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Research Article

Prognostic Factors Affecting on Survival in Patients with Resected Lung Adenocarcinoma

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Abstract

Objectives: Our aim in this study was to evaluate the impact of lymph node metastases and histopathological subgroups on survival in patients with resected lung adenocarcinoma.

Methods: We retrospectively evaluated a total of 172 patients with invasive adenocarcinoma who were operated on between January 2011 and December 2018. Nodal status was determined according to the number of involved lymph node stations (single or multiple).

Results: A total of 141 men (82%) and 31 women (18%) were included in the study. The 5-year survival rate was 37% overall and 72.2% for papillary adenocarcinomas (p=0.041). In patients with pN1a and pN2 disease, 5-year survival rates were 43.6% and 22.1%, respectively (p=0.020). In multivariate analysis, pN2 disease and not receiving adjuvant therapy were identified as poor prognostic factors (hazard ratio=2.02, p=0.019; hazard ratio=0.2, p<0.001, respectively).

Conclusion: The results of our study showed that patients with multiple pN1 lymph node metastases have similar survival outcomes to patients with pN2 disease. Most importantly, the main prognostic factor associated with poor survival was pN2 lymph node metastasis. Therefore, we believe that pN1 lymph node status should be evaluated as a separate subgroup in future staging systems.

Keywords: Factors associated with survival, Lung adenocarcinoma, Lymph node metastasis

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Lung cancer is the leading cause of cancer-related deaths. Surgery is the gold standard treatment method, especially for early-stage lung cancers. The main factors determining survival in lung cancer is disease stage and pathologic nodal (pN) status.

Although lymph node metastases are an important factor associated with survival in non-small cell lung cancer (NSCLC), they are still controversial due to their heterogeneity. Different meta-analyses in the literature have identified various parameters affecting survival, such as number of positive lymph nodes, pathological pN2 and multiple N1 metastases, and positive lymph node ratio. Evaluating nodal status in NSCLC helps predict survival and administer aggressive treatments to high-risk patients.

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There are publications in the literature suggesting that multiple pN1 and pN2 metastases have similar survival outcomes. Some authors recommend evaluating separate subgroups in pN1 disease, as in pN2 disease. In addition, it is emphasized that the histopathological heterogeneity of pulmonary adenocarcinomas influences survival. In 2014, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) proposed reclassifying adenocarcinomas with different subtypes.[1] In recent studies, investigators have argued that these new classifications should now be considered the most important prognostic factors.

Our objective in this study was to evaluate the effect of lymph node staging and histopathological subtypes on survival in patients with resected lung adenocarcinoma.

Methods

The records of 1698 patients with NSCLC who underwent surgery between January 2011 and December 2018 were screened. A total of 172 patients who underwent resection for invasive adenocarcinoma were included in the study. Data from a prospective database were evaluated retrospectively. Patients were excluded if they had histopathologic types other than adenocarcinoma, had stage 4 tumors, did not undergo lymph node dissection, underwent incomplete resection, or had missing data.

The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki (No: 2021-95/03/2021).

Patient Selection

Preoperative chest computed tomography (CT) was ordered for all patients, as well as positron emission tomography (PET-CT) and cranial magnetic resonance imaging (MRI) to evaluate for distant metastases. Pulmonary function tests were done to assess pulmonary reserve. Lung perfusion scintigraphy was ordered for patients with a forced expiratory volume in 1 second (FEV1) of 40% or lower. Echocardiography was performed in patients with a cardiac history and those over 60 years of age. For all central and peripheral tumors, fiberoptic bronchoscopy was performed preoperatively to evaluate for endobronchial lesions. Preoperative mediastinal staging was performed in accordance with ESTS and ATS guidelines.[2]

The modified Naruke system was used for intraoperative hilar and mediastinal lymph node dissection.[3] Histological grading in patients with NSCLC was performed according to tumor differentiation. In accordance with the new adenocarcinoma classification, histopathological subtypes were defined as lepidic, acinar, papillary, micropapillary, and solid. The pattern with the highest percentage was selected as the predominant pattern.[4]

Nodal status was determined according to the number of involved lymph node stations (single or multiple). Single N1 station involvement was classified as pN1a, multiple N1 station involvement as pN1b, and single N2 station involvement or multiple N2 stations with N1 involvement as pN2.

Postoperative Follow-up

The patients' demographic data, histopathological characteristics, and 5-year survival rates were analyzed. Data regarding the patients' age, histopathology results, tumor stage, adjuvant and survival were obtained from hospital records and the national survival database. Pathologic staging was based on the 8th edition of the TNM classification system.[5]

Patients were followed with thoracic CT and physical examination in collaboration with oncologists every 3 months for the first 2 years, every 6 months between 2 and 5 years, and annually after 5 years. The mean follow-up time was 53.8 months.

Results

A total of 172 patients, 141 men (82%) and 31 women (18%), were included in the study. The patients' mean age was 59.5±8.6 years (range: 31-79). The mean tumor diameter was 4.6±2.5 cm (range: 0.7-18). Lobectomy was performed in 127 patients (73.8%), pneumonectomy in 42 patients (24.4%), and segmentectomy in 3 patients (1.7%). The demographic and histopathological characteristics of the patients are shown in Table 1.

The mean survival time was 39 months and the 5-year survival rate was 37%. The 5-year survival rate of patients with papillary adenocarcinomas was 72.2% (p=0.041). When evaluated according to pN status, the 5-year survival rate was 43.6% in pN1a and 22.1% in pN2 (p=0.020). Prognostic factors associated with survival are evaluated in Table 2.

In multivariate analysis, pN2 disease and not receiving adjuvant therapy were identified as poor prognostic factors (hazard ratio: 2.02, p=0.019; hazard ratio: 0.2, p<0.001, respectively). The results of multivariate analysis of factors associated with survival are shown in Table 3.

Discussion

Accurate evaluation of lymph node metastasis is critical for treatment decision making and predicting prognosis. The current lung cancer staging system, which is based solely on the anatomical sites of metastasis, has the advantage of direct evaluation using CT or PET-CT, and although it is

Table 1. Demographic and Histopathological Characteristics of the Patients

Variables	n	%
Age (Year)		
(Mean±StD)	59.5±8.6	
Gender		
Male	141	82
Female	31	18
Side		
Right	80	46.5
Left	92	53.5
Resection		
Lobectomy-Segmentectomy	130	75.6
Pneumonectomy	42	24.4
Stage		
2b	96	55.8
3a	59	34.3
3b	17	9.9
Histopathology		
Solid	64	37.2
Acinar	84	48.8
Micropapillary	4	2.3
Invasive Mucinous Carcinoma	8	4.7
Papillary	12	7

Std: Standart Deviation.

very well characterized, there are still many disagreements regarding lymph node staging. The main reason for this is the heterogeneity of lymph node metastases (single pN1 or multiple N1, single pN2, multiple pN2, and skip pN2). Furthermore, another important factor is defining N in lymph node mapping. The definition of and distinction between N1 and N2 lymph nodes may involve the subjective judgment of surgeons or pathologists.[6] Various studies have demonstrated the effectiveness of using lymph node metastasis, lymph node stations, or positive lymph node ratio to more accurately predict prognosis in NSCLC patients.[7-10] According to these studies, prognosis can also be estimated when classifying N stage based on number of positive lymph nodes. However, it is very difficult to evaluate the number of metastatic lymph nodes during clinical staging. In addition, the number of regional lymph nodes retrieved may be inaccurate as a result of crushing and disintegration during surgery or the subjective evaluation of the surgeon or pathologist.

In the 8th edition of the TNM classification, the criteria for the N category do not differ from the previous staging and are still based only on anatomical location. However, the IASLC stated that the location of metastatic lymph nodes, multiple versus single station involvement, and the presence of skip metastasis (i.e., categories N1a, N1b, N2a1, N2a2, and N2b) should be considered and that this assessment provides a more accurate prognosis.[11] Some studies have corroborated the N classification proposed by the IASLC and found that it better predicted prognosis; however, the separate categorization could not be fully clarified due to some similar results between the groups.[12,13]

Regarding N1 disease, it has been reported that survival in patients with multiple N1 involvement differs from that in single N1 disease according to cell type and adjuvant therapy protocol. In a study by Eichhorn et al.,[14] tumor-specific survival analysis of pN1a and pN1b adenocarcinoma patients showed that the 5-year survival rate for patients who received adjuvant therapy was 49.6% in the pN1b group and 80.4% in the pN1a group. In the squamous cell group, survival rates for patients who received adjuvant therapy were 79.7% in the pN1b group and 69.6% in the pN1a group (p=0.58). In patients who did not receive adjuvant therapy, there was no significant difference in survival between the N1a and N1b groups for either histolopathologic type (5-year tumor-specific survival, adenocarcinoma pN1a: 47.9%, pN1b: 56.4%, p=0.82; squamous cell carcinoma pN1a: 62.2%, pN1b: 69.1%, p=0.96). Kojima et al.[10] determined in their survival analysis between patients with N1a and N1b disease that prognosis was poorer in the N1b group (71.5% vs. 49.9%, p=0.04). Similarly, in a study by Park[12] that confirmed the IASLC's N factor recommendations, overall survival was 62.6% in the N1a group and 57% in the N1b group, and the difference was found to be statistically significant (p=0.014). Unlike these studies, we found that although overall survival tended to be higher in the pN1a group (43.6%) than in the pN1b group (32.5%), the difference was not statistically significant (p=0.147). We attribute this to the small number of patients with N1a and N1b in our study and the heterogeneous distribution of adenocarcinoma subtypes in the N1a and N1b groups.

Overall survival rates in N2 disease are lower than in N1 and N0 disease. However, in recent N1 and N2 subgroup analyses recommended with the 8th edition TNM staging, comparisons of N1b disease with single N2 or skip metastasis N2 (N2a1) and multiple N2 disease have been reported. In their study of the N factor, Chen et al.[13] reported overall survival rates for N0, N1, and N2 of 76.1%, 53.4%, and 26.3%, respectively. In the same analysis, evaluation of the N1 and N2 subgroups revealed no significant differences in overall survival between the multiple N1 (N1b) and single N2 (N2a) groups (39.3% vs. 40.3%, p=0.967) or between the N1b and multiple skip N2 (N2b1) groups (39.3% vs. 33.3%, p=0.559). The authors also determined that the N1a group had the best survival (60%) when compared with the N1b and N2 subgroups. In a study on the proposed changes to

Table 2. Prognostic factors affecting survival

Variables	n	5 Year Survial (%)	Mean Survival (Months)	95% CI	p
Gender					
Male	141	33.4	61	50-71	0.077
Female	31	52	67	51-82	
Side					
Right	80	39.7	68	53-82	0.649
Left	92	34.5	62	48-75	
Resection					
Lobectomy-Segmentectomy	130	37	67	56-78	0.563
Pneumonectomy	42	36	57	39-75	
Pleural Invasion					
No	151	37.2	65	55-76	0.970
Yes	21	34.9	66	37-94	
Histopathology					
Solid	64	22	47	36-59	0.041
Acinar	84	41.5	69	55-82	
Micropapillary	4	25	41	17-66	
Invasive Mucinous Carcinoma	8	12.5	30	11-48	
Papillary	12	72.2	89	67-111	
pN Status					
pN1a	71	43.6	51	40-61	0.020
pN2	17	22.1	40	20-60	
pN Status					
pN1b	84	32.5	75	60-90	0.187
pN2	17	22.1	40	20-60	
pN1					
pN1a	84	43.6	75	60-90	0.147
pN1b	71	32.5	51	40-61	
Adjuvant Therapy					
No	13	7.7	8	3-12	<0.001
Yes	159	39.5	44	35-52	

CI: Confidence Interval.

Table 3. Multivariate analysis of factors associated with survival

Variables	HR	95% CI	p
Histopathology			
Solid			0.397
Acinar	0.69	0.4-1.1	0.180
Micropapillary	1.06	0.3-3.5	0.921
Invasive Mucinous Carcinoma	0	0-2.1	0.969
Papillary	0.34	0.1-1.1	0.088
pN Status			
pN2	2.02	1.1-3.6	0.019
Adjuvant Therapy			
Yes	0.20	0.9-0.45	<0.001

CI: Confidence Interval; HR: Hazard Ratio.

the 8th edition TNM staging, Wang[15] reported no significant difference in prognosis between patients with multiple N1 (N1b) and skip single N2 (N2a1) (p=0.85). However, when 5-year survival outcomes were compared between patients with non-skip single N2 (N2a2) and N1b, there was a statistically significant difference (36.6% and 50.4%, respectively). Asamura et al.[11] reported that patients with N2a1 (skip metastasis single N2) had better survival rates than the N1b group. In our study, the difference in survival between patients with pN1b (32.5%) and pN2 (22.1%) was not statistically significant (p=0.187). We believe that multiple pN1 disease has a similar prognosis to pN2 disease and that for this reason, pN1 subgroups should be classified differently in future staging systems.

Adenocarcinomas are the most common histopathological subtype in lung cancer and comprise a heterogeneous

group of tumors with highly variable prognosis. In a study by Russell et al.,[16] 5-year survival rates in patients with early-stage adenocarcinomas were better for papillary and acinar subtypes (71% and 68%, respectively) than the micropapillary and solid subtypes (38% and 39%, respectively). In addition, N2 metastasis, lymphovascular invasion, and visceral pleural invasion were more common in the micropapillary-predominant subtype. Yoshizawa[17] divided lung adenocarcinomas into 3 prognostic groups, classifying adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) as low-grade; lepidic, acinar, and papillary-dominant types as intermediate-grade; and micropapillary, solid, colloid, and invasive mucinous adenocarcinoma predominant types as high-grade. Contrary to the results of univariate analysis in our study, survival was better in the papillary-dominant subtype (72.2%) compared to other subtypes (p=0.041). If we evaluate high-grade adenocarcinomas, Barletta[18] and Riquet[19] determined that the micropapillary-dominant subtype was a poor prognostic factor, while Motono[20] reported that the solid-dominant subtype was a poor prognostic factor. Again, unlike these studies, our univariate analysis showed the worst survival in the mucinous invasive adenocarcinoma-dominant subtype (12.5% at 5 years). However, the overall survival outcomes differ in advanced adenocarcinomas compared to early-stage disease. In patients with advanced adenocarcinomas, better survival results have been reported in high-grade subtypes (micropapillary, solid) than intermediate-grade subtypes (lepidic, acinar). In a study by Arrieta et al.,[21] 5-year survival was 36.9% in high-grade adenocarcinomas and 25.4% in the intermediate group. As a result, it has been emphasized that high-grade tumors may have a better response to chemotherapy in advanced disease. In our study, multivariate analysis revealed no survival differences between adenocarcinoma subtypes. This may be related to the responses to adjuvant therapy. Based on all of these results, we can say that adjuvant therapy should be considered and improves prognosis in high-grade, early-stage adenocarcinomas. However, there is insufficient literature data on this subject, and new studies are needed.

Limitations

The main sources of bias in this study are its retrospective design, the fact that the patients' operations were performed by multiple surgeons, the heterogeneity of pN2 and pN1 disease, and the lack of an analysis of disease-free survival. The exclusion of patients who received neoadjuvant treatment was intended to reduce heterogeneity of the patient sample but also caused selection bias. Another limitation of the study is that we did not have the results of mutation analysis of the adenocarcinomas.

Conclusion

The results of our study indicate that patients with multiple pN1 lymph node metastases have similar survival outcomes to patients with pN2 disease, whereas survival is better in single station pN1 metastasis than pN2 disease. Most importantly, the main prognostic factor associated with poor survival was pN2 lymph node metastasis. Therefore, we believe that pN1 lymph node status should be evaluated as a separate subgroup in future staging systems. However, multicenter prospective studies are still needed.

Disclosures

Ethics Committee Approval: The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki (No: 2021-95/03/2021).

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