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Performance Status and Its Changes Predict Outcome for Patients With Inoperable Stage III NSCLC Undergoing Multimodal Treatment

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Abstract. *Background/Aim: Patient performance scores are used widely in clinical practice to assess a patient's general condition. The aim of this study was to evaluate the prognostic role of Eastern Cooperative Oncology Group performance score (ECOG PS) before, after and its changes during chemoradiotherapy in patients with stage III non-small cell lung cancer (NSCLC). Patients and Methods: Records of 99 patients with stage III NSCLC were evaluated. ECOG PS before, during and after chemoradiotherapy was analyzed for prognostic impact on overall (OS) and event-free (EFS) survival. Results: Median OS considering the entire cohort was 20.8 months (range=15.3-26.2 months). Median OS, and 1- and 2-year survival rates were 26.4 months, 85% and 53% in patients with ECOG PS 0 versus 18.9 months, 69% and 37% in patients with ECOG PS 1 (p=0.1, log-rank test), respectively. After the first follow-up, 35% of patients presented worsening ECOG PS, while in 65% it was stable or improved. Median EFS according to ECOG PS 0, 1, 2 and 3 was 9.6, 9.0, 7.9 and 3.5 months, respectively, at the first follow-up (p=0.018, log-rank test). Deterioration of ECOG PS after chemoradiotherapy resulted in reduced OS in the subgroups with initial ECOG PS 0 and 1 (p=0.005 and p=0.001, log-rank test). Conclusion: ECOG PS and its changes have a strong impact on patient outcome. Deterioration of performance status was a strong negative prognostic factor for EFS and OS.*

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Lung cancer remains the leading cause of cancer-related mortality worldwide (1-4). Over 80% of all lung cancers are characterized as non-small cell lung cancer (NSCLC), mainly squamous cell carcinoma, adenocarcinoma and large-cell carcinoma (3-5). Stage III NSCLC represents a locally advanced stage with heterogenous characteristics such as extensive lymph node (N3) involvement, large tumour volumes or infiltration of surrounding structures *e.g.* mediastinum, heart or spinal column (3, 4, 6).

Karnofsky's performance status (KPS) or the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) are widely used methods of assessing the functional status of cancer patients (7-11). Success of the individualized multimodal treatment highly depends on general and functional patient performance. A multimodal approach including chemo-, immunotherapy and locoregional thoracic irradiation is considered a standard of care in the treatment of inoperable stage III NSCLC. Patients with a good performance status (ECOG PS 0 or 1) should receive definitive concurrent chemoradiotherapy (CRT) followed by consolidation programmed cell death 1 ligand 1 (PD-L1) inhibition (3, 4, 12, 13). However, not all patients will be able to tolerate intensified multimodal approaches and understanding the role of patient performance during the course of treatment is necessary for personalized decision making. The aim of this retrospective study was to evaluate the prognostic role of ECOG PS before, during and after CRT in stage III NSCLC.

Patients and Methods

Medical records of 99 patients consecutively treated with curative-intent multimodal treatment between December 2010 and December 2016 for stage IIIA/B NSCLC according to the seventh edition of the Union for International Cancer Control (UICC) classification were included (14). Pre-treatment evaluation included: patient history *i.e.* tobacco consumption, comorbidities, pulmonary function testing, radiographic imaging including computed tomography (CT) for all patients and positron-emission tomography (PET)-CT in 94%, routine blood work to assess kidney, liver function and blood cell count.

Tumor histology was obtained *via* transbronchial biopsy in 80 patients, *via* CT-guided-biopsy in nine patients and with mediastinoscopy in 10. Therapeutic approach was discussed in Multidisciplinary Tumor Boards with. Informed consent was given by all patients for evaluation of the acquired data for research purposes. There was Ethical Committee approval for analysis and publishing of the patients' data (approval number: 17-230).

Treatment. Treatment was planned and delivered at one European tertiary cancer center. Three-dimensional (3D) conformal radiotherapy was delivered to the primary tumor and involved lymph nodes to a median total dose of 66 Gy (range=45-70 Gy). Elective nodal irradiation included directly adjacent nodal stations and was delivered to a total dose of 45-54 Gy to 85% of patients. Radiotherapy was delivered on a linear accelerator with megavoltage capability (6-15 MV) using 3D-CRT in 60% of patients and Intensity-modulated radiotherapy in 40% of patients. Image guidance was performed with cone-beam CT two or three times a week.

Patient follow-up. Local and locoregional progression and new distant metastases were documented with CT, PET-CT and magnetic resonance imaging scans. For the first 2 years after therapy, all patients underwent CT or PET-CT scans, routine blood work, lung-function testing and clinical examination every 3 months, and afterwards twice a year. Event-free survival was calculated from the first day of radiation therapy.

Statistical analysis. All statistics were performed with IBM SPSS version 25 (IBM, Armonk, NY, USA). Survival curves were calculated with the Kaplan–Meier method and log-rank test (univariate analysis). Factors showing a significantly negative association with patient prognosis ($p<0.05$) were included in multivariate analysis using Cox regression.

Results

A summary of patient and tumor characteristics is shown in Table I. The median survival was 20.8 months (range=15.3-26.2 months) in the entire patient cohort. Squamous cell carcinoma was diagnosed in 42% of patients, adenocarcinoma in 50% and not otherwise specified in 8% at initial diagnosis. The majority of patients were male (63%) and the median age at diagnosis was 67.4 years (range=43-88 years). Overall, 56% of all patients had NSCLC stage IIIB according to the UICC (seventh edition). Patients were mostly diagnosed with T-stage 3 (30%) or 4 (40%) and N-stage 2 (36%) or 3 (45%). The majority of all patients (78%) received concurrent CRT. The predominant concurrent chemotherapy regimen consisted of cisplatin given intravenously at a dose of 20 mg/m^2 on days 1-4 and oral vinorelbine (Navelbine) 50 mg/m^2 on days 1, 8, and 15, every 4 weeks for two courses (46% of patients).

Patients with an initial ECOG PS 0 had a median OS of 26.4 months and an 1- and 2-year survival rate of 85% and 53% compared to patients with an ECOG PS 1 with a median OS of 18.9 months an 1- and 2-year survival rate of 69% and 37% ($p=0.1$, log-rank test) (see Table II). At the first follow-up after multimodal treatment, 34% of all patients had ECOG PS 0, 46% ECOG PS 1, 18% ECOG PS 2 and 2% ECOG PS 3. Median OS, 1- and 2-year survival rates were: 40.3 months, 88% and 64% in patients with ECOG PS 0 at the first follow-up; 19.3 months, 82% and 40% for ECOG PS 1; 11.9 months, 50% and 28% for ECOG PS 2; and 7.6 months, 0% and 0% for ECOG PS 3 ($p<0.001$, log-rank test), respectively. Decline of ECOG PS after multimodal treatment had a negative prognostic impact on OS in patients with initial ECOG PS 0 [median OS 19.1 *vs.* 31.4 months ($p=0.005$, log-rank test)] and 1 [median OS 22.9 *vs.* 11.1 months ($p=0.001$, log-rank test)]. In the multivariate analysis, male gender (hazard ratio=1.964; 95% confidence interval=1.201-3.211; $p=0.007$) and ECOG PS after treatment (hazard ratio=1.67, 95% confidence interval=1.082-2.577; $p=0.021$) achieved significance. Median EFS according to ECOG PS 0, 1, 2 and 3 was 9.6, 9.0, 7.9 and 3.5 months at the first follow-up ($p=0.018$, log-rank test). Deterioration of ECOG PS after CRT resulted in reduced EFS (median time 9.4 *vs.* 7.7 months, $p=0.049$, log-rank test). No factor achieved significance in the multivariate analysis for EFS.

Discussion

Management of inoperable stage III NSCLC is very heterogeneous and may include different treatment modalities such as chemotherapy, locoregional thoracic irradiation, concurrent CRT, immunotherapy, targeted therapy and best supportive care depending on the performance status patient's (3, 4). As a result of the PACIFIC trial, concurrent platinum-based CRT followed by consolidation PD-L1 inhibition for over 1 year represents the actual standard of care for patients with inoperable stage III with good initial performance status (13).

In the real-life setting, not all patients will be able to tolerate and successfully complete such an intensified multimodal approach. In this situation, clinicians need to assess the suitability for the defined treatment approach continuously. Since their development 50 years ago, the KPS and ECOG PS have been established as standard simple assessment tools to determine the patient functional status

Table I. *Patient- and tumor-related characteristics.*

Characteristic	Patients, n (%)	Initial ECOG PS, n (%)	
		0	1
Age			
≤65 Years	39 (39%)	26 (67)	12 (31)
>65 Years	60 (61%)	21 (35)	39 (65)
Gender			
Female	37 (37%)	24 (65)	13 (35)
Male	62 (63%)	23 (37)	38 (61)
T-Stage			
1-2	28 (28%)	13 (46)	15 (54)
3-4	69 (70%)	32 (46)	36 (52)
N-Stage			
0-1	19 (19)	7 (37)	12 (63)
2-3	80 (81%)	40 (50)	39 (49)
UICC stage			
IIIA	44 (44%)	17 (39)	27 (61)
IIIB	55 (56%)	30 (55)	24 (44)
Histology			
Squamous cell carcinoma	42 (42%)	16 (38)	25 (60)
Adenocarcinoma	49 (50%)	28 (57)	21 (43)
Not otherwise specified	8 (8%)	3 (38)	5 (63)
Tobacco consumption			
≤40 Pack years	57 (58%)	31 (54)	25 (44)
>40 Pack years	42 (42%)	16 (38)	26 (62)
Radiation dose			
≤60 Gy	34 (34%)	12 (35)	22 (65)
>60 Gy	65 (66%)	35 (54)	29 (45)
ECOG PS after treatment			
0	33 (33%)	30 (91)	3 (9)
1	45 (46%)	14 (31)	31 (69)
2	18 (18%)	3 (17)	15 (83)
3	2 (2%)	0 (0)	2 (100)

ECOG PS: Eastern Cooperative Oncology Group performance score; UICC: Union for International Cancer Control.

Table II. *Univariate analysis of overall survival.*

Characteristic	Overall survival		*p*-Value
	At 12 months (%)	At 36 months (%)	
Age			
≤65 Years	69	36	
>65 Years	80	28	0.348
Gender			
Female	87	48	
Male	70	22	0.007
UICC stage			
IIIA	77	40	
IIIB	75	25	0.23
ECOG PS before treatment			
0	85	36	
1	69	28	0.108
ECOG PS after treatment			
0	88	55	
1	82	22	
2	50	17	
3	0	0	<0.001
ECOG PS change			
Stable	84	40	
Increase	62	12	<0.001

ECOG PS: Eastern Cooperative Oncology Group performance score; UICC: Union for International Cancer Control.

(15, 16). KPS and ECOG PS have been shown to be correlated with response and tolerability to oncological treatment modalities, (overall) survival, and quality of life (8, 10, 17, 18). Assessing the patient's general condition with KPS or ECOG PS also has several limitations which need to be considered *e.g.* high interobserver variability and subjective scoring. Interestingly, according to the results of Buccheri *et al.*, KPS showed less ability than ECOG PS to discriminate patients with different prognoses and therefore they recommended the usage of ECOG PS over KPS (19). Despite limitations, important clinical decisions are based on these performance scores, including a definition of personalized therapeutic approach and follow-up intensity as well as eligibility for clinical trials. A poor performance status is associated with increased risk for treatment-related toxicity and poor oncological outcomes compared to patients with better performance status (20). In our study, patients with an initial ECOG 0 showed an improved median survival of 26.4 months compared to patients with ECOG PS 1 with 18.9 months. After the administered CRT, the performance status differed widely from ECOG PS 0 (34%), 1 (46%), 2 (18%) to 3 (2% of all patients). This important finding might be explained by the acute side-effects of the administered multimodal treatment, individual patient ability to recover, and through the course of treated cancer (non-response *vs.* response to applied therapy). The majority of patients benefit during CRT due to effective symptom and tumor control. Based on treatment response, some patients experienced a significant improvement of their initial performance status.

The principal finding of the present study was that ECOG PS at the first follow-up after CRT was highly correlated with the median survival duration ($p<0.001$). ECOG PS decline after multimodal treatment appears to be strong negative prognostic factor for OS in patients with initial ECOG PS of 0-1. Moreover, EFS was not affected by ECOG PS before multimodal treatment but was significantly impaired by decline of ECOG PS after CRT, with median time of 9.4 *vs.* 7.7 months, respectively.

Several limitations of this study must be considered, such as the retrospective nature and, therefore, a risk of including hidden selection biases. Accurate scoring of

performance status is of critical importance because decision-making needs to be based on its correct assessment, including the eligibility for and planning of clinical trials and allocation of healthcare resources such as palliative care. In our study, ECOG PS was scored by experienced radiation oncologists. However, we were unable to evaluate interobserver variability. Therefore, future studies need to prospectively confirm our findings and assess interobserver variations.

Conclusion

In inoperable stage III NSCLC, despite the prognostic value of the ECOG PS before multimodal treatment, ECOG PS after completion of CRT as well as its change during treatment application have a strong prognostic impact on patient OS and EFS.

Conflicts of Interest

The Authors have declared that there are no conflicts of interest with regard to this work.

Authors' Contributions

L.K., J.T., C.E., O.R., M.D., K.G., M.K., O.P., A.T., C.B. and F.M. contributed to the design and implementation of the research, L.K., J.T., C.E. and O.R. to the analysis of the results and L.K., J.T., C.E., O.R., and F.M. to the writing of the article.

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