

# Can the Risk of the N Diseases Development be Related to the Degree of Differentiation of Tumor Cells and the Presence of Peritumoral Lymphocytic Infiltration in the Non-Small Cell Lung Cancer

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## Abstract

**Introduction:** Lung cancer is a significant health problem with more than 170,000 new cases diagnosed annually in the United States. The most important factor in the survival of a patient with non-small cell lung cancer is the condition of the mediastinal lymph nodes. The influence of a number of factors on the occurrence of N1 and N2 metastases was investigated, the most common being lung cancer, tumor size and the degree of differentiation of malignancy.

**Patients and Methods:** The study included a sample of 331 patients, of all ages, both genders, with complete resection of proven lung cancer. Surgery was performed under separated general anesthesia, with prior zonal exploration of mediastinal lymph nodes and / or thoracoscopic exploration of the pleural cavity. The peritumoral compartment in which lymphocytic infiltration was sought was defined as the area around the intratumoral compartment that includes the edge of the tumor and a width of 1 mm beyond it<sup>4</sup>.

**Results:** In our sample the most common type of lung cancer was adenocarcinoma, with PTLI being more than 69% of cases. The calculated relative risk of nodal metastases with the presence of PTLI is 35.5. Therefore, there is a 35.5 times higher risk of developing N disease when there is PTLI rather than when there is none.

**Discussion:** PTLI was present in 86 (37.55%) patients with N0 descriptor, 128 (55.89%) patients with N1 descriptor and 15 (6.55%) patients with N2 descriptor. In retrospective presentation of surgical treatment of primary lung cancer by Bačić and authors, a sample of 146 resectates, NO disease was detected in 64.6% of cases, N1 in 21.0% and N2 in 14.4% of resectors<sup>7</sup>.

**Findings:** In the treated sample, the most common type of lung cancer was adenocarcinoma, with PTLI present in more than 69% of cases. It has been shown that there is a 35.5-fold higher risk of developing N disease when there is PTLI than when there is no PTLI.

**Keywords:** lung cancer, surgery, metastases, complications, lymph nodes, prognosis

## INTRODUCTION

Lung cancer is a significant health problem with more than 170,000 new cases diagnosed annually in the United States. About 45% of patients out of this number are confined to the chest, with surgery

still being the most effective method in controlling the disease( ). Therefore, only 25% of lung cancer patients are eligible for surgical treatment (stage I and II, selected IIIa, and only exceptionally IIIb and IV - eg, solid brain metastasis). The TNM system

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(The International Staging System for Lung Cancer (ISSLC)) is also used to evaluate the anatomical prevalence of cancer, which is also the best survival indicator. It serves as an international language for modifying clinician information and is a guide in the choice of therapy. N descriptor is of the interest to this paper. The most important factor in the survival of a patient with non-small cell lung cancer is the condition of the mediastinal lymph nodes. An analysis of the international IASLC database shows that the pre-existing N descriptor provides relevant survival stratification and is retained in the new 8th classification. The incidence of N1 and N2 metastases with respect to the presence of lymphovascular peritumoral infiltration and tumor grade in bronchial cancer are some of the under-researched data that can provide the clinician with valuable guidance on aggression, disease spread, prognosis, and treatment. The influence of a number of factors on the occurrence of N1 and N2 metastases was investigated, the most common being lung cancer, tumor size and the degree of differentiation of malignancy.

Only 25% of patients with lung cancer are suitable for surgical treatment (stage I and II, selected IIIa, and only exceptionally IIIb). The TNM system (The International Staging System for Lung Cancer (ISSLC)) is also used to evaluate the anatomical prevalence of cancer, which is also the best survival indicator. An analysis of the international IASLC database shows that the pre-existing N descriptor provides relevant survival stratification which is retained in the latest ISSLC classification<sup>1</sup>. Assessment of lymph node status can be done by examining only those lymph nodes that are associated with the resection specimen, taking biopsy specimens from only those lymph nodes that appear pathologically altered, systematic biopsy of each lymph node, and complete dissection of mediastinal lymph nodes<sup>2,3</sup>. The incidence of N1 and N2 metastases with respect to the presence of peritumoral lymphatic infiltration<sup>4</sup> and tumor grade in lung cancer are some of the under-researched data that can provide clinicians with valuable guidance on aggression, disease spread, prognosis, and treatment<sup>5</sup>.

### THE AIM OF THE STUDY

The aim of this study is to attempt to determine the association between the degree of differentiation of tumor cells (G stage) and the presence of peritumoral

lymphatic infiltration (PTLI) with the occurrence of N1 and N2 metastases in non-microcellular lung cancer.

### PATIENTS AND METHOD OF WORK

The study included a sample of 331 patients, of all ages, both genders, with complete resection of proven lung cancer. Preoperative diagnostic protocol contained at least a CT scan of thoracic and upper abdominal organs in a contrast series with determination of cTNM stage of the disease, bronchoscopy with biopsies, some of which were performed transthoracic, pathohistological, cytological and immunohistochemical analyzes, verification of lung status functionality for planned resection level, and cardiac evaluation of the possibility of introducing the patient to general anesthesia.

Surgery was performed under separated general anesthesia, with prior zonal exploration of mediastinal lymph nodes and/or thoroscopic exploration of the pleural cavum. In addition to resection of the pulmonary parenchyma with the tumor, enlarged lymph nodes were dissected.

Within the histopathologic examination in HE (hematoxylin and eosin) staining, particular attention has been paid to the presence of PTLI, the degree of tumor differentiation, and metastases in the hilar and mediastinal lymph nodes. The peritumoral compartment in which lymphocytic infiltration was sought was defined as the area around the intratumoral compartment that includes the edge of the tumor and a width of 1 mm beyond it<sup>4</sup>.

PTLI status data were marked as PTLI + (peritumoral lymphatic infiltration found) and PTLVI - (peritumoral lymphatic infiltration not found). The classification of tumor cell immaturity is indicated by the scale: well-differentiated tumor cells (G1 immaturity), medium differentiated (G2 immaturity), poorly differentiated (G3 immaturity).

### STATISTICAL ANALYSIS

The obtained data were processed by standard statistical methods, using the SPSS computer program for statistical analyzes (SPSS-Statistical Package for Social Sciences) version 21.0. The results are expressed as absolute numbers (N) and percentage values. Spearman's rank correlation coefficient was used to evaluate the association between the degree of differentiation of tumors and metastases into regional

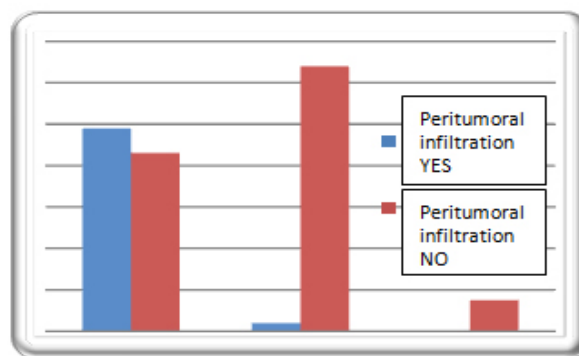
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lymph nodes, as well as the relationship between PTLI and metastases to regional lymph nodes. Direct logistic regression was used to evaluate the impact of PTLI and the degree of tumor differentiation as independent variables on metastases to regional lymph nodes as a dependent variable (negative outcome). In the analysis of the dependence between the categorical variables, the value of  $p < 0.05$  was taken as statistically significant.

**Table 1.** Patients and cancer characteristics.

Characteristics		p - value
Gender		
Male	257 (77,64%)	< 0,005
Female	74 (22,36%)	
Age average (years)	62,69±7,46 (cover 21 – 86years)	
Hystological type		
Adenocarcinoma	182 (55%)	< 0,0001
Squamocellular carcinoma	140 (42,3%)	
Large cell carcinoma	9 (2,7%)	
Peritumoral lymphocytic infiltration (PTLI)		
Present	229 (69,18%)	
Absent	102 (30,82%)	
Degree of differentiation		
G1	31(9,36%)	< 0,0015
G2	199(60,12%)	
G3	101(30,52%)	
N descriptor		
N0 (negative)	184 (55,59%)	< 0,154
N1 (positive)	132 (39,88%)	
N2 (positive)	15 (4,53%)	

PTLI was present in 86 (37.55%) patients with N0 descriptor, 128 (55.89%) patients with N1 descriptor and 15 (6.55%) patients with N2 descriptor



**Fig1.** Ratio of PTLI and N stages of disease in observed resected sample of the lung cancer.

## RESULTS

As can be seen from Table 1, in our sample the most common type of lung cancer was adenocarcinoma, with PTLI being more than 69% of cases. The sample was dominated by a medium degree of tumor cell immaturity (60.12%), with metastasis in the hilar lymph glands in about 40% of cases and mediastinal lymph glands in only 4.53% of the cases.

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The Spearman rank correlation coefficient showed a significant association between PTLI and the occurrence of metastases to hilar and mediastinal lymph nodes ( $p = 0.544$ ,  $n = 331$ ,  $p < 0.0001$ ). When it comes to the relationship between the degree of

differentiation of tumor cells and the occurrence of metastases to hilar and mediastinal lymph nodes, Spearman's rank correlation coefficient showed a slight correlation between these variables ( $p = 0.225$ ,  $n = 331$ ,  $p < 0.0001$ ).

**Table 2.** Prediction of the influence of two independent variables on the occurrence of metastases in regional lymph nodes by logistic regression model.

Logistic regression model	B	Std. error	Loose degree	p	Probability quotient	95% confidence interval for the probability quotient	
						Lower border	Higher border
Differentiation degree	1,065	0,719	1	0,1385	2,9014	0,7088	11,8764
PTLI	3,569	0,532	1	<0,0001	35,4963	12,5204	100,6351
Constant	-5,1572						

Table 2 presents an assessment of the prediction of the impact of PTLI and the degree of differentiation of tumor cells, as independent variables, on the occurrence of metastases to regional lymph nodes. The logistic regression model also showed that PTLI, as an independent variable, had a statistically significant difference ( $p < 0.0001$ ) regarding the importance of findings for predicting metastasis to regional lymph nodes as opposed to the degree of tumor cell differentiation ( $p = 1385$ ). In other words, the calculated relative risk of nodal metastases with the presence of PTLI is 35.5. Therefore, there is a 35.5 times higher risk of developing N disease when there is PTLI rather than when there is none.

### DISCUSSION

PTLI was present in 86 (37.55%) patients with N0 descriptor, 128 (55.89%) patients with N1 descriptor and 15 (6.55%) patients with N2 descriptor.

Wakabayashi O and sar6 found PTLI in a sample of 178 patients resected for NSCLC in 64.9% of cases with N0 descriptor and 37.15% of cases with N1-2 descriptor, which is inversely different from the results of this study. The classification of tumor cell immaturity is indicated by the scale: well differentiated tumor cells (G1 immaturity-31 (9.36%), medium differentiated (G2 immaturity-199 (60.12%), poorly differentiated (G3 immaturity-101 (30.52%). The sample was dominated by a medium degree of tumor cell immaturity (60.12%), with metastasis in the hilar lymph glands in about 40% of cases and mediastinal lymph glands in only 4.53% of cases.

The incidence of metastases in hilar and mediastinal lymph nodes in patients of this sample registered postresection records that the most represented were resectors without the presence of malignant cells in lymph nodes N0 (184 = 55.59%), N1 metastases were present in 132 (39.88%), and N2 metastases at 15 (4.53%). In retrospective presentation of surgical treatment of primary lung cancer by Bačić and authors, a sample of 146 resectates, NO disease was detected in 64.6% of cases, N1 in 21.0% and N2 in 14.4% of resectors<sup>7</sup>.

### FINDINGS

In the treated sample, the most common type of lung cancer was adenocarcinoma, with PTLI present in more than 69% of cases. The sample was dominated by a medium degree of tumor cell immaturity (60.12%) with metastasis in the hilar lymph glands in about 40% of cases and mediastinal lymph glands in only 4.53% of cases. PTLI was present in 37.55% of cases with N0 descriptor, 55.89% of cases with N1 descriptor and 6.55% of patients with N2 descriptor. A significant correlation between PTLI and the occurrence of metastases to the hilar and mediastinal lymph nodes was found via Spearman's rank correlation coefficient. Using a linear logistic regression model, it has been shown that there is a 35.5-fold higher risk of developing N disease when there is PTLI than when there is no PTLI.

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