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Predicting overall survival in non-small cell lung cancer patients receiving concurrent radiochemotherapy and adjuvant durvalumab – a Polish real-world single-center experience

Barbara A. Łochowska[1, 2], Konrad Stawiski[2, 3], Kasper Kuna[3], Zuzanna Nowicka[3], Mariusz Łochowski[4], Jacek Fijuth[2]

[1]*Department of Sleep Medicine and Metabolic Disorders, Medical University of Lodz, Lodz, Poland*
[2]*Department of Radiotherapy and General Oncology, Copernicus Memorial Hospital, Lodz, Poland*
[3]*Department of Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland*
[4]*Clinic of Thoracic Surgery and Respiratory Rehabilitation, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland*

Introduction. Adjuvant durvalumab has become a standard treatment protocol for patients with locally advanced non-small cell lung cancer (LA-NSCLC). However, there is still limited knowledge about prognostic factors in a real-world setting across this specific patient group.

Materials and methods. In our single-center retrospective study, we evaluated 45 patients to identify predictors of overall survival (OS) in LA-NSCLC. We utilized the univariable Cox proportional hazards models, and we developed multivariable Cox models after adjusting for the known clinical predictors.

Results. In univariable analysis nodal status, the percentage of basophils in peripheral blood before treatment and D--dimers were associated with OS. Multivariable analysis, adjusted for age, sex, T characteristics, and nodal status revealed that the percentage of basophils is a significant predictor of OS. A higher percentage of basophils was associated with improved OS (HR = 0.077, 95% CI: 0.007–0.853, p = 0.037).

Conclusions. Our study indicates that a lower serum percentage of basophils may be associated with better OS in patients with LA-NSCLC. These findings should be validated in larger cohorts.

Key words: lung cancer, immunotherapy, durvalumab, prognostic biomarkers

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death worldwide [1], with locally advanced (LA)-NSCLC accounting for a significant portion of diagnoses [2]. Concurrent chemoradiation therapy (CCRT) has long been the standard of care for these patients, offering locoregional control and improved survival [3]. However, the emergence of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape. The original PACIFIC trial [4] published in 2017, established durvalumab – a monoclonal antibody targeting the PD-L1 receptor – as a new standard of care by demonstrating a significant improvement in overall survival (OS)

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compared to placebo in patients with unresectable stage III NSCLC receiving concurrent platinum-based chemotherapy and radiation therapy [5]. This landmark study paved the way for the widespread adoption of durvalumab consolidation therapy in clinical practice.

Investigations into biomarkers associated with a response to durvalumab are ongoing. Tumor PD-L1 expression has been shown to be a predictive factor in some studies, although its role remains controversial due to variations in testing methods and interpretation [5]. Other biomarkers, such as tumor mutational burden [6] and immune gene signatures [7], are also being investigated and may provide valuable insights into patient selection and treatment response. Additionally, emerging research suggests that genetic alterations, such as *KRAS* mutations, may hold promise for identifying patients who are less likely to benefit from durvalumab therapy [8].

Recent studies have explored the potential of various clinical and biological factors to predict survival in durvalumab-treated NSCLC patients. For instance, a study by Liu et al. identified the baseline neutrophils-to-lymphocytes ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as promising predictors of OS, highlighting the potential role of systemic immune status in treatment response [9]. Similarly, another study published in 2021 found that patients with low infiltration of CD8+ PD-L1+ T-cells and M2 macrophages achieved better progression-free survival (PFS) following durvalumab consolidation, suggesting the importance of pre-existing antitumor immunity [10]. In patients diagnosed with squamous cell carcinoma the higher percentage of basophils in tumor microenvironment (TME) was associated with longer OS [11]. The higher basophil counts were also demonstrated as significant predictors for a higher probability of tumor size reduction within three months, with an increased risk of immune-related adverse events [12]. In a study by Wang et al. the basophil-to-lymphocyte ratio was associated with a shorter OS [13]. Durvalumab has been available to the general patient population in Poland since 2021 via a government-controlled program.

In this single-center study, we aimed to contribute to the growing body of knowledge on predictive factors for OS in LA-NSCLC patients treated with CCRT and adjuvant durvalumab.

Material and methods

Population

In this retrospective cohort analysis, we examined cases of inoperable NSCLC that were treated with CCRT and with adjuvant durvalumab during the years 2021–2022 at our institution (Copernicus Memorial Hospital, Lodz, Poland). Since 2021, the cost of adjuvant durvalumab has been covered by the public healthcare system in Poland, thereby making it accessible to all patients in this cohort. The patients were followed up until December 31, 2023. Our group consisted of 16 (35.6%) women and the median age of participants was 70 years old (65–75). The majority of patients received cisplatin as a chemotherapeutic agent (62.2%), and the median radiation dose was 60 Gy.

All the participants who received durvalumab were enrolled in a strictly government-regulated program for the adjuvant treatment of histopathologically diagnosed NSCLC in Poland. To qualify for the durvalumab consolidation therapy, patients must be diagnosed with stage III NSCLC and demonstrate no disease progression following concurrent chemoradiotherapy. The absence of disease progression must be confirmed through a computed tomography (CT) scan, conducted within a six-week window following the completion of the radiotherapy. Moreover, the patients must have completed a course of CCRT involving platinum derivatives. The patient's overall health and wellness are also considered, with only those having a good performance status (Eastern Cooperative Oncology Group Performance Status, ECOG PS, 0 or 1) being deemed fit for the treatment. Furthermore, patients must not have any uncontrolled coexisting diseases or active autoimmune diseases, with the exception of diabetes, hypothyroidism, psoriasis, or vitiligo (which are manageable and do not interfere with the durvalumab treatment).

Additionally, before the treatment, the patients' bone marrow, kidney, and liver functions must be also assessed to ensure they are within the normal range and suitable for treatment. Pregnant women were not enrolled to study, and women of a maternal age were obliged to use appropriate contraception methods. Any contraindications to durvalumab or the presence of other uncontrolled malignancies disqualify a patient from the program. However, patients who have previously undergone durvalumab therapy may be considered for continued treatment, provided they met all the aforementioned criteria and showed no signs of disease progression.

Statistical analysis

Statistical analyses were performed using R software v4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered significant. Nominal variables are shown as numbers with percentages and continuous variables are shown as medians with the interquartile range. We used the Cox proportional hazards model to evaluate the prognostic value of clinical and laboratory results in univariable and multivariable analysis after adjusting for patient sex, age, T-characteristics, and nodal status. OS curves were analyzed using the Kaplan–Meier method; to calculate differences between groups a log-rank test was used.

Results

In the period spanning 2021–2022, CCRT and adjuvant durvalumab were administered to a cohort of 45 patients. The clinical characteristics of the study group are presented in table I. During the follow-up period, which extended to 42 months (with a median follow-up time of 14 months), 10 patients experienced fatal events (fig. 1A).

Table I. Study group description

Parameter	n (% or median – IQR)
female	16 (35.56%)
male	29 (64.44%)
age – years	70.0 (65.0–75.0)
smoking during RCHT – yes	12 (29.27%)
pack years	50 (40.0–70.0)
T characteristic	
1	9 (20.0%)
2	10 (22.22%)
3	20 (44.44%)
4	5 (11.11%)
x	1 (2.22%)
N characteristic	
1	6 (13.33%)
2	35 (77.78%)
3	4 (8.89%)
PTV volume – cm^3	321.1 (231.1–480.8)
treatment time – days	44.0 (41.0–46.0)
cisplatin *vs.* carboplatin	28 (62.22%)
histology	
adenocarcinoma	18 (40.0%)
squamous-cell carcinoma	20 (44.44%)
large cell neuroendocrine carcinoma	3 (6.67%)
not otherwise specified	4 (8.89%)
second agent	
etoposide	11 (24.44%)
paclitaxel	9 (20.0%)
vinorelibine	25 (55.56%)
time from end of RT to durvalumab administration – days	71.0 (60.5–79.0)
time from lab test to RT start	1.0 (0.0–3.0)
laboratory parameters	
white blood cell count – $10^3/\mu l$	7.18 (6.20–8.72)
red blood cell count – $10^6/\mu l$	4.26 (3.79–4.57)
hemoglobin – g/dl	12.60 (11.60–13.80)
hematocrit – %	37.60 (34.50–41.00)
PLT – $10^3/\mu l$	254.0 (204.00–301.00)
PCT – %	0.27 (0.21–0.31)
neutrophils – %	60.10 (51.10–66.30)
lymphocytes – %	26.10 (20.60–34.30)
monocytes – %	9.40 (8.20–11.90)
eosinophils – %	1.60 (0.70–3.20)
basophils – %	0.70 (0.40–0.90)
neutrophil count – $10^3/\mu l$	4.14 (3.30–5.09)
lymphocyte count – $10^3/\mu l$	1.88 (1.55–2.40)
monocyte count – $10^3/\mu l$	0.72 (0.56–0.93)
eosinophil count – $10^3/\mu l$	0.12 (0.06–0.22)
basophil count – $10^3/\mu l$	0.04 (0.03–0.06)
glucose – mg/dl	106.00 (96.00–130.00)
sodium – mmol/l	139.00 (137.00–142.00)
potassium – mmol/l	4.50 (4.20–4.90)
urea – mg/dl	38.30 (30.10–49.10)
creatinine – mg/dl	0.84 (0.72–1.10)
eGFR – ml/min/1,73 m^2	60.00 (60.00–60.00)
CRP – mg/l	4.65 (1.84–11.90)
D dimers	0.74 (0.55–1.29)
prothrombin time – seconds	12.20 (11.35–13.50)
INR	1.05 (0.97–1.17)
APTT – seconds	25.60 (25.25–28.60)
fibrinogen – mg/dl	401.00 (344.00–565.25)
procalcitonine – ng/ml	0.12 (0.06–0.25)
NLR	2.31 (1.51–3.08)
LMR	2.82 (1.98–3.34)
PLR	132.45 (103.64–184.71)
SII	571.67 (368.81–962.29)

EGFR – estimated glomerular filtration rate; INR – international normalized ratio; APTT – activated partial thromboplastin time; NLR – neutrophil to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index

As shown in table II, the univariable analysis revealed that nodal status (p = 0.015), (fig. 1C), a higher initial percentage of basophils (p = 0.020), though not their absolute number (p = 0.109), and d-dimers (p = 0.048) were significant predictors of OS in this group of patients. The smoking pack years did not demonstrate statistical significance in predicting overall survival (p = 0.731). In a multivariable analysis adjusted for patient age and sex, T characteristic, and nodal status, the percentage of basophils was a significant predictor of OS (p = 0.037) (tab. IV). After adjusting

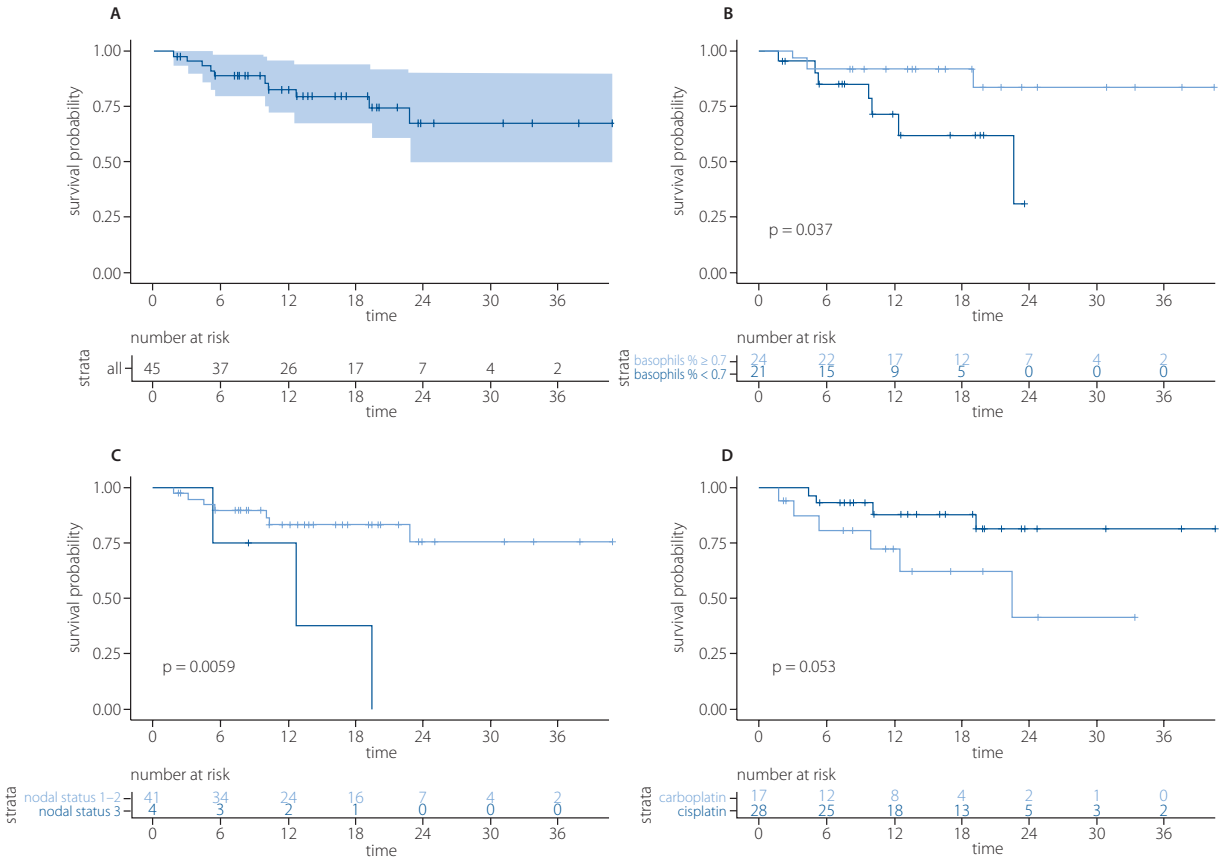

Figure 1. Panel A presents overall survival for the whole study group. Panel B represents a KM plot for groups with higher and lower percentages of basophils. Panel C presents a KM plot for groups divided according to their nodal status. Panel D presents a KM plot for groups treated with carboplatin or cisplatin

Table II. Univariable analysis with the Cox model based on clinical variables for OS

Characteristic	HR (95% CI)	p value
female	–	–
male	1.447 (0.374–5.602)	0.592
age – years	1.094 (0.985–1.210)	0.092
smoking during RCHT – yes	0.749 (0.144–3.90)	0.731
pack years	0.995 (0.970–1.020)	0.731
T characteristic		
1	–	–
2	4.126 (0.459–37.060)	
3	2.307 (0.269–19.750)	0.206
4	–	–
x	–	–
N characteristic		
1–2	–	–
3	5.653 (1.407–22.720)	0.015
PTV volume	2.718 (2.716–2.718)	0.195
treatment time	2.858 (2.557–3.287)	0.369
platin		
carboplatin	–	–
cisplatin	0.306 (0.086–1.088)	0.067
second agent		
etoposide	–	–
paclitaxel	0.989 (0.1650–5.927)	>0.9
vinorelibine	1.033 (0.242–4.417)	>0.9
durvalumab to RT time	1.020 (0.965–1.080)	0.485
time from lab test to RT start		
white blood cell count – 10^3/µl	0.973 (0.843–1.120)	0.704
red blood cell count – 10^6/µl	0.555 (0.156–1.980)	0.365
hemoglobin – g/dl	0.850 (0.562–1.290)	0.443
hematocrit – %	0.974 (0.848–1.120)	0.707
PLT – 10^3/µl	0.993 (0.982–1.000)	0.194

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Table II cont. Univariable analysis with the Cox model based on clinical variables for OS

Characteristic	HR (95% CI)	p value
PCT – %	0.000 (3.04 x 10^{-9}–10.1)	0.122
neutrophils – %	1.020 (0.973–1.060)	0.453
lymphocytes – %	0.983 (0.926–1.040)	0.575
monocytes – %	0.982 (0.849–1.140)	0.812
eosinophils – %	0.905 (0.67–1.220)	0.516
basophils – %	0.063 (0.006–0.642)	0.020
neutrophil count – 10^3/µl	0.989 (0.858–1.140)	0.88
lymphocyte count – 10^3/µl	0.865 (0.414–1.810)	0.699
monocyte count – 10^3/µl	0.840 (0.149–4.730)	0.843
eosinophil count – 10^3/µl	0.325 (0.007–14.700)	0.563
basophil count – 10^3/µl	1.26 x 10^{12} (3.37 x 10^{-27}–469.0)	0.109
glucose – mg/dl	1.010 (0.997–1.030)	0.125
sodium – mmol/l	0.960 (0.804–1.150)	0.648
potassium – mmol/l	0.942 (0.305–2.910)	0.918
urea – mg/dl	1.010 (0.981–1.030)	0.592
creatinine – mg/dl	2.930 (0.709–12.100)	0.137
eGFR – ml/min/1.73 m^2	0.966 (0.892–1.050)	0.406
CRP – mg/l	1.030 (0.980–1.070)	0.268
D dimers	1.240 (1.000–1.540)	0.048
prothrombin time – seconds	2.170 (0.877–5.340)	0.094
APTT – seconds	0.928 (0.601–1.430)	0.734
fibrinogen – mg/dl	1.000 (0.999–1.010)	0.165
procalcitonine – ng/ml	4.490 (0.994–20.300)	0.051
NLR	1.050 (0.808–1.370)	0.699
LMR	0.893 (0.600–1.330)	0.578
PLR	0.998 (0.990–1.010)	0.574
SII	1.000 (0.999–1.000)	0.705

HR – hazard ratio, CI – confidence interval; EGFR – estimated glomerular filtration rate; INR – international normalized ratio; APTT– activated partial thromboplastin time; NLR – neutrophil to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index

Table III. Multivariable Cox model of clinical factors and pack years on overall survival (OS)

Characteristic	HR (95% CI)	p value
female	–	–
male	0.800 (0.078–8.162)	0.851
age – years	1.316 (1.066–1.618)	0.010
T characteristic	0.820 (0.150–4.495)	0.819
nodal status	10.026 (1.017–98.846)	0.048
pack years	1.003 (0.969–1.039)	0.845

HR – hazard ratio, CI – confidence interval

Table IV. Multivariable Cox model of clinical factors and percentage of basophils on overall survival (OS)

Characteristic	HR (95% CI)	p value
female	–	–
male	2.728 (0.476–15.620)	0.257
age – years	1.080 (0.987–1.182)	0.093
T characteristic	0.996 (0.265–3.741)	0.995
nodal status	11.20 (1.746–71.827)	0.011
basophils – %	0.077 (0.007–0.853)	0.037

HR – hazard ratio, CI – confidence interval

for the same clinical prognostic factors, d-dimers were not associated significantly with OS (p = 0.115).

The best cutoff value for the percentage of basophils was 0.7% (fig. 1B). In the univariable Cox model, the group with a percentage of basophils below this value demonstrated a trend toward significantly shorter OS (HR = 3.917, CI: 0.991–15.480, p = 0.052).

Discussion

In this study, we conducted a comprehensive single-center analysis of lung cancer patients who were treated with concurrent radiochemotherapy and adjuvant durvalumab. We sought associations between pre-treatment clinical and laboratory variables with overall survival in a real-world setting. Ongoing studies are currently focused on exploring various factors associated with the benefits of durvalumab [14–17]. While the neutrophil-to-lymphocyte ratio (NLR) has previously been identified as a predictor of OS in lung cancer patients [18], in our cohort, NLR did not show any significance in predicting OS in both univariate and multivariable models. However, in the multivariable model adjusted for age, sex, T characteristic, and nodal status, the percentage of basophils was significantly associated with OS; while the mechanism behind this association is presently unclear, it may be validated in bigger cohorts. In a study by Krizova et al., higher baseline basophils were demonstrated as a significant predictor of longer PFS in NSCLC patients treated with ICIs [19]. The absolute count of basophils was also demonstrated as a potential biomarker

of ICI in advanced gastric cancer patients [20]. Another report by Liu et al. associated lower baseline basophil count with shorter disease-free survival [21].

In NSCLC patients, the main clinical predictors of survival are staging, ECOG status, weight loss, and serum albumin levels [22]. With the emergence of ICIs in the treatment of NSCLC, the PD-L1 expression was analyzed as a predictive factor. In a report by Bryant et al. [15], the group treated with durvalumab and with higher expression of PD-L1 had a longer PFS compared to the group that was not treated with ICI. Unfortunately, due to missing PD-L1 expression status in our cohort, we were not able to analyze its predictive value.

The tumor microenvironment is composed of various immune cells, and alterations in the composition of this infiltration have garnered significant interest in recent years [11, 25–27]. A study by Lavin et al. utilizing single-cell analysis to inspect the TME found fewer basophils in the TME of stage I adenocarcinoma compared to normal lung tissue [28]. Interestingly, a small proportion of basophils found in TME and non-involved lung parenchyma expressed PD-L1. The basophil levels in tumor-draining lymph nodes has been shown to be a useful predictor in pancreatic ductal adenocarcinoma, where, contrary to our results, higher levels were associated with poorer survival [29]. Additionally, a low percentage of basophils was found by Stankovic et al. in the immune infiltrate of NSCLC patients [30]. Future studies should explore the exact molecular alterations in basophils found in the TME.

One major limitation of our study is the small sample size. Additionally, our observation period was limited to two years, which may be considered relatively short. Furthermore, patients in our study received various chemotherapy regimens (carboplatin *vs.* cisplatin) (fig. 1D). To fully evaluate the significance of survival predictors in LA-NSCLC patients, more extensive studies with larger cohorts are needed.

Conclusions

In our univariate analysis significant predictors of OS in this group of patients were: nodal status, higher percentage of basophils, and D-dimer levels prior to the CCRT. In the multivariable Cox model, the percentage of basophils was associated with OS. The findings from this study could potentially contribute to the existing body of knowledge, influencing future studies search for predictors of OS, and illustrating the benefits of treatment with durvalumab in NSCLC.

Article information and declarations

Author contributions

Barbara A. Łochowska – conceptualization, investigation.
Konrad Stawiski – formal analysis, methodology, writing – review and editing.
Kasper Kuna – project administration, validation, writing – original draft preparation.
Zuzanna Nowicka – visualization, data curation, writing – review and editing.
Mariusz Łochowski – resources.
Jacek Fijuth – supervision.

Data availability

Datasets used for analysis for this study are available from the corresponding author upon reasonable request.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki.

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Conflict of interest

None declared

Barbara A. Łochowska
Copernicus Memorial Hospital in Lodz
Department of Radiotherapy and General Oncology
ul. Pabianicka 62
93-513 Łódź, Poland
e-mail: blochowska@op.pl

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