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DIAGNOSTIC AND THERAPEUTIC DILEMMAS IN LUNG CANCER

PhD THESIS

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Summary:

Publications :

- **Erhan I**., Dumitrache-Rujinski S., Toma C., Bogdan M.A, The role of biomarkers in the management of non-small cell lung cancer. *Pneumologia*, 2018; 67 (4): 161-164

- **Erhan I**., Dumitrache-Rujinski S., Toma C., Bogdan M.A**,** Systemic inflammation, TNM staging and survival in patients with lung cancer. DOI: 10.2478/*pneum-2020-0016* • 69 • 2020 • 81-86

Congress and national/international conferences publications :

- **I. Erhan**, S. Dumitrache-Rujinski, A. Muntean, E. Magheran, M. Alexe, M. Bogdan. "Unusual cause of bronchopleural fistula in a patient with long-term survival after initially inoperable adenosquamous lung carcinoma," poster at the European Pneumology Conference, Pneumo Update, Budapest, June 2015

- **I. Erhan**, S. Dumitrache-Rujinski, D. Zaharia, T. Nanea,, A. Iliesiu, H. Moldovan, D. Leonte, M. Bogdan, "Atypical presentation of a malignant cardiac tumor", 16th World Conference on Long Cancer, September 6-9, 2015 Denver, Colorado

- **I.Erhan**, S.Dumitrache-Rujinski, C.Saon, D.Leonte, M.A Bogdan, "Clinical presentation and atypical diagnostic approach in a lymphoma case", CONFER 2015, December 26-29, 2015, Iasi, Romania, ISSN 2344-5270

- **I. Erhan**, "TNM staging of bronchopulmonary cancer from the perspective of a clinical case", Congress of the Romanian Society of Pneumology, October 5-8, 2016, Poiana Brașov, Romania

- **I.Erhan**, S.Dumitrache-Rujinski, C.Stroescu, C.Toma, M.A Bogdan, "Neutrophil to lymphocyte and Platelet to lymphocyte ratios as markers of systemic inflammation in non-small cell lung cancer", Congress of the Romanian Society of Pneumology, October 5-8, 2016, Poiana Brașov, Romania

- **I.Erhan**, S.Dumitrache-Rujinski, C.Stroescu, M.A Bogdan, "Neutrophil to lymphocyte, Platelet to lymphocyte ratios and systemic inflammation in lung cancer stages ", 17th World Conference on Lung Cancer, December 4-7, 2016, Vienna, Austria

- E. Crișan, A. Croitoru, **I. Erhan**, "Trends of histopathological types of lung cancer diagnosed by bronchoscopy at the Marius Nasta Institute", National Conference of Respiratory Pathophysiology May 2017, Covasna, Romania

- **I. Erhan**, S. Dumitrache-Rujinski, C. Toma, M. Bogdan, „ Neutrophil to lymphocyte, Platelet to lymphocyte ratios as markers of lung cancer associated inflammation and their potential prognostic value", Congress of the Romanian Society of Pneumology , October 31- November 3, 2018, Poiana Brașov, Romani

ABBREVIATION

A

ADK : adenocarcinoma
AIS : adenocarcinoma in situ
ALK : anaplastic lymphoma kinase

B

BRAF- B-Raf proto-oncogene, serine/threonine kinase

C

CGA-Comprehensive Geriatric Assessment
CK-5/6/7- cytokeratin 5/6
COPD: chronic obstructive pulmonary disease
CT computerized tomography

E

EBUS-TBNA : endoscopic bronchial ultrasound – treansbronchial needle aspiration
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
ESR: erythrocyte sedimentation rate
ESMO: European Society for Medical Oncology
EUS: endoscopic ultrasound
EVALI: E-cigarette or Vaping Use-Associated Lung Injury

F

FIA: atrial fibrillation

G

GDNF: Glial Cell LineDerived neurotrophic factor

H

HIV: Human Immunodeficiency Virus
HP: histopathology
HTA: arterial hypertension

I

IARC: International Agency for Research on Cancer
ICAM-1: Intercellular Adhesion Molecule 1
CHF: congestive heart failure
IDR la PPD: intradermoreacție la derivat proteic purificat (tuberculină)
IHC: immunohistochemical examination
H: height
IL-6: interleukin 6
BMI: body mass index
IRM: imagistică prin rezonanță magnetică

K

Ki 67: indice de proliferare celulară
KRAS: Kirsten rat sarcoma virus gene

L

LBA: lavaj bronhoallveolar
LCC: carcinom pulmonar cu celulă mare
LCNEC: carcinom neuroendocrin cu celulă mare
LDCT: Low Dose CT scan (CT cu doză scăzută de radiații)
Ly: limfocite
LSD: lob superior drept
LSS: lob superior stang

M

MAPK/ERK: mitogen-activated protein kinases/ extracellular signal-regulated kinases

MEF50: debit expirator maxim instantaneu la 50% din capacitatea vitală
MIA: adenocarcinom minim invaziv

N

NAT2: Arylamin N-acetiltranzferaza
NCCN: National Comprehensive Cancer Network
NCAM-1: moleculă de adeziune a celulelor neurale
Nd:YAG: neodymium-doped yttrium aluminium garnet
NF- kb: factor de transcripție nucleară
NLST: National Lung Screening Trial
Ne: neutrofile
NELSON-Nederlands: Leuvens Longkanker Screenings Onderzoe
Ne/Ly: raport neutrofile/limfocite
NK: celule natural killer
NLR: Neutrophil-Lymphocyte Ratio
NSCLC: Non Small Cell Lung Cancer (cancer pulmonar nonmicrocelular)

O

OS: overall survival

P

PD-L1 : Programmed cell death-protein1ligand
PD-1: Programmed cell death-protein1
PET- CT: Tomografia cu Emisie de Pozitroni (PET) și Computer Tomografia (CT)
PFS: progression free survival
PLR: platelet-lymphocyte ratio
PS: performance status

R

RCRI: recalibrated thoracic revised cardiac risk index
RT: radiotherapy

S

SCIS- squamous carcinoma in situ
SCLC : Small Cell Lung Cancer (carcinom microcelular)

T

TTF-1- thyroid transcription factor

W

WHO: World Health Organisation

Introduction

Lung cancer is still the most diagnosed neoplasm worldwide, due to increased incidence of smoking in general population. There are also additional factors contributing to lung cancer development, such as environmental, professional and domiciliary pollution.

It remains the leading cause of cancer mortality worldwide, despite the advances in the recent years that have led to the diversification of diagnostic and treatment methods, with limited 5-year survival rate (approximately 18%).

There are data in the literature that attest the existence of systemic inflammation in patients with lung cancer, independent of the presence of comorbidities generally associated with smoking (COPD, cardiovascular diseases). This seems to be related to the degree of extension and invasiveness of the disease (staging), with impact on treatment response.

The assessment of systemic inflammation associated with lung cancer can have contributions to fundamental research and, also, implications in the therapeutic decision with a direct impact on patient survival.

The discussion of the case of the patient diagnosed with pulmonary cancer in a multidisciplinary team (pulmonologist, thoracic surgeon, oncologist/palliative care, radiotherapist, radiologist and anatomopathologist) has an important role in the diagnostic and therapeutic approach, the main objectives of the multidisciplinary approach being the choice of the most suitable diagnostic methods, improving pre-therapeutic assessment, optimizing and personalizing treatment in accordance with treatment guideline updates, extent of disease and patient performance status, with the ultimate goal of improving patient prognosis.

The present publication aims *to study the relationship that could exist between systemic inflammation, assessed by accessible biomarkers and disease staging, certain histopathological subtypes and performance status of lung cancer patients.*

It also has as a secondary aim: *case discussion in a multidisciplinary team and its impact on changing the diagnostic/therapeutic decision of the physician.*

1. GENERAL APPROACH

1.1 Lung cancer (Epidemiology and risk factors)

1.1.1 General epidemiological data

Epidemiological data from 2018, according to the GLOBOCAN database managed by the International Agency for Research on Cancer (IARC), places lung cancer as the most frequently diagnosed neoplasia, worldwide registering approximately 2.1 million new cases, 11.6% of all newly diagnosed cancer cases. (1), (2), (3)

It represents the main cause of cancer related death with approximately 1.8 million deaths registered in 2018 (18.4% of all deaths caused by cancer). (1), (2)

In Europe, it ranked third after breast and colorectal cancer in terms of the number of new cases (about 471,000, 11.1%) and it was the leading cause of cancer death in men and the second cause in women, after breast cancer. (1), (2)

In Romania, the global trend of new cases and cancer mortality can be found, with lung cancer being the most diagnosed neoplasia (in 2018: 11,340 new cases, representing 13.6% of the total number of new cases) and also the first cause of cancer related death (10,277 deaths, 20.2% of all deaths in 2018).). (1)

1.1.2 Epidemiological particularities in special population categories

1.1.2.1 Lung cancer in women

GLOBOCAN 2018 epidemiological data ranks this neoplasia as the second leading cause of cancer related death in women, after breast cancer.

Particularities of lung cancer in women:

- adenocarcinoma, the most common histopathological type of lung cancer both in smoking women (vs squamous cell carcinoma in smoking men) and non-smokers (20-30% of non-small cancers, even up to 80% in the Asian population), in the latter category , the prevalence of gene alterations (EGFR gene mutation, ALK translocation) amenable to targeted molecular therapy being much higher
- higher frequency in women of adenocarcinoma with lepidic pattern

- higher incidence rate of lung cancer in non-smoking women compared to non-smoking men (the same was not found for smoking women) (4)
- higher survival rate and better prognosis in non-small cell lung cancer (NSCLC) in women, regardless of disease stage or histopathological type. (5), (6)

1.1.2.2 Lung cancer in young people

Lung cancer is considered a relatively rare in young people, the percentage of those younger than 45 years at the time of diagnosis being between 1 and 3.5%. (7), (8)

Genetic predisposition, family history (risk between 3 and 7 times higher in those aged < 46 years and parents or first-degree relatives diagnosed with lung cancer) and smoking (pack-years, age of onset) are the main incriminated risk factors. (9)

Adenocarcinoma appears to be the most common histopathological type diagnosed in young adults (45-48% vs 11-13% squamous cell carcinoma), possibly due to lower smoking rates and lower prevalence of smoking among young compared to older adults. Approximately ½ of the cases (40-55%) have the EGFR gene mutation, and 1/3 of the cases (27-34%) the ALK translocation, with a direct impact on prognosis and survival. (8), (10)

1.1.2.3 Lung cancer in the elderly

According to epidemiological data, lung cancer is a neoplasia frequently diagnosed in the elderly, also having the highest mortality rate. (11)

Non-microcellular cancer represents approximately 85% of the number of lung cancer cases in the elderly, the average age of patients at diagnosis being 70 years. (12), (11)

The most frequently diagnosed histopathological type is epidermoid carcinoma, unlike young people in whom adenocarcinoma predominates.

In elderly patients, the therapeutic decision requires a multidisciplinary approach, with a complex assessment (The Comprehensive Geriatric Assessment (CGA)), the performance status alone having no significance/prognostic value. In this way, the risk of dying from cancer or due to age and/or comorbidities is assessed, determining the patients eligible for treatment with the oncology visa or for palliative care. (11)

1.1.2.4 Risk factors

Smoking, genetic predisposition, exposure to asbestos, other chemical compounds (nickel, chromium, silicon dioxide, polycyclic aromatic hydrocarbons) or ionizing radiation/radioactive compounds, environmental and domestic pollution, as well as certain structural lung diseases (COPD, pulmonary fibrosis, fibrous lesions) represent risk factors involved in the prevention of lung cancer.

The main risk factor shown to be responsible for both non-small cell and small cell lung cancer is smoking.

It has been found that approximately 85-90% of lung cancers are caused by smoking, with a smoker's risk of developing lung cancer being 30 times greater than a non-smoker's, closely related to the duration and amount of smoking. (13) Smokers with a pack-years index ≥10PA had a significant increase in the number of lung cancer deaths compared to non-smokers.

Replacing cigarette smoking with electronic cigarette devices, Iqos, recommended by some authors as part of smoking cessation, may be associated with immediate or medium-term risks, such as the development of EVALI (e-cigarette or vaping product use associated lung injury) and there is currently no consistent data on the impact of long-term use of these devices. (14)

Passive smoking appears to roughly double the risk of lung cancer, with the molecular profile of the cancer being more similar to that of nonsmokers than to that of smokers. (13)

There is also the notion of third-hand smoking, which involves the inhalation of toxic products resulting from the combustion of tobacco, which have become impregnated in the materials of the space where smoking was done (rooms, cars, hair, clothes, etc.) and which have been associated with an increased incidence of lung cancer.

1.2 Lung cancer screening

The 5-year survival of patients with localized stage lung cancer has been quoted as 59%, so the effort to diagnose early, before the onset of symptoms, through a screening program and treat this category of patients may increase significantly the rate of therapeutic success, reducing cancer mortality by approximately 20%. (15), (16)

Conventional methods such as sputum cytology or standard chest radiography have not proven useful in early detection of lung cancer in high-risk individuals, in contrast to low-dose chest CT examination (uses ~10-30 % of the radiation dose applied to the native CT examination), considered a highly sensitive diagnostic method. (16)

1.3 Diagnosis of lung cancer

The diagnosis of lung cancer can be established, before the patient becomes symptomatic, and can be achieved in two situations: the result of screening by performing chest CT with a low dose of radiation among people considered to be at high risk of developing lung cancer (see 1.2) or incidental finding during imaging evaluation (chest radiography/chest CT) for another associated pathology.

Of all patients diagnosed with lung cancer, only a small proportion, between 5% and 15%, are asymptomatic at the time of diagnosis, the rest having at least one "alarm" symptom (the average being 2-3) due to loco-regional extension, metastasis at a distance or paraneoplastic syndromes, denoting an advanced stage of the disease. (15), (17)

1.3.1 Clinical manifestations of lung cancer

- respiratory, signs and symptoms being due to localization and/or intrathoracic extension (cough, hemoptysis, dyspnoea, chest pain, dysphonia)
- non-respiratory, due to intrathoracic extension (superior vena cava syndrome, Pancoast-Tobias syndrome, dysphonia, dysphagia), extrathoracic secondary determinations (bone, cerebral, hepatic, adrenal, etc.) or paraneoplastic syndromes
- constitutional, suggesting an advanced stage of the disease

1.3.2 Imaging diagnosis in lung cancer

- Standard chest X-ray -diagnostic sensitivity approx. 77-80% (18)
- lung CT scan (native or with contrast substance), main investigation in the diagnosis of lung cancer with the role of guiding in the choice of the appropriate method of histopathological confirmation (bronchoscopy with bronchial biopsy/bronchoalveolar lavage with cytoblock, EBUS, mediastinoscopy, CT-guided transthoracic puncture or echographic, thoracentesis with pleural biopsy, classic surgical biopsy/VATS) as well as contributing to the pre-therapeutic staging of the tumor

- PET-CT, superior to CT scan examination and complementary to mediastinoscopy in the evaluation of mediastinal nodal stations during pre-therapeutic tumor staging. High specificity in identifying distant metastases
- MRI (Nuclear Magnetic Resonance): implication in the quantification of the invasion of the thoracic wall, mediastinum by the tumor or in case of suspicion of liver, epidural or vertebral metastases with algic syndrome/brachial plexalgia. Also, routine investigation for the staging of patients with SCLC, given that approximately 10% of them may have asymptomatic brain secondary determinations. (13)
- Bone scintigraphy, an inexpensive and fairly accurate imaging method in the identification and quantification of bone secondary determinations associated with lung cancer.

1.3.3 TNM staging (Tumor, Nodes, Metastases) of lung cancer

The correct staging of lung cancer at the time of diagnosis using the international TNM system, with assessment of the size and locoregional invasion of the tumor (T), the existence of mediastinal adenopathy (N) and/or intra or extrathoracic metastases (M) is essential for establishing severity, prognosis and stage-appropriate treatment with a view to improving prognosis/survival.

TNM staging of the tumor can be: (45)

- clinical (cTNM), pre-therapeutic, based on data from the clinical examination, imaging, bronchoscopic evaluation, biopsies through minimally invasive/surgical techniques, essential for the selection of the appropriate treatment
- histopathological (pTNM), post-surgical, based on the evaluation of the resection piece, with the establishment of the highest pT and pN categories, but also of the histopathological degree of tumor differentiation, with a role in the decision of adjuvant therapy, the estimation of therapeutic results and the prognosis of the patient It is considered: G1 (well differentiated), G2 (moderately differentiated), G3 (poorly differentiated), G4 (undifferentiated), GX (impossibility of assessing the degree of differentiation)
- *or* it can be address to tumor recurrence, after a disease-free interval (rTNM)
- *or* it can be performed during the patient's autopsy (aTNM)

The novelty of the 8th edition of TNM staging is that it can be used for staging both NSCLC and small cell lung cancer (SCLC) and carcinoid.

Lung cancer stages according to the classification of the 8th edition of the TNM: (45), (19)

Occult Carcinoma	Tx N0M0	
0 Stage	TisN0M0	
IA1	T1mi N0M0 or T1aN0M0	5 Years Survival: **90-92%**
IA2	T1b N0M0	5 Years Survival: **83-85%**
IA3	T1c N0M0	5 Years Survival: **77-80%**
IB	T2a N0M0	5 Years Survival: **68-73%**
IIA	T2b N0M0	5 Years Survival: **60-65%**
IIB	T(1-2) N1M0 or T3 N0M0	5 Years Survival: **53-56%**
IIIA	T(1-2) N2M0 or T3 N1M0 or T4 N0M0	5 Years Survival: **36-41%**
IIIB	T(1-2) N3M0 or T (3-4) N2M0	5 Years Survival: **24-26%**
IIIC	T(3-4) N3M0	5 Years Survival: **12-13%**
IVA	Any T, Any N, M1a,b	5 Years Survival: **10%**
IVB	Any T, Any N, M1c	5 Years Survival: **<1%**

Tab 1.3.3.2 Lung cancer stages

Depending on the extent of the disease at the time of diagnosis, assessed according to TNM staging, it can be localized (stages I and II, without evidence of lymph node involvement: N0), loco-regionally advanced (stages II and III with lymph node involvement: N positive) and advanced -metastatic (corresponding stage IV), with a significant impact on survival at 5 years, this being significantly higher in early stages (61.4%) compared to advanced ones (locoregional: 34.5% or metastatic: 6.1%). (20)

1.3.4 Methods of histopathological diagnosis in lung cancer

The diagnostic methods can be non-surgical or surgical (minimally invasive/ invasive), the main target being the sampling of a biopsy, which will later be processed by histopathological, immunohistochemical and molecular techniques.

1. Fibrobronchoscopy

- Bronchoscopy with autofluorescence

- EBUS-TBNA

- *Radial EBUS*

- *Bronchoscopy with electromagnetic or virtual field navigation,* with a similar diagnostic rate (65%) of lesions with peripheral localization.

- *Bronchoalveolar lavage*

2.Imaging-guided transthoracic biopsy (CT or ultrasound)

3. Thoracentesis

4. Surgical and non-surgical pleural biopsy

5. Mediastinoscopy

6. Surgical biopsy using the VATS technique (Video Assisted Thoracoscopic Surgery)

*7.Biopsy of other lesions suspected of secondary determinations (*echo-guided biopsy of liver/adrenal lesions, bone biopsy puncture, subcutaneous nodule biopsy, superficial adenopathy biopsy, lumbar puncture, pericardiocentesis)

1.3.5 Histopathological and molecular diagnosis of lung cancer

Lung cancer can be divided, depending on the type of tumor cell, into two categories: non-microcellular-NSCLC (adenocarcinoma, squamous carcinoma), predominant (85% of cases) and microcellular (SCLC), with different prognosis and therapeutic valences, but the histological types of lung tumors are much more varied, being systematized in the histological classification of lung tumors, the last edition being launched by the World Health Organization (WHO) in 2015.

One of the most important changes in the latest edition of the WHO classification of lung tumors consists in the reclassification of the histopathological subtypes of lung adenocarcinoma, in accordance with their prognosis and different response to treatment, with the grouping into preinvasive lesions, minimally invasive adenocarcinoma and invasive adenocarcinoma.

Immunohistochemistry, recommended whenever it is available, not only in the case of small biopsy fragments or cytologies but also for resected tumors, the goal being that of a histopathological typing/subtyping as accurate as possible, given the current concept of personalized therapy in lung cancer , but also the different prognosis for each histopathological type.

Molecular diagnosis in non-small cell lung cancer (NSCLC) is useful for the identification of gene mutations of various oncogenes involved in carcinogenesis against which targeted molecular therapies have been developed.

Gene mutations for which there is targeted therapy and recommendation to be tested in all advanced NSCLC cases, especially adenocarcinoma are as follows:

- *Epidermal growth factor receptor mutations: EGFREGFR* (20) (22), (23) (24), (25), (26) (27), (28), (29)

The most common EGFR activating mutations are:

- deletion at the level of exon 19 (EGFR 19-del)
- point substitution of leucine with arginine (L858R) at the level of exon 21 (EGFR 21-L858R)
- these two mutations together represent approximately 85-90% of all EGFR mutations
- mutations of exons 18, 19 and 21, associated with the sensitivity of tumor cells to targeted molecular therapy consisting of tyrosine kinase inhibitors (TKIs)

- *Fusion (rearrangement) of the ALK gene (aplastic lymphoma kinase)*
- *Chromosomal rearrangements of the ROS gene*
- *Mutations of exon 14 of the MET gene*
- *Chromosomal rearrangements of the RET gene*

In conclusion, the current lung cancer treatment guidelines recommend genetic testing for targeted molecular therapy in all cases of non-small cell, non-squamous, metastatic lung cancer, the routinely tested mutations being: EGFR, ALK, ROS1, BRAF, MET ex14 and RET.

Testing for PD-L1 (Programmed cell death-protein1) is also recommended in all cases of metastatic non-small cell cancer (NSCLC), where there is a link between PD-L1 expression on tumor cells (expressed as a percentage score) or PD-1 (receptor expressed by cytotoxic T lymphocytes infiltrating the tumor) and the probability of a favorable clinical response to immunotherapy (PD-L1 (atezolizumab and durvalumab) or PD-1 (nivolumab and pembrolizumab) inhibitory agents).

1.4 Treatment principles in lung cancer

There are three main principles of treatment of non-small cell lung cancer (surgical treatment, systemic therapy and radiotherapy), applied separately or combined with each other, depending on the stage of the tumor:

- ***Surgical treatment,*** addressed especially to non-advanced stages (I and II) of cancer non-small cell lung cancer (NSCLC) provided two important criteria are met: resectability of the tumor and operability of the patient.

Tumor resectability implies the absence of metastases (distant or in the contralateral lung), contralateral or supraclavicular mediastinal adenopathy (N3 histopathologically confirmed), invasion of the recurrent laryngeal nerve, trachea, carina or large vessels.

- ***Systemic therapy (chemotherapy, targeted molecular therapy, immunotherapy)***

Classical chemotherapy, based on various combinations with paltine salts, has a triple therapeutic value:

- *Neoadjuvant chemotherapy* recommended prior to surgical treatment for the purpose of tumor cytoreduction and micrometastases recovery, currently recommended for resectable stage III A (T3-4, N0-1, M0), combined with concurrent radiotherapy in resectable cases of superior trench tumors
- *Adjuvant chemotherapy,* administered after surgical intervention with the aim of <<sterilizing micrometastases>> and reducing relapses, it being known that a large part of patients with complete resection relapse in the first 3 years, and adjuvant chemotherapy reduces mortality by approximately 10%. It is recommended in stages IB, IIA (T2a,b N0) with resection margins not infiltrated by tumor, but with risk factors: low degree of tumor differentiation, vascular invasion, atypical resection or dimensions > 4 cm.
- *Chemotherapy addressed to advanced stages (IIIB, IIIC) or metastatic without mutations*

Targeted molecular therapy (tyrosine kinase inhibitors), recommended as first-line treatment in patients with metastatic NSCLC and identification of "targetable" mutations. (20),

EGFR+	ALK+	ROS1	BRAF	HER2
Osimertinib	Crizotinib	**Crizotinib**	**Dabrafenib+trametinib**	**Capmatinib**
Erlotinib	**Alectinib**	Entrectinib	Dabrafenib	Tepotinib

Gefitinib Afatinib Dacomitinib	Brigatinib Ceritinib		Vemurafenib	

Immunotherapy **-** 1st line of treatment in patients with metastatic squamous or nonsquamous NSCLC, without identified targetable mutations and without contraindications for immunotherapy, with:

-Radiotherapy

- different indications depending on the stage of the disease, the performance status of the patient, operability/resectability of the tumor

As for the treatment of small cell lung cancer (SCLC), it is done according to the limited or extensive stage of the disease.

As for the treatment of small cell lung cancer (SCLC), it is done according to the limited or extensive stage of the disease.

The novelty in the SCLC therapeutic approach consists in the possibility of applying surgical treatment (mandatory in association with extended mediastinal lymphadenectomy) in selected cases of patients with localized disease stages (I, II with cT1N0), reinforced by adjuvant chemotherapy and adjuvant radiotherapy in case of positive resection margins, the most recent studies describe a 5-year survival between 63.8% and 65.5% in the case of operated stages I/II, with a median overall survival of 48.6 months (compared to 28.7 months associated with chemoradiotherapy).). (30)

Palliative care is recommended for patients with an advanced or metastatic stage of lung cancer, most often symptomatic, having the role of supportive therapy aimed mainly at symptom control, preferably to be instituted as early as possible, simultaneously with oncological treatment, as well as for those in the stage end of disease evolution ("end of life"), the main goal being the improvement of the quality of life (and indirectly of survival by reducing morbidity*)*

The role of the multidisciplinary team consisting mainly of pulmonologist, thoracic surgeon, oncologist/ palliative care physician, radiologist, radiation therapist and pathologist is essential in the diagnosis and treatment of lung cancer

A shortening of the time between diagnosis and initiation of treatment was found in lung cancer cases that benefited from a multidisciplinary approach, with an improvement in care and an increase in the patient's quality of life. (31)

Regarding the survival data, the results of the studies are uneven, but most report an increase in survival at 5 years among patients who benefited from a multidisciplinary team discussion, regardless of the cancer stage. (31) (32)

1.5 The role of systemic inflammation in lung cancer

Systemic inflammation, by its inflammatory cells and cytokines, can induce changes in cellular DNA, promoting the carcinogenesis of various neoplasias, including lung cancer. Tumor cells, through the synthesis of pro-inflammatory cytokines and the expression of receptors, determine, in turn, the recruitment of inflammatory cells (neutrophils, dendritic cells, mast cells, eosinophils and lymphocytes) that will contribute to the development of a tumor microenvironment that favors the continuation of the tumorigenesis process (through stimulation of cell growth and proliferation, invasiveness/ ability to metastasize). (33)

There are studies in the specialized literature about the impact of systemic inflammation (via the constellation of cytokines and inflammatory cells) on treatment response and survival in patients diagnosed with lung cancer.

Prognostic value have been attempted for several accessible inflammatory biomarkers such as ESR (erythrocyte sedimentation rate), CRP (C-reactive protein) and, more recently, the neutrophil-to-lymphocyte ratio (NLR) as well as the platelet-to-lymphocyte ratio (PLR), with the aim of assisting the clinician in optimizing the diagnosis and treatment of lung cancer

2 PERSONAL CONTRIBUTION

2.1 Background

Systemic inflammation analyzed by different biomarkers may be involved in the degree of extension, response to treatment and survival of patients with different types of neoplasms, including lung cancer.

The systemic inflammation identified in the patient diagnosed with lung cancer can be in the context of the neoplastic disease and/or the patient's comorbidities (obesity, COPD, pulmonary

fibrosis), and its magnitude can be related to the patient's performance status but also to the staging and progression the disease.

The relationship between systemic inflammation and the degree of extension/staging of lung cancer is less studied, although there are a number of studies in the literature that estimate the prognostic value of different biomarkers of inflammation, including the ratio of neutrophils/lymphocytes and that between platelets and lymphocytes. (34), (35) (36) (37)

2.2 Aim

The main objective of the research consisted in evaluation of systemic inflammation in patients with lung cancer by simple and accessible methods (ESR, the ratio of neutrophils/lymphocytes: Ne/Ly and platelets/lymphocytes: Te/Ly) and the assessment of the relationship between these biomarkers of inflammation and extent of neoplasia (staging).

Secondary objectives:

- evaluation of the relationship between systemic inflammation and the histopathological type of lung cancer
- evaluation of the relationship between performance status and systemic inflammation
- changes of physician initial therapeutic decision after discussion of the case in multidisciplinary team

2.3. Material and Methods

The research is based on a non-interventional retrospective and partially prospective study, including consecutive patients addressed to the IV Pneumology Section of the "Marius Nasta" National Institute of Pneumology Bucharest between 2015-2017 for diagnosis and/or treatment of lung cancer, without oncological treatment (chemo or radiotherapy).

The analyzed data (age, gender, body mass index [BMI], haemogram-derived parameters, leukocyte count, neutrophil count, lymphocyte count, platelet count [NLR and PLR], erythrocyte sedimentation rate: ESR, histopathological type and TNM tumour stage) were obtained from the medical file of the patients. The informed consent signed at admission by patients allows us to use anonymized medical data for research and publication purposes.

The deceased patients were identified using online Integreted Unique Information System (SIUI) of the National Health Insurance House (CNAS), 3 years after diagnoses was established

172 medical files were analyzed, the patients being divided according to the main and secondary aims of the study, into 3 groups:

- **Group A,** 102 patients, analyzed from the point of view of the relationship between systemic inflammation and the degree of extension according to TNM staging. In a subgroup A1of patients 56 patients) was analyzed the relationship between histopathological type of lung cancer, staging and inflammation
- **Group B**, 58 patients, characterized in terms of ECOG performance status and the relationship between performance status and systemic inflammation or other clinical characteristics such as age, smoking history and the presence of comorbidities
- **Group C,** 51 patients which were discussed in multidisciplinary team, analyzing the impact of physician initial therapeutic decision

Statistical analysis

SPSS version 20 was used for the statistical analysis of the data. The results were expressed as mean values ± standard deviation or as an absolute number (percentages).

The Shapiro-Wilk test was used to analyze the distribution of variables.

To compare variables with normal distribution, Student T test was used and a statistically significant difference was considered at a value of $p < 0.05$.

The non-parametric Mann-Whitney U test was used to compare variables with abnormal distribution and a statistically significant difference was considered for a value of $p < 0.05$.

For the analysis of the association relationship between different categorical/qualitative variables, the Chi-square test was used, and the results were considered statistically significant for a value of $p<0.05$.

The results were presented in the form of tables, graphs, schemes.

2.3 **Results and discussions:**

The results obtained from the statistical processing of the database will be presented in detail according to the main and secondary aims of the research in the following 3 sub-chapters.

2.4.1 The relationship between systemic inflammation in patients with lung cancer, evaluated by surrogate biomarkers: the neutrophil/lymphocyte ratio (Ne/Ly), the platelet/lymphocyte ratio (Te/Ly), and the degree of disease extension according to TNM staging, as well as the possible link between inflammation, histopathological type and TNM staging

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Systemic inflammation associated with lung cancer, evaluated through different biomarkers (blood, tissues) seems to have prognostic value in terms of patient survival, most likely in relation to the degree of extension and invasiveness of the disease, favored by the inflammatory context, with an impact on the response to treatment.

The main aim of the research was to analyze the relationship between systemic inflammation in patients with lung cancer (assessed by surrogate biomarkers such as Ne/Ly ratio and the Te/Ly ratio) and the degree of disease extension according to TNM staging, with a subpoint which analyzes the possible connection between inflammation, histopathological type and staging.

172 medical files were analyzed, from which 102 eligible patients were selected, representing subjects of Group A. A number of 56 patients from group A constituted the subjects of subgroup A1.

Group A was divided into two groups, depending on the stage of the disease, according to TNM staging 7th edition (Group AR: resectable patients, respectively Group AN: unresectable patients), each of the two subgroups being later divided into survivors and deceased.

In the table below, are summarized the characteristics of patients included in Group A:

Group A – Characteristics of patients (N=102)	
Age (Years)	65.49 years old ± 9.35
Gender: Number, Procent (%)	Male: 86 (84.31%) Female: 16 (15.69%)
Body Mass Index (kg/m2)	25.45 ± 4.49 (N=94)
Smoker status: number, procent (%)	Smoker: 83 (81.37%) Non-Smoker: 19 (18.63%)
Tobacco Index: Number of Cigarettes Pack	40 [3-100]
Ne /mm^3)	6425 [1800-27892]
Ly (/mm^3)	1855 [500-15700]
Tr (/mm^3)	316500[23000-709000]
Ne/ Ly	3.33 [0.70-25.60]
Tr/Ly	156.75 [3.38-651.25]
ESR (N=94)	40 [3-135]
FEV1 (N=84)	1.98 ± 0.62
FVC (N=68)	2.73 ± 0.77
BPOC: număr, procent (%) (N=68)	26 (38.24%)

Statistic data exposed ± Standard deviation or Mediane Deviation [interval] Ne:Neutrophyles, Ly: Lymphocites, Tr : thrombocites, Ne/Ly: neutrophyle/lymphocyte rapport, Tr/Ly: thrombocytes/lymphpocyites rapport, ESR: Erytrcites Sedimentation Rate, BMI: Body Measure Index, FEV1 – Forces Expiratory Volume, first second measurement assay, FVC: Forced Vital Capacity, COPD: Chronic Obstructive Pulmonary Disease
Tab 2.4.1.1 Group A- Characteristics of patients

From the total of 102 patients with lung neoplasm included in the study, 86 (84.31%) were men, a significantly higher percentage ($X2(1, N=102)=48.04$, $p < .001$) than that of women, who were in number of 16, representing 15.69% similar aspect to data from the literature, one of the explanations being the higher prevalence of smoking among men, but also professional exposure more frequently encountered as a risk factor. (39) .

The average age in the studied group was 65.49 years ± 9.35, similar to the literature data, homogeneously distributed, men and women having close average ages (65.78 years ± 9.61 vs. 63.94 years ± 7 .82, p=0.47)

Most patients declared themselves smokers or ex-smokers, their percentage (81.37%) being significantly higher than that of non-smokers, who represented 18.63% of all patients ($X2(1, N=102)=40.16$, $p< .001$) , according to literature data, smoking being the main risk factor for lung cancer. (13)

Of the total number of smoking patients (no. 83), the majority were male (no. 77), their proportion (92.77%) being significantly higher than that of females (7.23%) ($X2(1, N=83)=60.74$, $p < .001$).

The median value of the smoking index, known as the number of pack-years, in smoking patients was 40 [3-100], higher than the lower limit of 30 PA, required to include patients in screening programs for lung cancer according to certain countries.

Also, the percentage of smoking patients with a smoking index greater than 10 PA, proven to be associated with a significant increase in the number of lung cancer deaths compared to non-smokers, was significantly higher than those with a smoking index < 10 PA (94% vs 6%, $X2(1, N=83)=64.20$, $p< .001$).

From the point of view of the histopathological type, non-small cell lung cancer (NSCLC) predominated, in a proportion of 89.19% (similar to data from the literature that estimates a percentage of 85% for NSCLC), microcell cancer (SCLC) being in a percentage of 10.81% .

Regarding non-small cell lung cancer, the dominant histopathological type was adenocarcinoma, followed by squamous cell carcinoma and other types represented by adenoid cystic carcinoma and pleiomorphic carcinoma, consistent with the upward trend in the incidence of adenocarcinoma in recent decades (since 1990), this histopathological type, becoming the majority since 2004, in both men and women. (42), (43), (44), (45)

The trend of latency in diagnosis of lung cancer, validated by studies, is also found in case of patients included in group A, 69.6% of them being diagnosed with advanced/unresectable disease stage (IIIB, IV) according to TNM staging, a significant percentage statistically higher ($X2(1, N=102)=15.68$, $p< .001$) than those with resectable disease stages (IA,IB, IIA, IIB, IIIA)

To achieve the main objective of the research, **group A** of patients (N=102) was divided into two groups: Group AR consisting of the **31 patients with resectable stages** of lung cancer and Group AN, consisting of the remaining **71 patients with non-resectable stages.**

Regarding the descriptive analysis of the subjects included in the AR Group (N=31), the results are illustrated in the table below:

Age (years)	64.71 years old ± 7.34
Gender: Number, procent (%)	Male: 23 (74.2%), Female: 8 (25.8%)
Body Mass Index (kg/m2)	25.80 ± 4.54
Smoker status: Number, Procent (%)	Smoker: 23 (74.2%), Non-Smoker: 8 (25.8%)
Tobacco Index: Number of Cigarettes Pack (N=23)	43.6 ± 23.22
Ne (/mm^3)	6380 [2600-22000]
Ly (/mm^3)	2000 [1020-13.600]
Tr (/mm^3)	294.000 [111.000-709.000]
Ne/ Ly	**2.74** [0,87-12,94]
Te/Ly	**133.95** [21,61-416,66]
ESR (N=94)	35 [6-135]
Statistic data exposed ± Standard deviation or Mediane Deviation [interval]	
PA: pachete- an, Ne:Neutrofile, Ly: Limfocite, Tr : trombocite, Ne/Ly: raport neutrofile limfocite, Te/Ly: raport trombocite limfocite, VSH: viteza de sedimentare a hematiilor, IMC: Index de Masă Corporală	
Tab 2.4.1.2 Group AR (N=31)	

71 patients with advanced/unresectable stages of lung cancer (IIIB, IV) were included in Group AN, their characteristics being summarized in the table below (Tab. 3.1.3):

Age (years)	65.83 years old ± 10.13

Gender: Number, procent (%)	Male: 63 (88.7%), Female: 8 (11.3%)
Body Mass Index (kg/m2)	25.28 ± 4.48 (N=63)
Smoker status: Nr, procent (%)	Smoker: 60 (84.5%), Non-Smoker: 11 (15.5%)
Tobacco Index: Number of Cigarettes Pack (N=60)	40 [4-90]
Ne (/mm^3)	6450 [1800-27892]
Ly (/mm^3)	1800 [500-15.700]
Tr (/mm^3)	327.000 [23.000-661.000]
Ne/ Ly	**3.51** [0,70-25,60]
Te/Ly	**170.37** [3.38-651.25]
ESR (N=64)	40 [3-120]
Date prezentate ca medie± DS sau ca mediană [interval] PA: pachete- an, Ne:Neutrofile, Ly: Limfocite, Tr: trombocite, Ne/Ly: raport neutrofile limfocite, Te/Ly: raport trombocite limfocite, VSH: viteza de sedimentare a hematiilor, IMC: Index de Masă Corporală	
Tab 2.4.1.3 Group AN (N=71)	

Regarding the comparative analysis of the two groups of patients (AR Group vs AN Group), the following were objectified:

- no statistically significant relationship was found between disease stages (resectable or unresectable) and patients' gender (X2(1,N=102)=3.44, p=0.07). The percentage of men (88.7%) or women (11.3%) of the AN group not being significantly higher than that of the counterparts in the AR group (74.2% and 25.8%)
- no statistically significant relationship was found between disease stages (resectable or non-resectable) and patients' gender, regardless of whether they were smokers (X2(1,N=19)=0.54, p=0.46) or non-smokers (X2(1, N=83)=1.60, p=0.20)
- average age of the subjects of the two groups was similar (65.83 years ± 10.13 in the AN Group vs. 64.71 years ± 7.34 in the AR group), with no statistically significant difference (p=0.58)
- no statistically significant relationship was found between resectable or unresectable disease stages and smoking status, the percentages of smokers and non-smokers in the two groups being similar (X2(1,N=102)=1.51, p=0.21), regardless of whether the subjects were male (X2(1,N=86)=0.22, p=0.63) or female (X2(1,N=16)=0.001, p=1).
- also, there was no statistically significant difference between the value of the smoking index in smokers in the AR group, compared to those in the AN group

For the evaluation of systemic inflammation in patients with lung cancer included in the study, accessible biomarkers were used. Those are neutrophil/lymphocyte ratio (Ne/Ly), the platelet/lymphocyte ratio (Te/Ly), cited in the literature as sensitive determinants in assessing the degree of systemic inflammation in different types of cancer, including lung cancer, as well as erythrocyte sedimentation rate (ESR).

The aim was to characterize the relationship between these biomarkers of inflammation and the extent of neoplasia (TNM staging).

The two groups of patients, with respectively resectable and non-resectable stages of lung cancer (AR Group vs. AN Group), were compared in terms of the level of inflammation and the possible relationship between it and the degree of extension, the results being the following :

- the median value of the Ne/Ly ratio in the AN Group was 3.51 [0.70-25.60], statistically significantly higher (U=823, p=0.043) than the median Ne/Ly ratio in the AR Group, which was 2.74
- the median value of the Te/Ly ratio in the AN Group was 170.37 [3.38-651.25], statistically significantly higher (U=840, p=0.05) than the median Te/Ly ratio in the AR Group, which was 133.95 [21.61 -416.66]
- no statistically significant difference was found between the VSH value, an inflammatory marker used routinely, in the group of patients with resectable stages compared to the group of those with unresectable stages (U=924, p=0.77)

Further, the two groups of patients, AR (resectable stages) and AN (non-resectable stages), were divided into two subgroups according to the status of the patients as survivors or deceased.

- **Ars subgroup** (surviving resectable stage patients): 11 subjects
- **ARd subgroup** (deceased patients with resectable stages): 20 subjects
- **ANs subgroup** (surviving unresectable stage patients): 8 subjects
- **ANd subgroup** (deceased patients with unresectable stages): 63 subjects

The values of inflammation markers for each subgroup are shown in the table below:

	NeLy	TeLy	VSH
Subgroup ARs (N=11)	**2.36** [0.88- 8.36]	**132.58** [41.11- 371.18]	**15** [6-110]

Subgroup Ard (N=20)	**2.77** [1.26-12.94]	**138.82** [21.62- 416.67]	**62** [11-135]
Subgroup ANs (N=8)	**1.53** [1.32- 10.86]	**112.89** [59.69- 554.29]	**31** [9-90]
Subgroup And (N=63)	**3.72** [0.70- 25.60]	**183.50** [3.38- 651.25]	**44** [3-120]

Tab 2.4.1.4 Values of inflammation markers

Within the group with resectable disease stages, no statistically significant difference was found between the value of the two ratios NeLy and TeLy.

Regarding the group of subjects with advanced/non-resectable stages of the disease, the value of the ratio Ne/Ly and Te/Ly was significantly higher in the case of subjects who died (Subgroup ANd) compared to those who survived (Subgroup ANs): p =0.017 for Ne/Ly and p=0.032 for Te/Ly

The median value of the Ne/Ly ratio in the subgroup of patients with advanced disease who died (ANd) was 3.72, similar to data in the literature, with reported pretreatment cut-off values between 3.25 and 5, associated with reduced survival in patients with advanced stages of non-small cell lung cancer.

The median value of the Te/Ly ratio was 183.50, close to the results of a meta-analysis that demonstrated that an increased value of this ratio could be a negative prognostic factor for patients with non-small cell lung cancer. (47)

A subpoint of the analysis performed was to evaluate the relationship between systemic inflammation and the histopathological type of non-small cell lung cancer (NSCLC) as well as the possible link between inflammation, histopathological type and staging in a subset (A1) of 56 patients.

The 56 subjects of subgroup A1 were divided, according to histopathological type, into two groups: NSCLC-ADK (patients with adenocarcinoma) and NSCLC-SC (patients with squamous cell carcinoma), also divided into two subgroups according to resectability of disease stage

The characteristics of the A1 subgroup as well as the two groups resulting from the division of the A1 subgroup patients according to the histopathological type are highlighted in the tables below:

Subgroup A1 (56 pacienți)	
Age (years)	65.83 years old ± 10.13
Gender: Number, procent (%)	Male: 49 (87.5%), Female: 7 (12.5%)
Body Mass Index (kg/m2)	25.70 ± 4.53
Smoker Status: Number, Procent (%)	Smoker: 45 (80.4%), Non-Smoker: 11 (19.6%)
Tobacco Index: Number of Cigarettes Pack (N=45)	40 [3-100]
Ne/ Ly	**3.58** [0.70-20.72]
Te/Ly	**166.25** [3.38-651.25]
ESR	30 [3-120]
Statistic data exposed ± Standard deviation or Mediane Deviation [interval]	
PA: pachete- an, Ne:Neutrofile, Ly: Limfocite, Tr: trombocite, Ne/Ly: raport neutrofile limfocite, Te/Ly: raport trombocite limfocite, VSH: viteza de sedimentare a hematiilor, IMC: Index de Masă Corporală	
Tab 2.4.1.5 Subgroup A1	

Characteristics of pattients with NSCLC- ADK and NSCLC-SC:

	NSCLC-ADK	NSCLC-SC
Age (years)	63.29 years old ± 9.07	64.09 years old ± 9.26
Gender: Number, procent (%)	Bărbați: 30 (88.2%) Femei: 4 (11.8%)	Bărbați: 19 (86.4%), Femei: 3 (13.6%)
Body Mass Index (kg/m2)	25.21 ± 4.49	26.55 ± 4.58
Smoker Status: Number, Procent (%)	Smokers: 27 (79.4%), Non-Smokers: 7 (20.6%)	Smokers: 18 (81.8%), Non-Smokers: 4 (18.2%)
Tobacco Index: Number of Cigarettes Pack (N=45)	38.48± 20.02	41.11± 22.91
Ne/ Ly	**3.94** [0.70-14.67]	**3.56** [1.26-20.72]
Te/Ly	**186.51** [13.82-651.25]	**157.45** [3.38-416.25]
ESR	28 [3-120]	42 [6-110]
Statistic data exposed ± Standard deviation or Mediane Deviation [interval]		
PA: pachete- an, Ne:Neutrofile, Ly: Limfocite, Tr: trombocite, Ne/Ly: raport neutrofile limfocite, Te/Ly: raport trombocite limfocite, VSH: viteza de sedimentare a hematiilor, IMC: Index de Masă Corporală, NSCLC-ADK (Non Small Cell Lung Cancer- Adenocarcinom), NSCLC-SC (Non Small Cell Lung Cancer- Carcinom Scuamos)		

Following the statistical analysis of the data, no statistically significant difference was found in terms of the value of the markers of systemic inflammation, represented by the ratios Ne/Ly (U=368, p=0.920), Te/Ly (U=343, p=0.603) and ESR (U=319.50, p=0.360), in the group of patients with NSCLC-ADK compared to the group of patients with NSCLC-SC

Also, the two groups of patients with adenocarcinoma (NSCLC-ADK) and squamous cell carcinoma (NSCLC-SC), respectively, were divided into two subgroups, depending on disease stages (resectable: NSCLC-ADK-R, NSCLC-SC-R vs non-resectable: NSCLC-ADK-NR, NSCLC-SC-NR) and the possible relationship between inflammation, histopathological type and staging being was assessed.

The values of inflammation markers for each subgroup are shown in the table below:

	NeLy	TeLy	VSH
NSCLC-ADK-R (N=10)	**2.54** [0.88- 6.20]	**128.60** [21.62- 416.67]	**17.50** [10-120]
NSCLC-ADK-NR (N=24)	**5.65** [0.70-14.67]	**215.42** [13.82- 621.25]	**35** [3-120]
NSCLC-SC-R (N=9)	**3.4** [2.01- 8.36]	**151.26** [67.54- 307.84]	**50** [10-110]
NSCLC-SC-NR (N=13)	**3.72** [1.26- 20.72]	**158.47** [3.38- 416.25]	**40** [6-110]

Tab 2.4.1.7 Values of Ne/Ly, Te/ Ly, VSH in all four subgroups of Group A1

The statistical analysis performed on the A1 subgroup of patients revealed that the values of Ne/Ly and respectively Te/Ly do not differ significantly depending on the histopathological type (adenocarcinoma vs squamous carcinoma), in accordance with data from the literature (48), however the values of these ratios are statistically significantly more high in unresectable adenocarcinoma stages compared to resectable ones

In conclusion, systemic inflammation assessed by accessible biomarkers such as neutrophil lymphocyte ratio (Ne/Ly) and platelet lymphocyte ratio (Te/Ly) is more pronounced in advanced, unresectable stages of lung cancer and seems to negatively influence, along with disease stage, prognostic of patients. Consequently, both the neutrophil lymphocyte ratio (Ne/Ly) and the lymphocyte platelet ratio (Te/Ly), simple and accessible methods for evaluating systemic inflammation, could have clinical applicability in the personalized therapeutic decision of patients with advanced stages of lung cancer .

2.4.2 Evaluation of the relationship between performance status (PS) and systemic inflammation

There are studies in the literature that have demonstrated that a high level of systemic inflammation in lung cancer, assessed by different biomarkers (ESR, WBC, PLT, CRP, albumin) is a negative prognostic factor in terms of survival especially in advanced stages of cancer nonmicrocellular lung, comparable in prognostic value to that of performance status PS >2. (49), (50)

Group B consisting of 58 patients who were characterized in terms of performance status (PS) according to the ECOG scale and systemic inflammation (Ne/Ly, Te/Ly, VSH) was the basis of the analysis of the relationship between the status of performance and systemic inflammation in lung cancer.

The characteristics of Study Group B are shown in the table below:

Lotul B (58 pacienți)	
Age (years)	63.50 years old [30-84]
Gender: Number, procent (%)	Male: 47 (81%), Female:11 (19%)
Performance Status (SP) PS=0 PS=1 PS=2 PS=3 PS=4	 5 (8.6%) 30 (51.7%) 12 (20.7%) 9 (15.5%) 2 (3.4%)
Body Mass Index (kg/m2) (N=43)	26.33 ± 6
Smoker Status: Number, Procent (%)	Fumători: 46 (79.3%), Nefumători: 12 (20.7%)
Tobacco Index: Number of Cigarettes Pack (N=46)	39.28 ± 20.84
Comorbidities: Number, Procent (%)	Absent: 11 (19%) Prezent: 47 (81%): • Cardio-metabolic disease (AHT, AFI, ICB, ICC, DM type2): 21 (44.7%) • BPOC: 4 (8.5%) • Cardiometabolic + COPD: 22 (46.8%)
Histopatologycal Type: Procent (%), Number NSCLC-ADK NSCLC-SC SCLC	 31% (18) 24.1% (14) 4% (4)

Carcinom slab diferențiat Others Without confirmed type	27.6% (16) 5.2% (3) 5.2% (3)
Ne/ Ly (N=40)	**3.42** [0.70-15]
Te/Ly (N=40)	**166.25** [3.38-763.33]
VSH (N=49)	30 [1-110]

Group B was divided in two subgroups, depending on the performance status, as follows:

• **Subgroup B-PS [0-2], consisting of 46 patients** considered to have good performance status

• **Subgroup B-PS [3-4], consisting of 12 patients** considered to have low performance status

• The relationship between performance status and systemic inflammation was analyzed by comparing the level of inflammation, assessed by Ne/Ly, Te/Ly ratios in the two subgroups of patients: those with good performance status PS [0-2] and those with low PS performance [3-4], the results being the following:

• The median Te/Ly value in the B-PS [3-4] subgroup was 182.87 [3.38-763.33], higher than the TeLy value in the B-PS [0-2] subgroup (149.42 [13.82-416.67]), but without statistical significance (U=112, p=0.235) (Fig.3.2.1)

2.4.3 Analysis of the impact of the multidisciplinary discussion on the physician's therapeutic decision

In order to study the impact of the multidisciplinary discussion regarding the management of patients with lung cancer, we analyzed a group of 51 patients (Group C) discussed in multidisciplinary team meeting.

The cases of patients with diagnostic difficulties, as well as those questionable from the point of view of staging, resectability or operability, were subjected to multidisciplinary discussion.

As for the initial therapeutic decision of the physician, it underwent changes following the discussion within the multidisciplinary team, in a number of 10, representing 19.6% of the cases, a percentage similar to the data in the literature, there being only a few studies that refer to this

aspect of the multidisciplinary approach to lung cancer: Takeda et al. reporting a percentage of 24.1%, Kee et al. 26%, and Ungg et al. 19%.

Considering the fact that most patients benefited from classic oncological treatment (chemotherapy, RT), targeted therapies based on genetic mutations or immunotherapy in advanced stages, being to a small extent available at the time of the study, two illustrative cases with long survival were presented, in which their discussion within the multidisciplinary team had an important contribution.

2.5 Conclusions

Regarding the main aim of the study which was the evaluation of relationship between systemic inflammation (assessed by the NeLy and TeLy ratio) and lung cancer TNM staging/ histopathological types, statistically significantly higher values were found in the case of patients:

- with non-resectable stages of lung cancer compared to the resectable ones
- deceased compared to survivors for unresectable stages
- deceased compared to survivors for unresectable metastatic stages

Regarding the second aim was found:

- statistically significantly higher values of NeLy, TeLy ratio in unresectable stages of adenocarcinoma compared to resectable ones
- the NeLy ratio value in the subgroup of patients with low performance status was statistically significantly higher in the subgroup of patients with good performance status

• the initial therapeutic decision of the physician was modified in approximately 20% of the cases, following the discussion of cases in multidisciplinary team, a percentage similar to the data in the literature.

In conclusion,, it can be stated that there is a relationship between systemic inflammation associated with lung cancer and the extension of the disease (according to TNM staging), performance status of patients and certain histopathological types.

Consequently, both the neutrophil lymphocyte ratio (Ne/Ly) and the lymphocyte platelet ratio (Te/Ly), simple and accessible methods for evaluating systemic inflammation, could have clinical applicability in the personalized therapeutic decision of patients with advanced stages of lung cancer .

The discussion of patients within the multidisciplinary team has an important contribution in establishing the appropriate diagnostic and a personalized treatment

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