

PhD THESIS SUMMARY

THE IMPACT OF HISTOPATHOLOGICAL SUBTYPES OF LUNG CANCER ON THE VARIATIONS OF THE SYSTEMIC INFLAMMATORY RESPONSE AND SARCOPENIC CHANGES IN BRONCHOPULMONARY TUMOURS

PhD student: Mărginean (Mariean) Claudia-Raluca

Scientific supervisor: Prof. Univ. Dr. Ovidiu S. Cotoi

Lung cancer remains the leading cause of death among both men and women worldwide, with patients often being diagnosed in advanced stages of the disease, when the prognosis is poor and the survival rate is much reduced.

The pathophysiology of bronchopulmonary carcinogenesis is a complex one, often finding local and systemic inflammatory changes, as well as sarcopenic changes, as an integral part of the phenomenon of cachexia associated with malignancy. In addition, the different histopathological subtypes of lung cancer have individual characteristics, which impact the metabolism and bioactivation of the therapeutic regimens administered. Therefore, it is necessary to identify early those neoplastic patients with associated inflammatory and sarcopenic changes, as they present a higher severity of the disease and the risk of developing side effects related to the therapeutic regimens more frequently.

The present doctoral thesis aimed to evaluate the systemic inflammatory response by determining nine cost-effective biomarkers, derived from the analysis of the Complete Blood Count, an investigation routinely performed in clinical practice. The assessed inflammatory biomarkers were the following: eosinophil-neutrophil ratio (ENR); neutrophil-to-lymphocyte ratio (NLR); derived-neutrophil-to-lymphocyte ratio (d-NLR); eosinophil-to-monocyte ratio (EMR); monocyte-to-lymphocyte ratio (MLR); platelet-to-lymphocyte ratio (PLR); Systemic Inflammatory Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISi), and Systemic Inflammatory Index (SII). The identification of sarcopenic changes was performed using Computer-Tomographic examinations, which quantified the skeletal muscle area at the level of the anatomical reference region, lumbar vertebra 3 (L3).

The present work aimed to deepen the relationship between inflammatory and sarcopenic changes, as well as the histopathological findings and TNM staging of the bronchopulmonary tumours. In this regard, the last part of the doctoral research focused on integrating these four essential characteristics of the tumour microenvironment with the biological status of the patient into a common score called HISLIS: Histology, Sarcopenia, and Lung Inflammation Score. The study focused on the relationship between the histopathological type and the TNM stage of the primary tumor, along with the associated inflammatory and sarcopenic changes, aiming to guide the early identification and personalization of therapy for patients with increased disease severity.

The present research was structured in four extensive studies.

The first study was conducted in the form of a narrative review of the literature, focused on deepening the inflammatory and sarcopenic changes associated with a diagnosis of malignancy and on integrating them into the phenomenon of cachexia, often found in patients with bronchopulmonary cancer.

Studies number two and number three were interlinked, as they focused on tracking the main inflammatory changes found among patients with bronchopulmonary cancer and identifying specific markers of disease severity, with a key characteristic being the tumors' histopathological subtype. The results of study two provided valuable scientific information, confirming the intensification of the systemic inflammatory response as the TNM stage advanced. In this regard, we observed that in patients diagnosed in stage III, ENR ($p = 0.002$), EMR ($p = 0.006$), AISI ($p = 0.017$), eosinophil count ($p < 0.001$), and platelet count ($p = 0.022$) showed statistically significant differences between the different histological subtypes. In patients diagnosed in stage IV, AISI ($p = 0.032$), SIRI ($p = 0.036$), and SII ($p = 0.041$) varied significantly between histological subtypes. AISI and SII have the highest levels in patients with adenosquamous carcinoma and the lowest levels in those with adenocarcinoma. In addition, SIRI was highest in patients with NSCLC-NOS and adenosquamous carcinoma and lowest in patients with SCLC. In addition, the number of eosinophils showed statistically significant variations between the histological subtypes of NSCLC ($p=0.003$), with significantly higher counts in patients with adenosquamous cell carcinoma and adenocarcinoma compared to those with NSCLC-NOS.

The third study primarily focused on identifying independent predictors of severity for the different histopathological subtypes of bronchopulmonary cancer. Therefore, leukocyte counts ($p = 0.01$), neutrophil counts ($p = 0.011$), and male gender ($p = 0.014$) were found to be significant predictors of severity in patients with NSCLC. In contrast, for patients with SCLC, these counts were significantly increased. Male gender ($p = 0.0002$), COPD ($p = 0.0001$), abnormal levels of four cell lines, and seven inflammatory indices were identified as predictors of severity for this category of patients. Subsequently, we observed that previously identified severity predictors also varied between the histopathological subtypes of NSCLC, with more predictors (4 versus 3) found in patients diagnosed with squamous cell carcinoma. These findings are particularly valuable, as the topic of histology in the prognosis of lung cancer is still poorly studied and remains an essential part of carcinogenesis processes. To our knowledge, this was the first study to analyze and correlate nine inflammatory markers derived from blood count analysis with the histological subtype of lung carcinoma, thereby raising awareness of the importance of histology and inflammation in the proper evaluation and management of cancer patients.

The final study of the doctoral research focused on integrating inflammatory and sarcopenic changes with the histopathological type of the tumor and its TNM stage into a new severity score, which has prognostic value: HISLIS: Histology, Sarcopenia, and Lung Inflammation Score. HISLIS could be used as a triage tool to identify cancer patients at high risk of severity from the moment of initial diagnosis. According to HISLIS, patients with an

advanced TNM stage at the time of initial diagnosis, especially those with associated sarcopenia, exhibited the highest levels of disease severity. These were correlated with systemic inflammatory changes, with the strongest correlations found for the following inflammatory markers: PLR, NLR, MLR, and SIRI. HISLIS is the first score of its kind cited in the international literature, representing an essential step for the initial stratification of patients with bronchopulmonary cancer and the personalization of their therapeutic approach, integrating in a single variable the main attributes of the tumor microenvironment and the clinical-biological characteristics of the patient.

Identifying and integrating these essential components into the approach of oncologic patients can be the key to improving the prognosis of patients with bronchopulmonary cancer and advancing personalized medicine.