

# Lymph Node Status in the Different Histologic Subtypes of Lung Adenocarcinoma

## Akciğer Adenokarsinomunun Farklı Histolojik Subtiplerinde Lenf Nodu Durumu

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### Abstract

### Özet

**OBJECTIVE:** Lymph node status represents a relevant prognostic factor in lung adenocarcinoma. Some authors proved that the histologic subtype is the most reliable predictive factor of lymph node status. In addition, a correlation between molecular profile of adenocarcinoma and lymph node metastases has recently been proved. This fact induces a necessity to assess the existence of a difference in lymph node status between the newly identified histologic subtypes of lung adenocarcinoma.

**MATERIAL AND METHODS:** In order to explore this hypothesis, 70 surgically resected specimen of lung adenocarcinoma with lymph node dissection were reviewed retrospectively and reclassified according to the new classification of the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS).

**RESULTS:** The relation between lymph node stage and the histologic subtypes was evaluated with the chi-square test and we established that there was a statistical difference between histologic subtypes of lymph node metastases.

**CONCLUSION:** This result should be confirmed by other multivariate studies using statistical tests with greater power.

**KEY WORDS:** Lymph node metastases, invasive adenocarcinoma, acinar predominant adenocarcinoma, solid predominant adenocarcinoma, papillary predominant adenocarcinoma, lepidic predominant adenocarcinoma

**AMAÇ:** Lenf nodu durumu akciğer adenokarsinomunda uygun bir prognostik faktörü temsil etmektedir. Bazı otörler histolojik subtipin lenf nodu durumunun daha güvenilir prediktif faktörü olduğunu kanıtladı. Ayrıca, adenokarsinomun moleküler profili ile lenf nodu metastazları arasında bir korelasyon yakın zamanda kanıtlanmıştır. Bu durum akciğer adenokarsinomunun yeni tanımlanmış histolojik subtipleri arasında lenf nodu durumunda bir farklılık olup olmadığını araştırma ihtiyacı doğurmuştur.

**GEREÇ VE YÖNTEMLER:** Bu hipotezi araştırmak için, lenf nodu disseksiyonu ile birlikte akciğer adenokarsinomundan 70 cerrahi rezeksiyon örneği retrospektif olarak gözden geçirildi ve Uluslararası Akciğer Kanseri Çalışma Grubu (International Association for the Study of Lung Cancer, IASLC), Amerika Toraks Derneği (American Thoracic Society, ATS) ve Avrupa Solunum Derneği (European Respiratory Society, ERS) yeni sınıflamasına göre tekrar sınıflandırıldı.

**BULGULAR:** Lenf nodu evresi ve histolojik subtipler arasındaki ilişki ki-kare testi ile değerlendirildi ve lenf nodu metastazları açısından histolojik subtipler arasında istatistiksel fark olduğu tespit edildi.

**SONUÇ:** Bu sonuç, daha fazla güç ile birlikte istatistik testler kullanılarak diğer çok değişkenli çalışmalarla doğrulanmalıdır.

**ANAHTAR SÖZCÜKLER:** Lenf nodu metastazları, invaziv adenokarsinom, asiner predominant adenokarsinom, solid predominant adenokarsinom, papiller predominant adenokarsinom, lepidik predominant adenokarsinom

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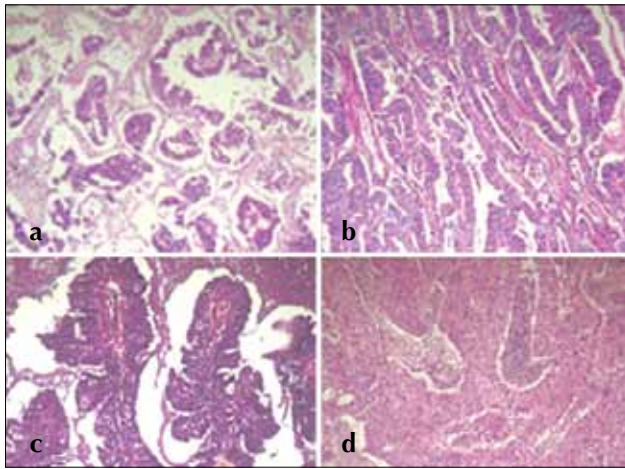
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### INTRODUCTION

Lung cancer represents a major public health problem, resulting in 1, 3 million deaths annually [1]. The last decades showed an increase in the incidence of lung adenocarcinoma, which became the most frequent histological type, accounting for 40% of lung tumors [1]. This change in the epidemiology of lung adenocarcinoma induced the establishment of a new histologic classification in order to improve their management. The new classification system was established by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [2]. This classification introduced new terminologies which are; the in situ adenocarcinoma or minimally invasive adenocarcinoma and it highlighted new histological subtypes of invasive adenocarcinoma. These new subtypes have been reported to be of prognostic value [1]. Thus, lepidic adenocarcinoma was reported to have a good prognosis, the acinar and papillary adenocarcinomas were reported to have an intermediate prognosis and solid and micropapillary adenocarcinomas were reported to have a poor prognosis [1,3]. The prognostic implication of these new subtypes was proved by the comparison of patients' survival curves. Since, lymph node metastases represent a relevant prognostic factor in lung non small cell carcinoma, a few authors tried to determine the predictive factors of lymph node status. Zhang





**Figure 1.** a) Microscopic features of a lepidic predominant adenocarcinoma (HE x400), b) Microscopic features of a acinar predominant adenocarcinoma (HE x250), c) Microscopic features of a papillary predominant adenocarcinoma (HE x400), d) Microscopic features of a solid predominant adenocarcinoma (HE x400)

and colleagues reported recently that tumor histology is the more reliable predictive factor [4]. This fact made us try to assess a possible difference in lymph node status between the different histologic sub-types of lung adenocarcinoma.

**MATERIAL AND METHODS**

Seventy surgically resected specimens of lung adenocarcinoma with lymph node dissection, which were diagnosed over a 2-year-period between 2010 and 2011, were reviewed. All the patients treated surgically were included in our study even in cases where neo-adjuvant chemotherapy was mandatory. All the cases were diagnosed in the Department of Pathology and they were reviewed by 2 pathologists (MM, AA) and reclassified according to the new classification of the IASLC, ATS and ERS.

The lymph node status was established according to the 2009 Union Internationale Contre le Cancer (UICC) classification.

pN0 was used when no lymph node metastasis was noticed. pN1 was used when ipsilateral, hilar and/or intra-parenchymal lymph nodes were invaded. pN2 was used when a metastasis was noticed in ipsilateral mediastinal and/ or sub-carinal lymph nodes. pN3 was used when contralateral mediastinal or hilar or supraclavicular lymph nodes were invaded [3].

**Statistical Analysis**

The relation between lymph node stage and the histologic subtypes were evaluated using the chi-square test (X<sup>2</sup> test) in order to compare multiple distributions.

In order to perform statistical analyses, the formula of the chi-square test was used to compare the different frequencies between the different histologic groups.

**RESULTS**

This study included 63 men and 7 women. All the patients were treated surgically with or without neo-adjuvant chemotherapy. The tumors were located in the superior left lobe in 24 cases, in the upper right lobe in 23 cases, in the lower right lobe in 9 cases, in the lower left lobe in 4 cases and in 2 adjacent lobes in 10 cases. The mean tumor size was 5 centimeters (range, 3-7 cm). The 70 surgically resected specimen of lung adenocarcinoma were reviewed. These cases were classified according to the IASLC, ATS and ERS as lepidic predominant adenocarcinoma in 4 cases (Figure 1a), acinar predominant adenocarcinoma in 26 cases (Figure 1b), papillary predominant adenocarcinoma in 15 cases (Figure 1c) and solid predominant adenocarcinoma in 25 cases (Figure 1d). A mean of 13 lymph nodes were dissected for each case. In the majority of the cases, superior mediastinal nodes, inferior mediastinal nodes and N1 nodes were dissected in addition to aortic nodes in left adenocarcinomas. In order to assess the relationship between the histologic subtypes and lymph node metastases, we focused on the group of cases with metastatic lymph nodes. The different results are represented in Table 1. Metastatic lymph nodes were observed in 4 cases of papillary subtype, 10 cases of solid subtype, 9 cases of acinar subtype and no case of lepidic subtype.

In this group of 23 metastatic lymph nodes, the expected frequency in each group is 5.75. The critical Chi-square value with 3 degrees of freedom and  $\alpha=0.05$  is 7.81. This result reflects a significant difference between the observed and the expected frequencies, with  $p<0.001$ . Our post-hoc analysis is based on the analysis of the difference between the observed frequencies and the expected ones by examining the (fo-fe) / fe values and fo-fe values for each subtype (Table 2). We can observe that solid and acinar sub-types are more likely to give rise to metastatic lymph nodes, whereas, lepidic and papillary sub-types are less likely to result in lymph node metastases.

**DISCUSSION**

The increase of the incidence of lung adenocarcinoma places emphasis on the necessity of uniform diagnostic criteria and terminology to improve the reproducibility for diagnosis and treatment planning of these tumors. As invasive adenocarcinoma represents more than 70 to 90% of surgically resected lung cases, one of the most important aspects of the new classification was to present a practical way to address these tumors that are composed of a complex heterogeneous mixture of histologic subtypes and that are usually classified as mixed adenocarcinoma, according to the 2004 World Health Organization classification [1]. For invasive adenocarcinoma, it was suggested that comprehensive subtyping was used to assess histologic patterns

**Table 1.** The distribution of the different histologic subtypes according to the lymph node status

Lymph Node	Histologic subgroups				Total
	Lepidic	Acinar	Papillary	Solid	
N1	0	4	1	3	8
N2	0	5	3	7	15
N3	0	0	0	0	0
Total	0	9	4	10	23

**Table 2.** Illustration of the post-hoc analysis: Fo-fe values show that solid and acinar sub-types are more likely to give rise to metastatic lymph nodes

Group	fo	Fe	Fo-fe	(fo-fe) <sup>2</sup>	(fo-fe) <sup>2</sup> /fe
Lepidic	0	5.75	-5.75	33.06	5.75
Acinar	9	5.75	3.25	10.56	1.84
Papillary	4	5.75	-1.75	3.06	0.53
Solid	10	5.75	4.25	18.06	3.14

$\chi^2=7.81, p<0.001$

semi-quantitatively in 5% increments, choosing a single predominant pattern. According to this classification, acinar predominant adenocarcinoma shows a majority component of glands, which are round to oval shaped with a central luminal space surrounded by tumor cells. Papillary predominant adenocarcinoma shows a major component of a growth of glandular cells along central fibro-vascular cores. Micropapillary adenocarcinoma has tumor cells growing in papillary tufts which lack fibrovascular cores. Solid predominant adenocarcinoma shows a major component of polygonal tumor cells forming sheets, which lack recognizable patterns of adenocarcinoma [2]. Many authors reported that these histologic features are promising candidates for components of a grading system [1,5]. Therefore, the following prognostic associations have been reported: poor (solid and micropapillary), favorable (nonmucinous lepidic) and intermediate (papillary and acinar) [5].

On the other hand, lymph node status has been reported to represent an important prognostic factor and some authors showed the existence of a correlation between the molecular profile of adenocarcinoma and lymph node metastasis [6,7]. Because of the establishment of the recent histologic classification, we also tried to explore the existence of a relation between the histologic subtype of lung adenocarcinoma and lymph node metastasis. In this research, statistical analysis showed a significant difference between histologic subtypes of invasive adenocarcinoma concerning lymph node metastases. This result may be considered of limited value because of the small number of patients in each group, but it remains indicative of the prognostic impact of the histologic sub-type.

In conclusion, the management of lung adenocarcinoma is still debated and the new classification of the IASc induced new interrogations and questions. As lymph node dissection has been debated by some authors in early stage adenocarcinoma, we tried, in this brief report, to explore an eventual correlation between lymph node status and histologic subtypes of lung adenocarcinoma. These results showed a correlation between them and emphasized the presence of a close relationship between molecular profile and lymph node metastases.

#### Conflict of Interest

No conflict of interest was declared by the authors.

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#### Author Contributions

Conception - M.M.; Design - M.M.; Supervision - F.M.; Materials - A.A.; Data Collection and/or Processing - S.L., S.B.; Analysis and/or Interpretation - M.M.; Literature Review - H.B.; Writer - M.M.; Critical Review - F.M.

#### Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

**Hakem değerlendirmesi:** Dış bağımsız.

#### Yazar Katkıları

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