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Palliative Radiotherapy for Non-metastatic Non-small-cell Lung Cancer: Impact of Blood Test Results on Survival

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Abstract. *Background/Aim: Non-small-cell lung cancer (NSCLC) not amenable to curative treatment can be managed with palliative thoracic radiation or chemoradiation, however, with variable success. This study evaluated the prognostic impact of the LabBM score [serum lactate dehydrogenase (LDH), C-reactive protein, albumin, hemoglobin, platelets] in 56 patients who were scheduled to receive at least 10 fractions of 3 Gy. Patients and Methods: Uni- and multivariate analyses of prognostic factors for overall survival were employed in a retrospective single-institution study of stage II and III NSCLC. Results: The first multivariate analysis showed that hospitalization in the month before radiotherapy (p<0.001), concomitant chemoradiotherapy (p=0.03), and LabBM point sum (p=0.09) were the leading predictors of survival. A second model with individual blood tests rather than the sum score suggested that concomitant chemoradiotherapy (p=0.002), hemoglobin (p=0.01), LDH (p=0.04), and hospitalization before radiotherapy (p=0.08) played important roles. Surprisingly long survival was seen in patients without prior hospitalization who received concomitant chemoradiotherapy and had favorable LabBM score (0-1 points): median 24 months, 5-year rate 46%. Conclusion: Blood biomarkers provide relevant prognostic information. The LabBM score has 1) previously been validated in patients with brain metastases and 2) demonstrated encouraging results in a cohort irradiated for different palliative non-brain indications, e.g., bone metastases. It might be helpful in predicting survival in patients with non-metastatic cancer, e.g., NSCLC stage II and III.*

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Patients with non-small-cell lung cancer (NSCLC) in non-metastatic stages, especially stage III (1), *i.e.,* disease amenable to curative treatment, might nevertheless receive palliative therapy for a variety of reasons (2). The latter include poor lung function, other comorbidity, very advanced age or difficulty with adhering to safe dose constraints in case of large-volume disease managed with radiotherapy (3, 4). Palliative treatment might consist of systemic anti-cancer drugs, thoracic radiotherapy or combined chemoradiotherapy, albeit to lower total radiation doses than in curative regimens (5). The factors mentioned earlier are crucial when deciding about the intensity of palliative thoracic radiotherapy, where many patients present with symptomatic T3-4 and/or N3/bulky N2 disease (6). Symptom relief can be achieved with rather simple short-course radiation regimens, including 10 fractions of 3 Gy (7). Younger and fitter patients might be considered for more intense treatment, *e.g.,* 15 fractions of 2.8 Gy plus platinum-based chemotherapy. In the randomized Norwegian CONRAD trial from the pre-immunotherapy era, 4 cycles of carboplatin/vinorelbine were combined with 15 fractions of 2.8 Gy in a sequential fashion, where one cycle was administered during thoracic radiotherapy (8). The 1- and 2-year survival rates were 53% and 28%, respectively. In the comparison group treated with chemotherapy alone, these figures were 34% and 7% ($p<0.01$), respectively.

In order to provide personalized treatment, a thorough understanding of prognostic factors determining overall survival after radiotherapy is necessary. Previous analyses were often performed in patients managed with potentially curative radiotherapy or included those with stage IV disease, where thoracic symptoms necessitated some type of palliative thoracic radiotherapy (9, 10). Besides typically studied prognostic factors, such as age, T stage, N stage or

tumor volume, blood test results might contribute relevant information. For example, low serum hemoglobin and high lactate dehydrogenase (LDH) have been tied to inferior survival outcomes (11, 12). A more comprehensive, yet affordable and widely available test panel, the already validated LabBM score (13, 14), has been studied by our group in different settings, such as radiotherapy for brain metastases and extracranial lesions, including oligometastases (15, 16). The score provided excellent discrimination between patients with different survival outcomes. Besides LDH and hemoglobin, C-reactive protein (CRP), albumin, and platelets are included. Completely normal tests result in a LabBM score of 0 and, thus, favorable survival expectation. Based on previous results with the LabBM score, the hypothesis of the present study was that the score might also be applicable in the setting of palliative (chemo)radiotherapy for non-metastatic NSCLC. If true, a single prediction model would be sufficient to support decision making in a wide variety of palliative radiotherapy scenarios (metastatic and non-metastatic).

Patients and Methods

Patients and treatment. This retrospective study included patients with NSCLC stage II or III (1) managed at Nordland Hospital in the time period 2008-2022, identified from a continuously updated database, which is utilized to monitor treatment outcomes (4, 7). The multidisciplinary lung cancer tumor board had recommended a palliative strategy that included thoracic radiotherapy or chemoradiotherapy for these patients. Radiotherapy fractionation and technique (2-dimensional simulator-based, 3-dimensional conformal, intensity-modulated, volumetric modulated arc) were chosen by the treating clinical oncologist. Patients managed with low-dose radiotherapy (less than 10 fractions of 3 Gy) were excluded. However, those who failed to complete radiotherapy were included, regardless of administered dose (intention to treat). Later, appropriate systemic treatment and, if necessary, additional local therapy [including re-irradiation (17)] were administered. Staging relied on computed tomography (CT), supplemented with positron emission tomography (PET)-CT in the majority of patients. For logistic reasons (long travel distance), frail patients were not routinely referred to PET-CT (18). Blood tests including LDH, CRP, albumin, hemoglobin, and platelets were assessed during treatment planning (in the week before radiotherapy). The LabBM score (13) was calculated as originally proposed by Berghoff *et al*. (1 point: LDH or CRP above institutional upper limit of normal, 0.5 points: albumin, hemoglobin or platelets below institutional lower limit of normal; resulting point sum 0-3.5).

Statistical methods. 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 28, IBM Corp., Armonk, NY, USA). Eight patients were alive in December 2022 when data were analyzed. They were censored after a median follow-up of 30 months. Uni- and multivariate Cox regression analyses (forward stepwise conditional) were also performed. We defined statistical significance as $p<0.05$ for all

Table I. *Patient characteristics*.

Baseline parameter	Number	Percent
Female	28	50
Male	28	50
Chronic obstructive pulmonary disease	20	36
Active smoker	19	34
Cardiac comorbidity	16	29
Previous other cancer diagnosis	11	20
Left-sided primary tumor	21	38
Right-sided primary tumor or bilateral cancer	35	63
T stage (primary tumor)		
- T1	6	11
- T2	10	18
- T3	18	32
- T4	16	29
- Previously resected	6	11
N stage (lymph nodes)		
- N0	10	18
- N1	1	2
- N2	21	38
- N3	24	43
Overall stage		
- II	8	14
- IIIA	13	23
- IIIB	35	63
Histology		
- Adenocarcinoma	23	41
- Squamous cell carcinoma	27	48
- Other/mixed	6	11
Concomitant chemoradiotherapy	25	45
Sequential immune checkpoint inhibitor for relapse	10	18
Treatment technique		
- 2-dimensional	5	9
- 3-dimensional conformal	38	68
- Intensity-modulated	9	16
- Volumetric modulated arc	4	7
Dose and fractionation		
- 15 fractions of 2.8 Gy	27	48
- 10 fractions of 3 Gy	9	16
- 13 fractions of 3 Gy	6	11
- 15 fractions of 3 Gy	4	7
- others	10	18
Incomplete radiotherapy	6	11
Inpatient during radiotherapy	9	16
Hospitalized in the month before radiotherapy	16	29
Weight loss ≥5 kg	19	34
Treated with concomitant corticosteroid (any reason)	13	23
Low albumin	5	9
Low hemoglobin	30	54
Low platelet count	1	2
High C-reactive protein	35	63
High lactate dehydrogenase	11	20
High leukocyte count	14	25
LabBM score 0-1 point	27	48
LabBM score 1.5-2 points	23	41
LabBM score 2.5 points	6	11

LAbBM: Serum lactate dehydrogenase, C-reactive protein, albumin, hemoglobin, platelets.

Table II. *Prognostic factors for overall survival.*

Parameter	Median survival (months)	*p*-Value univariate	*p*-Value multivariate[1]	*p*-Value multivariate[2]
Inpatient	5.1	0.02	>0.1	>0.1
Outpatient	11.7			
Previous hospitalization	3.9	<0.001	<0.001	0.08
Not hospitalized before RT	14.9		Hazard ratio=3.2	
Concomitant chemoradiotherapy	19.1	0.008	0.03	0.002
Radiotherapy alone	6.9		Hazard ratio=0.5	
Lactate dehydrogenase high	7.4	0.007	Not included	0.04
Lactate dehydrogenase normal	12.3			Hazard ratio=2.4
C-reactive protein high	9.2	0.03	Not included	>0.1
C-reactive protein normal	15.2			
Hemoglobin low	6.9	0.01	Not included	0.01
Hemoglobin normal	14.9			Hazard ratio=2.7
Albumin low	5.0	0.08	Not included	>0.1
Albumin normal	9.7			
Leukocytes high	5.1	0.05	>0.1	>0.1
Leukocytes normal	9.8			
On corticosteroid	9.7	0.08*	>0.1	>0.1
Not on corticosteroid	9.6			
LabBM score 0-1	15.2	0.002	Not included	Not included
LabBM score 1.5-2	7.9			
LabBM score 2.5	2.6			
LabBM as continuous variable	n/a	<0.001	0.09	Not included

RT: Radiotherapy; LabBM: serum lactate dehydrogenase, C-reactive protein, albumin, hemoglobin, platelets/*long-term survival was very different despite similar median. [1]multivariate model without individual components of the LabBM score. [2]multivariate model with individual blood tests rather than LabBM score.

analyses. Due to the limited study size, parameters with $p<0.1$ in univariate analysis were included in the multivariate model.

Results

The study included 56 patients with a median overall survival of 9.6 months. Median age was 72 years, range=49-88 years. Median clinical target volume (CTV) size was 104 ml, range=20-860 ml. The corresponding values for planning target volume (PTV) size were 421 (95-1,272) ml, respectively. Twenty-five patients (45%) received treatment according to the CONRAD protocol outside of the prospective trial, *i.e.,* 15 fractions of 2.8 Gy with carboplatin/vinorelbine. Most patients (63%) had stage IIIB disease. In 48%, the LabBM score predicted favorable survival (0-1 points). Additional baseline information is shown in Table I.

All parameters mentioned in the previous paragraph and Table I, except platelets (only one patient had low platelets), were included in univariate analyses of factors predicting overall survival. Those with *p*-value <0.1 are displayed in Table II. The LabBM score was significantly associated with median, 1-year and 3-year survival (Figure 1). The three strata had 1-year survival rates of 60, 28, and 17%, respectively. The corresponding figures for 3-year survival were 24, 0, and 0%, respectively. Two different multivariate analyses were performed: 1) with LabBM score as continuous variable and 2) with individual blood tests rather than LabBM. Version 1 showed that hospitalization before radiotherapy ($p<0.001$), concomitant chemoradiotherapy ($p=0.03$), and LabBM point sum ($p=0.09$) were the leading predictors of survival. Version 2 suggested that concomitant chemoradiotherapy ($p=0.002$), hemoglobin ($p=0.01$), LDH ($p=0.04$), and hospitalization before radiotherapy ($p=0.08$) played important roles. Surprisingly long survival was seen in patients without prior hospitalization who received concomitant chemoradiotherapy and had LabBM score 0-1: median 24 months, 5-year rate 46%. The presence of a LabBM score of 1.5-2 reduced median survival to 19 months and the single patient with score 2.5 died after 7.4 months.

All 6 patients who failed to complete radiotherapy (medical reason in 4, patient decision in 2) had LabBM scores of 1.5-2.5. LabBM score was not associated with overall stage or T stage. However, patients with lower N stage were more likely to have score 0-1 (82% of N0/1 patients had score 0-1, compared to 45% of N2, and 37% of N3; $p=0.05$, chi-square test). Adding N stage, which was not significantly associated with overall survival in univariate log-rank test, to the parameters in the two multivariate analyses, did not change the results.

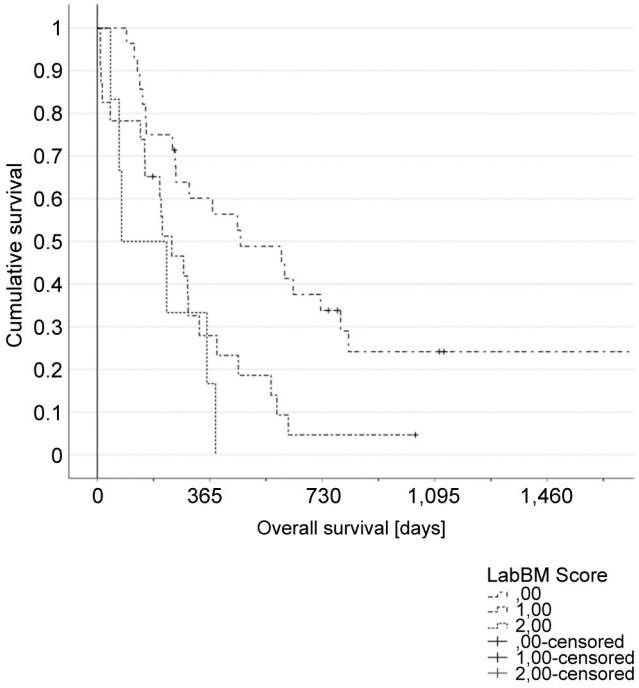

Figure 1. *Actuarial overall survival stratified by LabBM (serum lactate dehydrogenase, C-reactive protein, albumin, hemoglobin, platelets) score, log-rank test p=0.002.*

Discussion

We conducted this study as an addition to previous work, which has validated the LabBM score in patients with brain metastases (14) and suggested its applicability in the broad population of patients undergoing palliative radiotherapy for other conditions (15). The latter study included many patients with bone and/or lymph node metastases and very few with non-metastatic cancer. In addition, contemporary patients were not included. Therefore, it was necessary to perform the first study of the LabBM score in a narrowly defined, contemporary cohort of patients with non-metastatic cancer. NSCLC was selected because it is a common cancer type where palliative local (in this case thoracic) radiotherapy is more common than, *e.g.*, in bladder, colorectal or prostate cancer. If this first proof-of-principle study confirms previous observations, *i.e.,* the excellent ability of the LabBM score to predict survival, efforts are warranted to continue its exploration as an universally applicable score, covering all palliative radiotherapy indications. This would simplify decision-making compared to a strategy of assigning site- and indication-specific models, *e.g.*, one for palliative irradiation of bone metastases, one for radiosurgery of brain metastases, one for thoracic irradiation of NSCLC *etc*.

The study population was dominated by elderly patients (median age 72 years) with stage IIIB NSCLC, often treated with the so-called CONRAD regimen [15 fractions of 2.8 Gy combined with carboplatin/vinorelbine (8)] in first line after the multidisciplinary tumor board had recommended against curative chemoradiotherapy, which would have included a total radiation dose of 60-66 Gy. Treatment completion was satisfactory (89%), and interestingly, patients with low LabBM score (0-1 points) were always able to complete radiotherapy. The three LabBM strata had 1-year survival rates of 60, 28, and 17%, respectively. Hospitalization in the month before radiotherapy ($p<0.001$), concomitant chemoradiotherapy ($p=0.03$), and LabBM point sum ($p=0.09$) were the leading predictors of survival in a multivariate Cox regression analysis, outperforming variables, such as age, weight loss, CTV size, and NSCLC stage. Given that the score consists of five blood test results and our cohort did not include a sufficient number of patients with low platelet count, we opted for a second multivariate Cox regression analysis where the continuous LabBM point sum was replaced by the individual LabBM components LDH, CRP, albumin, and hemoglobin. Under these conditions, concomitant chemoradiotherapy ($p=0.002$), hemoglobin ($p=0.01$), LDH ($p=0.04$), and hospitalization before radiotherapy ($p=0.08$) played important roles. Also, a previous study that included stage IV NSCLC in addition to lower stage had shown that LDH and CRP contribute to survival prediction models (19). Therefore, blood test results should be a part of decision-making.

The LabBM score likely reflects inflammation and/or cachexia, which are present not only in patients with metastatic cancer. In the present study, a correlation between N stage and LabBM score was observed. Intriguingly, patients without prior hospitalization who received concomitant chemoradiotherapy and had LabBM score 0-1 had median overall survival of 24 months (5-year rate 46%) without administration of consolidation or planned immune checkpoint inhibitors. These figures are close to those reported after curative treatment (20). On the other hand, individual patients often live for less than one year after palliative (chemo)radiotherapy, both in this and other studies in the literature (8, 21, 22). It is therefore important to assess prognosis before embarking on futile or too ambitious treatment. In light of the observed median survival of 2.6 months in patients with LabBM score of 2.5 (the highest point sum observed in our patients), extremely hypofractionated radiotherapy should be considered, *e.g.*, 2 fractions of 8.5 Gy, in order to shorten time spent on treatment.

The present study is limited by its size and the statistical power of subgroup analyses with often <15 patients and its retrospective, monocentric design. Statistical power should also be considered when interpreting *p*-values just outside of

the significance limit, *e.g.*, in the Cox models. The staging was not uniformly based on PET-CT. The multidisciplinary tumor board decisions against curative treatment were based on heterogeneous factors, such as disease- or patient-related contraindications. Performance status was not always recorded and thus not included in the study, despite its possible interaction with hospitalization and eligibility for chemoradiotherapy.

Standard blood tests, such as the components of the LabBM score are not the only biomarkers that have been studied so far. Inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), which can be viewed as surrogate biomarkers of host immune status, are of interest (23). Suwinski *et al*. studied 337 patients who were referred for curative or palliative thoracic radiotherapy for NSCLC (24). The concentration of osteopontin (OPN), vascular endothelial growth factor (VEGF), erythropoietin (EPO), high mobility group box 1 protein (HMGB1), insulin-like growth factor 1 (IGF-1), and platelet-derived growth factor (PDGF) in serum was studied. In this unselected heterogeneous cohort, dichotomized concentrations of OPN and VEGF emerged among the strongest independent prognosticators of overall survival. Additional work has also tied such biomarkers and serum tumor markers to overall survival (11, 25). Emerging biomarkers accessible by liquid biopsy, such as circulating tumor cells (CTC) represent promising tools for optimized decision making and patient selection (26, 27), also for multimodal management of oligometastatic disease (28). However, head-to-head comparison of different options including cost analysis is still lacking.

Conclusion

Blood biomarkers provide relevant prognostic information. The LabBM score has previously been validated in patients with brain metastases and demonstrated encouraging results in a cohort irradiated for different palliative non-brain indications, *e.g.* bone metastases. It might be helpful in predicting survival in patients with non-metastatic cancer, *e.g.* NSCLC stage II and III. Therefore, the LabBM score should be assessed in additional databases from larger institutions.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

CN was responsible for the design of the study and performed the statistical analysis. CN and KI collected patient data and drafted the article. All Authors read and approved the final article.

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