or Karnofsky performance status ≤50 or uncontrolled primary tumour with extracranial metastases to at least two organs. Patients with a combination of three new adverse features (elevated LDH plus low albumin plus extracranial metastases to at least two organs) might also be considered for best supportive care. Furthermore, it appears warranted to study whether scores such as DS-GPA can be optimised by integrating information on these three parameters.

Key words: Albumin; best supportive care; brain metastases; lactate dehydrogenase; prognostic factors; radiotherapy

Introduction

The diagnosis-specific graded prognostic assessment (DS-GPA) score for patients with brain metastases from renal cell carcinoma, malignant melanoma, lung, breast and gastrointestinal cancers has gained increasing acceptance since its publication [1,2]. This four-tiered score has been validated in different patient populations and provides useful survival estimates, e.g. in the context of choosing between different treatment options and counselling patients who wish to plan their future [3–6]. We have recently shown that patients with a poor DS-GPA score (0–1.5 points out of a maximum of 4) and additional adverse prognostic features (age ≥75 years or Karnofsky performance status (KPS) ≤50 or uncontrolled primary tumour with extracranial metastases to at least two organs, e.g. lung and liver) have very limited survival, irrespective of the management approach [best supportive care (BSC), whole brain radiotherapy (WBRT) or radiosurgery] [7]. A significant proportion of these patients would probably decide to forego active treatment if aware of their survival expectation. In parallel, we were able to analyse additional factors, known from prognostic models that predict survival of patients with terminal cancer [8], but not yet part of established brain metastases scores. These factors, elevated

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serum lactate dehydrogenase (LDH) and low albumin, looked promising in the small patient groups available for the initial analysis ($n = 100$ for LDH and $n = 71$ for albumin) [9,10]. Therefore, we carried out a larger study of LDH, albumin and their relationship to the extent of extracranial metastases, other disease characteristics and prognosis. Further optimisation of current scores might improve our ability to make informed decisions about which treatment will probably be appropriate.

Materials and Methods

We analysed patients from a previously described brain metastases database, which is expanded and updated at the first author's institution [11,12]. For this retrospective intention-to-treat study, 189 patients with available information on LDH and albumin treated with primary WBRT were selected (common regimens included 30 Gy in 10 fractions and 20 Gy in five fractions; no upfront surgery or radiosurgery, but salvage treatment in the case of progression was allowed; eight patients failed to complete WBRT). All patients were treated between 2006 and 2013 at two different institutions in northern Norway. LDH and albumin was part of routine blood chemistry and imaging assessment in patients with newly detected brain metastases treated in these institutions (patients treated before 2006 were not eligible for the study because LDH and albumin were rarely measured and we wanted to minimise sources of bias). LDH and albumin measurement no older than 2 weeks before the first fraction of WBRT was required. Elevated LDH was defined as ≥205 U/l according to the hospitals' reference value (low albumin <34 g/l). All patients had computed tomography scans of the chest, abdomen and pelvis within 2 months before start of WBRT. Typically re-staging was carried out at brain metastases diagnosis in order to decide whether aggressive local treatment or WBRT was appropriate, unless such scans had already been completed as part of routine follow-up shortly before the diagnosis of brain metastases. Supplemental bone isotope scans, liver ultrasound and liver or bone magnetic resonance imaging (MRI) was carried out when needed to confirm suspicious findings. Prognostic scores for each patient were determined as originally described [DS-GPA [1,2], recursive partitioning analysis (RPA) [13], basic score for brain metastases (BSBM) [14]]. 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. For multivariate analysis of survival, Cox regression analysis was used (backward stepwise method). Associations between different variables of interest were assessed using the chi-square test. A P-value ≤ 0.05 was considered statistically significant. Twenty patients were alive at last follow-up (10 November 2013) with a median follow-up of 4.8 months. The date of death was known in all other patients. The patient characteristics are shown in Table 1.

Table 1
Patient characteristics ($n = 189$)

Parameter	n	%
Female patients	108	57
Male patients	81	43
Primary tumour type		
Small cell lung cancer	16	8
Non-small cell lung cancer	62	33
Breast cancer	49	26
Malignant melanoma	25	13
Renal cell carcinoma	12	6
Colorectal cancer	13	7
Bladder cancer	4	2
Unknown primary	3	2
Other	5	3
Primary tumour status		
Controlled primary tumour	126	67
Uncontrolled primary tumour	63	33
Extracranial metastases		
Absent	28	15
Present	161	85
At least two organs involved	92	49
Extent of brain metastases		
One	31	16
Two or three	58	31
More than three	100	53
DS-GPA prognostic group		
Poor	95	50
Intermediate–poor	50	26
Intermediate–good	29	15
Good	7	4
Not defined	8	4
RPA prognostic group		
Class 1	8	4
Class 2	106	56
Class 3	75	40
BSBM prognostic group		
BSBM 0	37	20
BSBM 1	103	55
BSBM 2	43	23
BSBM 3	6	3
Median age, years (range)	63	24–93
Median KPS, range	70	30–100

DS-GPA, diagnosis-specific graded prognostic assessment (0–1 point: poor; 1.5–2 points: intermediate–poor; 2.5–3 points: intermediate–good; 3.5–4 points: good; not defined for unknown primary, bladder cancer and others); RPA, recursive partitioning analysis; BSBM, basic score for brain metastases; KPS, Karnofsky performance status.

Results

Most patients had extracranial metastases (85%) and more than three brain metastases (53%). The median KPS was 70, range 30–100. The primary tumour type did not significantly correlate with the presence of elevated LDH, $P > 0.2$. Elevated LDH was present in more than 30% of patients in each group. No significant association was found between LDH and primary tumour control ($P = 0.88$) or LDH and the number of brain metastases ($P = 0.67$). However, elevated LDH was often seen in patients with extracranial

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