The LabPS score: inexpensive, fast and site-agnostic survival prediction

Carsten Nieder, MD[1,2], Ellinor C. Haukland, MD PhD[1,3], Bård Mannsåker, MD[1], Astrid Dalhaug, MD[1]

[1]Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway;

[2]Department of Clinical Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway;

[3]SHARE – Center for Resilience in Healthcare, Faculty of Health Sciences, Department of Quality and Health Technology, University of Stavanger, Stavanger, Norway

Abstract

Objectives: To provide a widely applicable, blood-biomarker- and performance-status (PS)-based prognostic model, which predicts the survival of patients undergoing palliative non-brain radiotherapy. This model has already been examined in a cohort of patients treated for brain metastases and performed well.

Methods: This was a retrospective single-institution analysis of 375 patients, managed with non-ablative radiotherapy to extracranial targets such as bone, lung or lymph nodes. Survival was stratified by LabPS score, a model including serum hemoglobin, platelets, albumin, C-reactive protein, lactate dehydrogenase and PS. Zero, 0.5 or 1 point was assigned and the final point sum calculated. A higher point sum indicates shorter survival.

Results: The LabPS score predicted overall survival very well (median 0.6-26.5 months, 3-months rate 0-100%, 1-year rate 0-89%), p=0.0001. However, the group with the poorest prognosis (4.5 points) was very small. Most patients with comparably short survival or radiotherapy administered in the last month of life had a lower point sum. Additional prognostic factors such as liver metastases, opioid analgesic use and/or corticosteroid medication were identified.

Conclusions: If busy clinicians prefer a general prognostic model rather than a panel of separate diagnosis-/target-specific scores, they may consider validating the LabPS score in their own practice. In resource-constrained settings, inexpensive standard blood tests may be preferable over imaging-derived prognostic information. Just like other available scores, the LabPS cannot identify all patients with very short survival.

Introduction

Despite its impressive track record and repeatedly confirmed clinical efficacy throughout different global healthcare settings, efforts towards optimization of palliative radiotherapy continue to impact the evolution of clinical care pathways [1-4]. Different stakeholders have emphasized the need for global access to radiotherapy, and optimal resource allocation also includes measures reducing futile treatment [5, 6]. For example, prescribing 10 fractions of palliative thoracic radiotherapy in a hypothetical patient with terminal lung cancer who has failed several systemic therapies, harbors widespread extrathoracic metastases, is in reduced performance status (PS) and likely to survive for maybe few weeks, would occupy the time slots that radiation oncology departments could allocate to several patients with uncomplicated painful bone metastases, who are likely to benefit from a single fraction of 8 Gy.

To optimize resource allocation and individual patients' benefit from "just-as-much-as-needed" radiotherapy approaches, life expectancy should be estimated [7]. As recently pointed out by Kraft et al., who applied a large number of published prognostic scores predicting survival in patients with newly diagnosed brain metastases treated with upfront radiosurgery, the most complex model is not necessarily better than simpler ones [8]. A simple assessment of PS already provided very useful information in their study. An extreme approach in daily practice would be implementation of several highly complex site-specific models, e.g. one each for brain metastases, bone metastases, thoracic radiotherapy etc. [9-12]. However, especially in countries with highly limited resources, time-consuming assessment cannot be implemented. An inexpensive, fast, universally applicable model predicting survival would likely gain higher acceptance.

In the context of general palliative radiotherapy, Chow's 3-item model (non-breast primary cancer, metastases other than bone only, and Karnofsky PS ≤ 60) is amongst the simplest models providing validated, clinically implementable information [13]. The TEACHH model (type of cancer, Eastern Cooperative Oncology Group (ECOG) PS, age, prior palliative chemotherapy, prior hospitalizations, and hepatic metastases) divides patients receiving palliative radiotherapy into 3 distinct life expectancy groups, but is more complex and also prone to the influence of international practice variation [14]. For example, some healthcare systems provide excellent outpatient services or home care, which might render hospitalization less likely. Identical patients in other countries might have no alternative to hospitalization.

Parallel to other efforts, our group has studied the three-tiered LabBM score, which originally was developed in the patient subgroup with brain metastases and includes serum albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), hemoglobin and platelets, i.e. inexpensive standard blood tests [15, 16]. The test results can be considered surrogates of organ function, inflammation and nutrition status (influenced by overall disease extent and comorbid conditions). Imaging to assess disease burden is not required. We have already shown that the LabBM score can be utilized in patients treated with general, non-brain palliative radiotherapy [17]. In the current study we evaluated its already presented, expanded version, the LabPS [18], which features the blood test results combined with ECOG PS, a well-established component of several previous predictive models.

Materials and Methods

A single-institution database with all patients irradiated for common palliative indications in non-hematological malignancies such as bone metastases, thoracic symptoms from lung cancer, hematuria, pelvic pain from different primary tumors, painful lymph node metastases etc. was employed. Brain metastases data have already been published [18]. Classical external beam fractionation regimens were prescribed such as 10-13 fractions of 3 Gy, 5-6 fractions of 4 Gy and single fraction 8 Gy x1 (both completed and interrupted treatment courses according to the intention-to-treat principle, as also described in our previous study [17]). Stereotactic ablative radiotherapy was not included. Radiotherapy prescription was individualized, and so was systemic treatment. The patients were treated between July 2007 and December 2013. Staging relied on computed tomography (CT). If clinically relevant, other modalities were added to clarify CT findings, e.g., isotope bone scan, ultrasound, positron emission tomography etc.

All 5 blood tests needed to calculate the LabBM score were routinely assessed during treatment planning, typically 3-7 days before radiotherapy (normal values in our hospital: hemoglobin 11.7-15.3 g/dl (females) and 13.4-17.0 g/dl (males); platelets 130-400 $x10^9$; albumin 34-45 g/l; LDH <255 U/l; CRP <5 mg/l). At the same time, ECOG PS was recorded in the electronic patient record. We calculated the LabBM score as suggested by Berghoff et al. in the original study [15], i.e. 1 point in case of LDH and CRP measurement 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 (all blood tests normal) indicates a favorable prognosis. The maximum point sum is 3.5 (all blood tests abnormal). The same principle (0/0.5/1 point) was applied to ECOG PS, after having confirmed its prognostic impact. PS 3-4 resulted in 1 additional point, PS 2 in 0.5 additional point, and

PS 0-1 in 0 points on top of the point sum from the blood tests. For the final score, a maximum point sum of 4.5 was possible.

Overall survival (time to death) from the first day of radiotherapy was calculated employing the Kaplan–Meier method. Different groups were compared using the log-rank test (SPSS 28, IBM Corp., Armonk, NY, USA). Only nine patients were censored after median 87 months of follow-up (minimum 72 months). Date of death was known in all other patients, n=366. A multivariate forward conditional Cox regression analysis was employed too. P-values <0.05 were considered statistically significant. Chow's 3-item score [13] was also utilized, in contrast to TEACHH [14] because the component "prior hospitalizations" was not recorded in our patient records. Furthermore, Gönen & Heller's concordance probability estimate (CPE) [19] was compared between Chow's 3-item score, LabBM and LabPS (r-project.org).

Results

The study cohort (n=375) included 35% patients with prostate, 19% with lung and 15% with breast cancer (Table 1). The median time interval between initial cancer diagnosis and radiotherapy was 35 months, range 0-360. A median age of 66 years was recorded, range 31-95. Low hemoglobin (65%), abnormal CRP (64%) and elevated LDH (53%) was commonly recorded. Twenty patients (5%) did not complete radiotherapy as prescribed and 33 (9%) received it in the last month of life. Median actuarial survival was 6.9 months (95% confidence interval 5.4-8.4). One-, 2- and 5-year survival was 37, 20 and 5%. Chow's 3-item model stratified our patients into 3 groups with significantly different median survival of 16, 13 and 3 months (Figure 1).

Regarding the impact of components of the LabPS score, Cox regression analysis showed that ECOG PS ranked highest (p=0.0001, selected in step 1), followed by CRP (p=0.001, step 2), LDH (p=0.001, step 3), hemoglobin (p=0.009, step 4), platelets (p=0.03) and albumin (p=0.05), Table 2. Age and sex were not associated with survival, while time interval between diagnosis and treatment, number of treated target volumes, concomitant steroid medication, opioid medication, non-breast primary and presence of liver metastases were (single variable Cox regression). A Cox model with all 6 variables showed that 5 of them achieved statistical significance (step 1: opioids, step 2: liver metastases, step 3: non-breast primary, step 4: time interval, step 5: steroids). In other words, all variables except for number of treated target volumes contributed prognostic information. To maintain model simplicity and eliminate imaging needs, we nevertheless proceeded with the LabPS score.

The actuarial overall survival curves are shown in Figure 2 (p=0.0001 over all strata). Median overall survival ranged from 0.6 to 26.5 months (further data are shown in Table 3). Patients with LabPS 0 had very distinct survival outcomes. Only 4 patients (1%) had 4.5 points. All had died after a maximum time period of 1.2 months, resulting in the fact that 3 of 4 had received treatment in the last 30 days of life. It should also be noted that none of the 150 patients with LabPS score 0-1.5 was irradiated in the last 30 days of life. The CPE results were similar for all 3 models: 0.74 (LabPS), 0.75 (LabBM) and 0.75 (Chow's 3-item).

Discussion

This study represents the final step in our comprehensive evaluation of the blood-test-based LabBM score. We have already shown that it is equally applicable to patients with

brain metastases and those receiving non-brain palliative radiotherapy [17]. In addition, we demonstrated how to integrate ECOG PS, moving from LabBM to LabPS [18]. The latter study in patients with brain metastases has now been replicated in a cohort irradiated for other indications, which we believe resembles other institutions workload or daily practice of palliative radiotherapy (all-comers). The median overall survival was 6.9 months (minimum 2 days, maximum 9 years). This tremendous prognostic heterogeneity has long been a clinical challenge for those trying to determine the required treatment intensity in each patient [20-22]. Inter-institutional variation in reported rates of palliative radiotherapy near the end of life reflects the difficulties in decision-making and prediction of life expectancy [21]. As repeatedly shown, also in Figure 1, Chow's 3-item model [13] provides valuable prognostic information, with CPE similar to that of LabBM and LabPS. Other, more complex models such as TEACHH [14] and NEAT [23] have been proposed, and as recently reviewed [24, 25] these and many others have demonstrated their ability to stratify patients referred to radiation oncology consultation.

In contrast to our study (Figure 2), many others did not publish the full data set, i.e. all survival curves. They rather aggregated data and collapsed information, resulting in only 3 or 4 survival curves. This methodology may result in unfortunate loss of information, because it would for example go unnoticed how soon after radiotherapy all patients with 4.5 points passed away, if they were lumped together with additional subgroups. The Chow et al. score (Figure 1) nicely illustrates how to create a poor-prognosis-group that features a tail of long-term survivors.

Ideally, one would develop a score (the ultimate one) that identifies all patients with very short survival, thus facilitating an early discussion about care preferences and best

supportive care or hospice referral as reasonable alternative to radiotherapy (or any other oncological intervention). Even short-course radiotherapy may not be warranted in patients dying within a couple of days. Just like other models, the LabPS did not assign all patients with very short survival to the most unfavorable prognostic groups. An identical observation was made in the brain metastases study [18], leading us and others [8] to conclude that LabPS is not able to outperform all other scores. As suggested by our different Cox regression models, this may be explained by the fact that multiple baseline parameters were confirmed as independent prognostic factors, e.g. medications which likely reflect symptom severity. On one hand, one may argue that all these parameters are needed to develop a perfect prognostic model. On the other hand, unforeseeable medical situations such as cardiac arrest and life-threatening infection may occur at any time, thus rendering the future unpredictable. Highly complex, more time-consuming models may not gain the necessary support for broad clinical implementation. LabBM and LabPS had similar CPE in the present study. However, LabPS provides 10 distinct survival curves, while LabBM, due to its lower maximum point sum, only provides 8.

We also believe that a broadly acceptable model should be implementable throughout different healthcare settings including regions with limited access to imaging resources or those with advanced outpatient care preventing hospitalization. We acknowledge that even standard blood tests may not be affordable in all regions, but believe that the LabPS or LabBM score likely represent a feasible approach in many countries. Radiation oncologists without sub-specialization who have to manage a broad spectrum of disease sites may find it easier to apply only one, rather straightforward score instead of numerous site- or metastasis-specific predictive tools.

Limitations of the present study include the number of patients (not small, but not huge either), statistical power of subgroup analyses, retrospective single-institution design, lack of external validation and changing treatment paradigms because treatment took place between 2007 and 2013. For almost all tumor types, a patient treated in 2013 (final year of inclusion) had fewer and less efficacious systemic therapy options than a patient treated in 2022. We did not attempt to evaluate patient satisfaction or symptom palliation. Again, we acknowledge that we chose not to include all prognostic factors to create another expansion of the LabBM. We did so to maintain simplicity, low resource utilization and universal applicability. There is of course room for employing BMETS, TEACHH, NEAT or other validated scores in institutions that prefer to do so. Institutions interested in the LabPS or LabBM score should validate its suitability, e.g. by applying the sequential testing approach in a limited number of own patients [26, 27]. The worst strategy would be refraining from estimating life expectancy at all.

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Figure Legend

Figure 1. Actuarial overall survival stratified by Chow's 3-item score (n=35, 159, 181), p=0.0001.

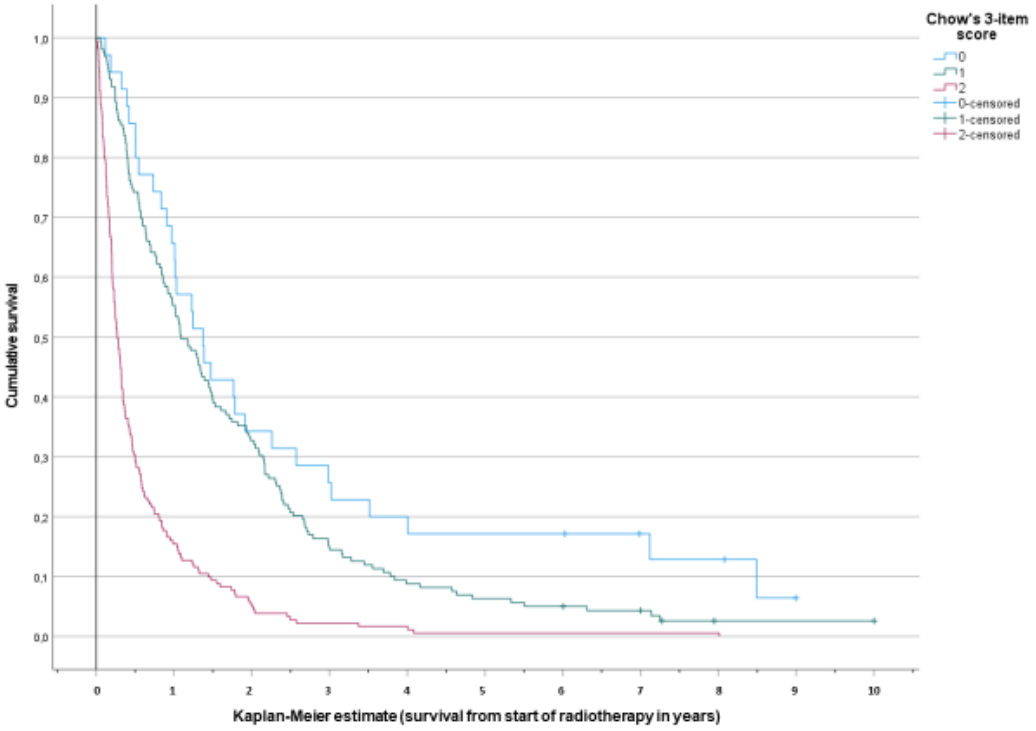

Figure 2. Actuarial overall survival stratified by LabPS score, p=0.0001.

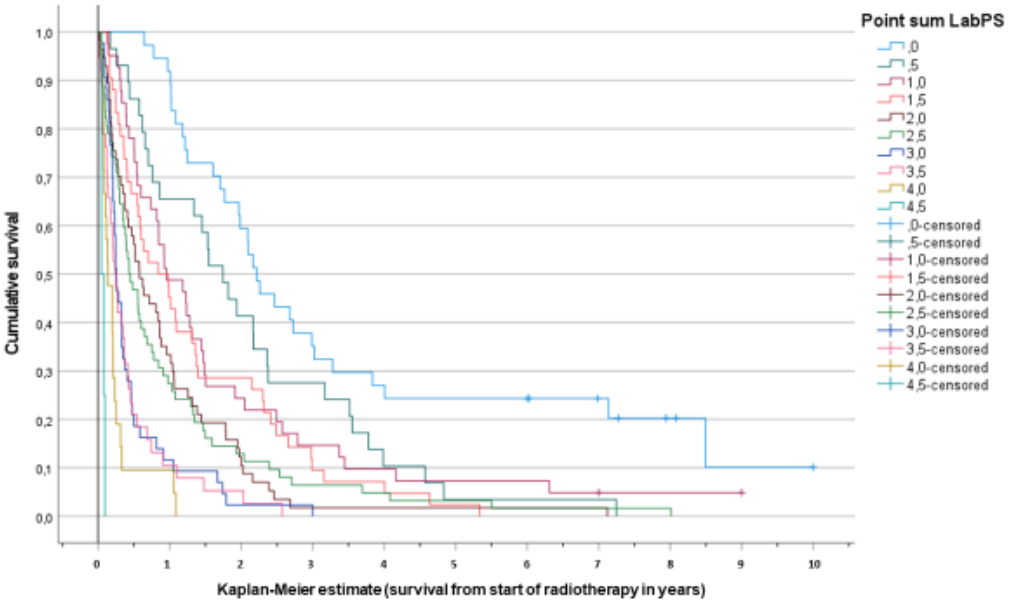

Table 1.

Patient characteristics, n=375.

Baseline parameter	Number	Percent
Female sex	119	32
Male sex	256	68
Age ≤60 years	90	24
Age 61-70 years	146	39
Age 71-80 years	97	26
Age ≥81 years	42	11
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
Malignant melanoma	8	2
Other primary tumors	41	11
ECOG PS 0	53	14
ECOG PS 1	120	32
ECOG PS 2	115	31

Baseline parameter	Number	Percent
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 RT (curative or palliative)	224	60
No previous RT	151	40
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

Baseline parameter	Number	Percent
Low platelets	19	5
No systemic therapy	133	36
Previous or ongoing systemic therapy	242	65
Corticosteroid concomitant to RT	199	53
No corticosteroid concomitant to RT	176	47
Opioid analgesic concomitant to RT	270	72
No opioid analgesic concomitant to RT	105	28
Palliative care team involved	90	24
Palliative care team not involved	285	76

ECOG: Eastern Cooperative Oncology Group; RT: radiotherapy

Table 2.

Prognostic factors for survival: impact of score components.

Parameter	Median survival (mo)	Univariable HR	p-value	Multivariable HR	p-value
ECOG PS					
0-1	14.7				
>1	3.7*	4.0	0.0001	2.1	0.0001
CRP					
Normal	17.3				
High	4.3	4.0	0.0001	2.0	0.001
LDH					
Normal	11.4				
High	4.7	2.4	0.0001	1.6	0.001
Hemoglobin					
Normal	12.2				
Low	5.1	2.4	0.0001	1.5	0.009
Platelets					
Normal	10.9				
Low	6.7	1.6	0.02	1.3	0.03
Albumin					
Normal	9.3				
Low	2.5	3.8	0.01	1.3	0.05

ECOG PS: Eastern Cooperative Oncology Group performance status; CRP: C-reactive protein, LDH: lactate dehydrogenase
* PS 2: 4.9 months, PS 3: 2.3 months

Table 3.

The LabPS score with survival outcomes stratified by prognostic group.

Score	Number, percent	1-year survival (percent)	3-months survival (percent)	Median survival (mo)	RT last month (percent
LabPS 0	37, 10	89	100	26.5	0
LabPS 0.5	30, 8	66	97	20.9	0
LabPS 1.0	41, 11	49	95	11.4	0
LabPS 1.5	42, 11	45	85	10.1	0
LabPS 2.0	57, 15	33	75	6.9	5
LabPS 2.5	62, 17	27	72	5.2	15
LabPS 3.0	43, 11	12	51	3.0	7
LabPS 3.5	38, 10	10	47	2.8	21
LabPS 4.0	21, 6	9	24	1.6	33
LabPS 4.5	4, 1	0	0	0.6	75

RT: radiotherapy