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Absence of $CD4^+$ and $CD8^+$ T cell expansion after primary multimodal treatment predicts early progression in inoperable stage III NSCLC.

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Background: There are no blood-based biomarkers for survival prediction in inoperable stage III NSCLC patients. We propose a method for calculation of novel area under curve (AUC) biomarkers of the dynamic change of multiple leukocyte subpopulations before, during, and after thoracic irradiation (TRT), chemoradiotherapy (CRT), and chemo-radio-immunotherapy (CRT-ICI) in this patient cohort. The extracted biomarkers identify patients with early progression after TRT. **Methods:** 20 patients (17 male, 3 female), at median age of 65.5 years (range 34 to 79) were enrolled in the study. The median follow-up time was 60 weeks. Eleven patients suffered from adenocarcinoma, 8 squamous cell carcinoma, and 1 undifferentiated NSCLC. They received TRT (2/20, 10%), CRT (11/20, 55%), or CRT-ICI (7/20, 35%). One patient (1/20, 5%) withdrew consent and was excluded from analysis. Primary endpoints were progression free survival (PFS) at 6 and 12 months. Patient blood was analyzed via flow cytometry for 7 circulating leukocyte populations at baseline, twice during radiotherapy, at the end of radiotherapy (RTend), and 10, 20, 35, 48, and 60 weeks after enrollment. We analyzed $CD3^+$ total T cells, $CD4^+$ T cells, $CD8^+$ T cells, CD19+/$CD20^+$ B cells, $CD3^-CD56^+$ NK cells, CD56 bright NK cells, and CD56 dim NK cells. Here, we report on $CD4^+$ and $CD8^+$ T cells. The AUC from RTend to zenith of absolute cell counts provided aggregate measures for the time-course data. We performed hierarchical clustering and cluster characterization. Relevant features were selected by stepwise drop-out. **Results:** Clustering of the AUC between RTend and zenith for $CD4^+$ T cells and $CD8^+$ T cells delineated two prognostic groups. The favorable group was characterized by higher AUC values for $CD4^+$ and $CD8^+$ T cells compared to the unfavorable group. All patients (9/9, 100%) in the favorable group versus 36.4% (4/11) patients in the unfavorable group were progression-free at 6 months (Fisher's exact test, two-tailed: p-value = 0.00472). This effect was observed as a trend with PFS at 12 months. Here 66.6% (6/9) of patients had PFS at 12 months in the favorable group versus 27.3% (3/11) in the unfavorable group (Fisher's exact test, two-tailed: p-value = 0.175). There is a directly proportional relationship of the reported AUC values to PFS at 6 months and 12 months. **Conclusions:** Patients who responded with T cell expansion after immunogenic cell death by TRT, CRT, or CRT-ICI had significantly longer PFS compared to those without increase. Longitudinal monitoring of $CD4^+$ and $CD8^+$ T cells and the AUC from RTend to zenith is a promising biomarker for detecting early progression in the present study which is the subject of validation in an ongoing prospective study (PRECISION, NCT05027165). Research Sponsor: None.