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The LabBM score is an excellent survival prediction tool in patients undergoing palliative radiotherapy

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ABSTRACT

Background and aim: The prognostic assessment of patients referred for palliative radiotherapy can be conducted by site-specific scores. A quick assessment that would cover the whole spectrum could simplify the working day of clinicians who are not specialists for a particular disease site. This study evaluated a promising score, the LabBM (validated for brain metastases), in patients treated for other indications.

Materials and methods: The LabBM score was calculated in 375 patients by assigning 1 point each for C-reactive protein and lactate dehydrogenase above the upper limit of normal, and 0.5 points each for hemoglobin, platelets and albumin below the lower limit of normal. Uni- and multivariate analyses were performed.

Results: Median overall survival gradually decreased with increasing point sum (range 25.1–1.1 months). When grouped according to the original three-tiered model, excellent discrimination was found. Patients with 0–1 points had a median survival of 15.7 months. Those with 1.5–2 points had a median survival of 5.8 months. Finally, those with 2.5–3.5 points had a median survival of 3.2 months (all p-values ≤ 0.001).

Conclusion: The LabBM score, which is derived from inexpensive blood tests and easy to use, stratified patients into three very distinct prognostic groups and deserves further validation.

Key words: radiation therapy; palliative radiotherapy; prognostic factors; survival prediction; biomarkers

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Introduction

Patients with distressing symptoms from malignant tumors often experience considerable relief after moderate doses of palliative radiotherapy and therefore such treatment should be readily available in clinical cancer care [1–3]. Patients in need of palliative radiotherapy represent a tremendously heterogeneous group. In case of malignant diseases with long natural history and responsiveness to systemic therapy, survival may extend beyond 5 years. Such prolonged survival results in an enduring, though overall low risk of inappropriate utilization of palliative radiotherapy near the end of life [4–6]. In contrast, inappropriate overtreatment is more likely in patients with short survival expectation. However, it is often challenging to predict whether or not a sufficiently long time period of symptom relief is achievable [7]. Several research groups have developed prognostic models, which may provide guidance [8, 9]. For example, Chow et al. have combined information about performance status, primary tumor type and presence of non-bone distant metastases in their survival prediction score [10],

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which later was validated in independent studies [11, 12]. Afterwards, the more complex TEACHH model (primary tumor type, performance status, age, prior palliative chemotherapy, prior hospitalization, and hepatic metastases), which divides patients receiving palliative radiotherapy into 3 distinct groups, was propagated [13].

In parallel, specific subgroups of patients were studied, e.g. those receiving palliative radiotherapy for brain metastases [14, 15]. This strategy appeared justified, given that survival after diagnosis of brain metastases typically is measured in months, largely irrespective of primary tumor type [16, 17], while patients with bone or other symptomatic metastases often survive much longer [18]. The brain metastases research has recently resulted in a unique, readily accessible prognostic model, the 3-tiered LabBM score [19]. Inexpensive routine blood tests (hemoglobin, platelets, albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH) were sufficient to predict survival, without any need for imaging studies or other assessments. In addition, score assignment is a matter of seconds. After successful external validation of this probably site-agnostic score [20], our group hypothesized that it may be applicable to palliative radiotherapy in general. To test this hypothesis, a group of patients without brain metastases treated for different indications (bone pain, thoracic symptoms etc.) with standard fractionation regimens, including re-irradiation (unselected all-comers), was studied.

Materials and methods

This was a retrospective single-institution study, which included consecutive patients treated with palliative radiotherapy, irrespective of age, performance status, symptom burden, tumor stage, treatment completion, etc. The following exclusion criteria were applied: brain metastases (originally, the LabBM score was developed and validated for these patients); primary brain tumors, lymphoma and other hematological malignancies (distinct natural history and treatment algorithms); high-dose radiation, e.g. stereotactic body radiotherapy in the oligometastatic setting. Typical treatment regimens included a single fraction of 8 Gy, five fractions of 4 Gy, and 10–13 fractions of 3 Gy. Both 2-D and 3-D treatment planning was employed. In case of prematurely terminated radiotherapy, e.g. due to worsening of the general condition, the prescribed fractionation regimen was recorded. All treatment was based on national tumor-specific guidelines and discussions in multi-disciplinary tumor boards. A previously established, regularly updated database [9] (radiotherapy in the years 2007–2013) and the hospital's electronic patient records were utilized to collect baseline and follow-up information through 2019. As mentioned above, patients with brain metastases, lymphoma or other hematological malignancies were removed from the database. The same is true for patients with missing blood test results.

Included patients had blood tests needed to calculate the LabBM score taken at the time of treatment planning, approximately one week before radiotherapy (no missing information; institutional normal values: hemoglobin 11.7–15.3 g/dL (females) and 13.4–17.0 g/dL (males); platelets 130–400 x 10^9; albumin 34–45 g/L; LDH < 255 U/L; CRP < 5 mg/L). The LabBM score was calculated as described in the original study [19]. Briefly, one point was given for LDH and CRP above the upper limit of normal and 0.5 points for hemoglobin, platelets and albumin below the lower limit of normal. A point sum of 0 indicates a favorable prognosis. The maximum point sum is 3.5. A separate analysis stratified the patients by administration of re-irradiation of a previously treated target volume (mostly bone metastases, lung tumors and lymph node metastases). Re-irradiated patients were included repeatedly, i.e. with a new dataset reflecting the characteristics at the time of the new radiotherapy course. Overall survival (time to death) from the first day of radiotherapy was calculated employing the Kaplan–Meier method, and different groups were compared using the log-rank test (SPSS 25, IBM Corp., Armonk, NY, USA). The median follow-up in the study cohort was calculated using the reverse Kaplan-Meier method. Nine patients were censored after a median follow-up of 87 months (minimum 72 months). Date of death was known in all other patients. Beside univariate log-rank tests, multivariate Cox regression analysis (forward step-wise method) was employed. Post hoc, a modified variant of the LabBM score was compared to the original version. The platelet parameter was removed, because it was not significantly associated with survival.

Symptom relief was not assessed, due to the well-known difficulties of retrospective judgement of this endpoint. This study followed the principles of the Declaration of Helsinki and did not require approval by the Regional Ethics Committee, because the underlying database has been classified as a quality of care monitoring project.

Results

The study included 375 patients with a median age of 66 years (range 31–95 years). Common primary tumors were prostate, breast and lung cancer (69%), as displayed in Table 1. The median time interval from cancer diagnosis to palliative radiotherapy was 35 months (range 0–160 months). The median time interval from diagnosis of metastatic disease (stage IV) to palliative radiotherapy was 9 months (range 0-149 months). A majority of patients had anemia (65%), elevated CRP (64%) or elevated LDH (53%). Low albumin (21%) or platelets (5%) were present in a minority of patients. Univariate log-rank tests showed that low platelets were not significantly associated with overall survival ($p = 0.18$), in contrast to all other blood tests (each $p \leq 0.0001$, Kaplan-Meier curves not shown). The Cox regression analysis with all five blood tests showed that CRP, LDH and albumin had a greater impact ($p \leq 0.001$) than hemoglobin ($p = 0.02$), whereas platelets were not significantly associated with overall survival. The hazard ratios were 2.2 [95% confidence interval (CI): 1.6–2.8] for high CRP, 1.7 (95% CI: 1.5–1.9) for low albumin, 1.5 (95% CI: 1.1–2.0) for high LDH, 1.3 (95% CI: 1.1–1.6) for low hemoglobin, and 1.8 (0.8–2.8) for low platelets.

In line with the original study hypothesis, the LabBM score was based on all five blood tests. As shown in Table 2, median overall survival gradually decreased with increasing point sum (range 25.1–1.1 months; log-rank test combined over all strata $p < 0.0001$). When grouped according to the original 3-tiered model, excellent discrimination was found. Patients with 0-1 points (n = 126, 34%) had a median survival of 15.7 months (95% CI: 12.4–19.0 months). Those with 1.5-2 points (n = 133, 35%) had a median survival of 5.8 months (95% CI: 4.2–7.3 months). Finally, those with 2.5–3.5 points (n = 116, 31%) had a median survival of 3.2 months (95% CI: 2.5–4.0 months) (Fig. 1). All pair-wise

Table 1. Patient characteristics

Baseline parameter	Number	Percent
Female sex	119	32
Male sex	256	68
Prostate cancer	131	35
Non-small cell lung cancer	60	16
Breast cancer	57	15
Small cell lung cancer	12	3
Renal cell cancer	33	9
Colorectal cancer	17	5
Bladder cancer	16	4
Other primary tumors	49	13
ECOG PS 0	53	14
ECOG PS 1	120	32
ECOG PS 2	115	31
ECOG PS 3–4	87	23
One target volume irradiated	211	56
Two target volumes irradiated	129	34
Three or more target volumes irradiated	35	9
Previous radiotherapy (curative or palliative)	224	60
No previous radiotherapy	151	40
Re-irradiation of a previously treated target volume	73	20
Spinal bone metastases irradiated	223	59
Pelvic bone metastases irradiated	117	31
Other bone metastases irradiated	135	36
Lung primary or metastases irradiated	31	8
Nodal metastases irradiated	13	3
Prostate or bladder irradiated	4	1
Other targets irradiated, e.g. adrenal metastases	14	4
Prescribed regimen of 10 fractions	154	41
Prescribed regimen of 1 fraction	70	19
Prescribed regimen of 2–9 fractions	112	30
Prescribed regimen of > 10 fractions	39	10
Presence of liver metastases	88	24
Low albumin	78	21
High lactate dehydrogenase	197	53
High C-reactive protein	240	64
Low hemoglobin	243	65
Low platelets	19	5
No systemic therapy	133	36
Previous or ongoing systemic therapy	242	65

ECOG PS — Eastern Cooperative Oncology Group performance status

Table 2. The LabBM score and overall survival

Point sum	Number of patients	Percent	Median survival [mo]	3-mo survival (%)	6-mo survival (%)	12-mo survival (%)
0	47	13	25.1	98	92	81
0.5	33	9	20.9	91	85	64
1	46	12	9.8	91	72	41
1.5	78	21	6.7	73	55	36
2	55	15	4.5	60	42	24
2.5	72	19	4.1	64	33	19
3	37	10	2.5	38	19	11
3.5	7	2	1.1	29	14	14

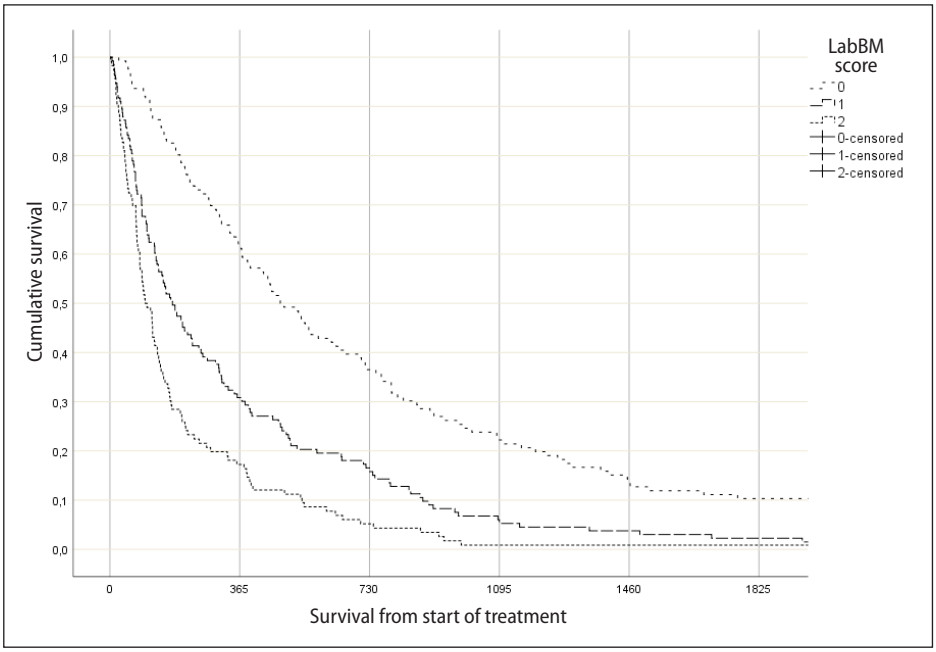

Figure 1. Overall survival in days (Kaplan-Meier estimates) stratified for LabBM score, p < 0.0001 over all three strata

comparisons had p-values of 0.001 or less. The score was valid in re-irradiated and non-re-irradiated patients. Interestingly, survival of the re-irradiated patients was longer than survival of the non-re-irradiated group. The median values were 23.2 *vs.* 8.6 and 3.9 months, p < 0.001 (re-irradiated), and 14.8 *vs.* 5.1 and 3.2 months, p < 0.001 (non-re-irradiated).

Post hoc, the LabBM score was modified, because the present study failed to confirm that low platelets contribute prognostic information. We tested a score based on the remaining four parameters (1 point for CRP and LDH, 0.5 points for hemoglobin and albumin, i.e. original weighting) and another score with different weighting of the four parameters (1 point for CRP, LDH and albumin, 0.5 points for hemoglobin, based on the results of the Cox regression analysis mentioned earlier). However, neither score provided clearly better discrimination of the three survival curves than the original LabBM score (Fig. 2).

Also regarding failure to complete radiotherapy, the original LabBM score provided relevant information. All patients with 0-1 points completed radiotherapy, compared to failure in 12/133 (9%) with 1.5–2 points and 8/116 (7%) with 2.5–3.5 points (p = 0.004, chi-square test).

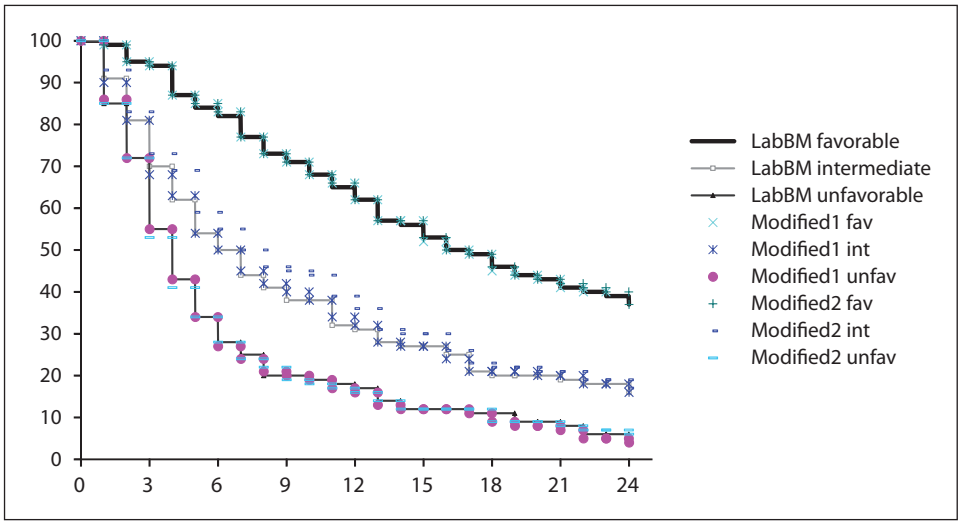

Figure 2. Overall survival in months (Kaplan-Meier estimates) stratified for original and two modified LabBM scores, $p < 0.0001$ over all three strata regardless of score variant. Modification 1 is the score based on four parameters (1 point for CRP and LDH, 0.5 points for hemoglobin and albumin, i.e. original weighting). Modification 2 is the score with different weighting of the four parameters (1 point for CRP, LDH and albumin, 0.5 points for hemoglobin, based on the results of the present Cox regression analysis)

Discussion

This study suggests that the LabBM score is valid not only in patients treated for brain metastases (median survival 11, 7 and 3 months in the development cohort) [19], but also in those treated for a variety of other indications. The latter included bone pain, thoracic symptoms and symptomatic lymph node metastases, amongst others. We had hypothesized that this might be the case, because patients with brain metastases commonly have different additional extracranial metastases, which have an impact on organ function [17, 21]. As already discussed by Berghoff et al. who developed the LabBM score [19], the five blood test results likely mirror the total tumor burden, bone marrow reserve, inflammatory processes and cachexia. Their assessment is independent of radiological studies, inter-observer variation and healthcare system. It does not create troublesome economic consequences and is done in less than a minute after the test results have arrived in the patient record. Automated calculation in electronic patient records is feasible, too. Due to these advantages and its performance in the primary and re-irradiation setting, the LabBM score can be considered one of the easiest and most applicable survival prediction tools.

It has been shown by various groups that blood test results are not the only parameters that can be used to predict survival. Performance status, primary tumor type, pattern of metastases, age, previous treatment, patient-reported symptom burden and measures of quality-of-life have all been identified in previous studies [10, 13, 22–24]. Some of these parameters are also components of the TEACHH model, as is prior hospitalization [13]. Hospitalization is a variable that depends on a healthcare system and certain financial aspects (access, affordability, incentives). If excellent out-patient facilities and ambulatory palliative care teams exist, a patient that would have to be hospitalized in a hypothetical care system "A" could be managed differently in system "B".

The present study included consecutive real-world patients with different primary tumors throughout the age and cancer progression continuum, managed with standard chemotherapy regimens and other drugs that were recommended in the Norwegian national guidelines, if such treatment was considered feasible and safe. Bone pain was the prevailing indication for palliative radiotherapy. A majority of patients had anemia (65%), elevated CRP (64%) or elevated LDH (53%). Only 13% had "perfect" blood test results, i.e. a LabBM score of 0. Most patients had 1.5–2.5 points. How-

ever, the three prognostic strata had comparable group sizes between 31 and 35%, another advantage of this prognostic score. As suggested by the results in Table 2, additional insight can be gained when looking at the actual point sum in addition to the score group. For example, patients with 3.5 points had a median survival of 1.1 months only. In contrast, those with 0 points were almost guaranteed to survive the first 3 months.

Interestingly, these results were seen despite the presence of a score component that was not clearly related to survival, i.e. low platelets. Attempts to modify the LabBM score as a consequence of our multivariate results did not lead to a better prognostic model. Low platelets were present in only 5% of the patients and this fact might explain our findings. Obviously, a larger database providing sufficient statistical power is needed to shed more light on the role of the platelet parameter. Given that the previous LabBM score validation was limited to patients with brain metastases [20], additional external validation in the larger non-brain metastases group is necessary. Ideally and to strengthen generalizability, a validation study should include more patients irradiated for indications other than bone metastases. It would also be interesting to collect prospective blood test results, e.g. as a secondary endpoint of a clinical trial in the field of palliative radiotherapy, and to correlate the likelihood and duration of symptom relief with the LabBM score, given that palliative radiotherapy typically aims at reduced burden of pain and other complaints.

Conclusion

The LabBM score, which is derived from inexpensive blood tests and easy to use, stratified patients irradiated for indications other than brain metastases into three very distinct prognostic groups and deserves further validation.

Conflict of interest

None declared.

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