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Prognosis analysis according to the predominant histological pattern in cases with lung adenocarcinoma undergoing complete resection

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Abstract

Lung adenocarcinoma accounts for over 40% of lung cancer cases. There is still uncertainty in terms of prognosis, particularly because of limited pathological information among the predominant sub-patterns of adenocarcinomas. In this study, we evaluated the prognostic relationship with the predominant histological patterns in adenocarcinoma cases that underwent complete resection in one year. We retrospectively evaluated 100 patients with lung adenocarcinoma, whose pathological stage was determined after complete resection. Six patients were excluded from the study because of missing data in their files. The mortality rates and tumor stages of the patients were analyzed according to their histopathological subtypes with the predominant pattern. Seventy-four (79%) of the cases were male and 20 (21%) were female. The predominant pattern was solid in 41 (43.6%) patients, acinar in 31 (33%) patients, papillary in 10 (10.6%) patients, lepidic in 9 (9.6%) patients and micropapillary in 3 (3.2%) patients. Lymph node involvement was N0 in 30 (73.2%) patients, N1 in 9 (22%) patients and N2 in 2 (4.9%) patients in the solid group; N0 in 22 (71%) patients, N1 in 3 (9.7%) patients, and N2 in 6 (19.4%) patients in the acinar group. In the solid group, 23 (56.1%) patients survived, and 18 (14.6%) patients died, whereas 21 (67.7%) patients survived, and 10 (32.2%) patients died in the acinar group. The mean follow-up period of the patients was 32 months. In the mean follow-up of all patients, 58 (61.7%) survived and 36 (38.3%) died. No significant difference was observed between the subtypes in terms of mortality ($p>0.05$). N2 involvement was higher in acinar adenocarcinomas compared with the solid pattern, and the advanced stage due to the T factor was observed more in the solid pattern. Acinar-type adenocarcinoma shows similar prognostic characteristics to those with the solid pattern.

Keywords: Lung adenocarcinoma, acinar-type adenocarcinoma, solid type adenocarcinoma

Introduction

Lung cancer is an important health problem and the most common cause of cancer-related death in the world. Adenocarcinoma is the most common subtype of lung cancer and accounts for nearly half of all lung cancers [1]. The classification and definition of histopathological subtypes in lung adenocarcinoma were changed in the multidisciplinary consensus meeting of the International Association Lung Cancer, American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) in 2011 [2]. Lung adenocarcinomas differ from other organ adenocarcinomas in that they are heterogeneous tumors with morphological diversity [3].

The presence of more than one sub-histopathological pattern in lung adenocarcinomas is found in 80-90% of the disease. Therefore, determining the dominant histopathological type is important for the prognosis of the disease [4].

A significant relationship was observed with the predominant type in terms of prognosis and survival in 514 patients who underwent surgery for stage I lung adenocarcinoma [5]. However, Sakao

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et al. [6]. stated that the histological subtype is not important, and the prognosis is poor in cases with clinical stage IA lung adenocarcinoma of 2 cm and above. There are conflicting data in the literature regarding the prognosis of lung adenocarcinomas [5,6].

Because of the heterogeneous nature of lung adenocarcinomas, the pathological examination of the surgically resected material provides accurate information in terms of types. Small biopsies may not provide accurate information to detect the predominant pattern. For these reasons, we retrospectively evaluated the relationship between pathological stage and mortality in the patients who underwent complete resection for lung adenocarcinoma within a year.

Materials and Methods

We retrospectively evaluated 100 patients with adenocarcinoma from 475 patients who were diagnosed with primary lung non-small cell carcinoma and underwent complete resection in University of Health Science, Sureyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital within one year (between January 1, 2013 -December 31, 2013). Baseline demographic information and clinical data were collected from surgical charts and hospital records. Ethics committee approval numbered 116.2017.041 was obtained by the SUAM Clinical Research Ethics Committee and informed consent from the patients was obtained. Six patients were excluded from the study because of missing data in their files (Figure 1).

Patients who underwent surgical resection due to primary lung adenocarcinoma and patients with complete file data were included in the study. Patients with missing data in the file information or missing data in the database, patients with small cell lung cancer, and NSCLC patients who were not suitable for surgical resection were excluded from the study.

Patients were staged postoperatively (pTNM) using the 7th edition of the TNM staging system. The stage and mortality rates of these patients during the postoperative 3-year follow-up were analyzed according to their predominant histopathological subtypes. Patients were assigned a date of death or were identified as living on January 31, 2018. Three-year survival was calculated for the subtypes with patients. Mayor subgroups were determined histopathologically. T, N, visceral pleural invasion, and M staging were determined according to each subgroup, and differences between subgroups were evaluated.

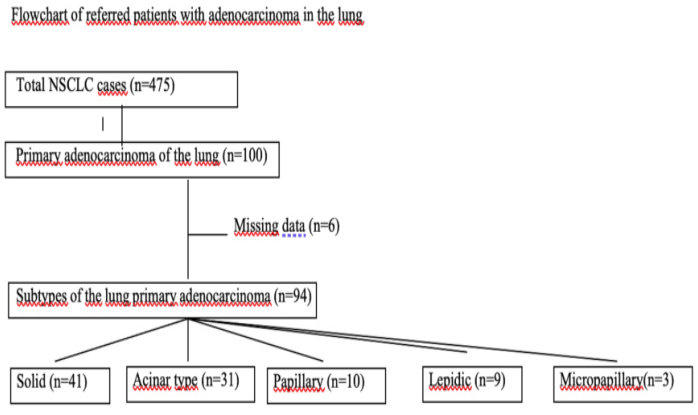

Figure 1. Flowchart of the patients

Diagnostic pathological examination

All resection specimens were fixed with 10% formalin and stained with hematoxylin and eosin in routine practice. Mucin dyes were applied to evaluate the presence of mucin in cases deemed necessary. All sections sampled as tumor sites, with different numbers in each case, were evaluated microscopically by the pathologist. The histological patterns were evaluated in 5% slices in each case, and histological subtyping was performed by determining the predominant histological pattern according to the 2011 IASLC/ATS/ERS classification. The predominant pattern is defined as the pattern with the largest percentage, without necessarily being 50% or more [2]. Major histological patterns were identified as follows: lepidic (proliferation of type II pneumocytes and Clara cells along the alveolar wall surface), acinar (round-oval-shaped malignant glandular cells invading fibrous stroma), papillary (malignant cubic-columnar tumor cells growing on the surface of fibrovascular centers), micropapillary (secretory cells that proliferate in small papillary clusters within the air spaces and do not have fibrovascular centers) and solid (tumor cells with prominent nucleoli, mostly vesicular nucleus and proliferating in layers with abundant cytoplasm).

Statistical analysis

The compatibility of numerical variables with normal distribution was tested by the Shapiro–Wilk Test. Categorical variables were described using frequency and percentage and numerical variables using the mean and standard deviation or median and interquartile difference values. Over two independent means were compared using analysis of variance test. More than two independent medians were compared using the Kruskal–Wallis test and paired comparisons were made using the Mann–Whitney U test. The relationship between categorical variables was investigated using the Chi-squared test. Survival was calculated using the Kaplan–Meier method and the log-rank test was used to compare survival between groups. Uni- variate and multivariate analyses were done using Cox regression analysis to assess the histologic subtype as a prognostic factor for survival. The following variables were used in the univariate analysis: Histological subtype, and group TNM stage. The study was conducted at a 95% confidence level ($p<0.05$ statistically significant difference was accepted).

Results

General characteristics of the patients

Seventy-four (79%) of the cases were male and 20 (21%) were female. The mean age was 60.±9.4. Tumor diameter was a median of 3.5 (SD±2.7) cm in all groups. The mean follow-up period of the patients was 32 (SD±22) months. At the median follow-up, 58 (61.7%) of the patients survived and mortality was observed in 36 (38.3%) patients.

TNM analysis according to the histopathological pattern

Predominant pattern

The predominant pattern was determined as solid in 41 (43.6%) patients, acinar in 31 (33%) patients, papillary in 10 (10.6%) patients, lepidic in 9 (9.6%) patients, and micropapillary in 3 (3.2%) patients (Table 1).

Table 1. Predominant pattern distribution according to sub-types

Tumour diameter (cm) (Median,CAF)	**3.5 (2.7)**
Predominant pattern (n, %)	
Lepidic	9 (9.6)
Acinar	31 (33)
Papillary	10 (10.6)
Micropapillary	3 (3.2)
Solid	41 (43.6)

Pleural invasion

In regards to visceral pleural (VP) invasion, 20 (48.8%) patients were observed to have PL0 (no involvement in the elastic layer), 14 (34.1%) patients had PL1 (involvement in the elastic layer), 2 (4.9%) patients had PL2 (invasion in the visceral pleura) and 5 (12.2%) had patients PL3 (invasion in the parietal pleura) in the solid group; whereas 18 (58.1%) patients had PL0, 8 (25.8%) patients had PL1, 3 (9.7%) patients had PL2 and 2 (6.5%) patients had PL3 in the acinar group.

Lymph node involvement

Regarding lymph node involvement, 30 (73.2%) patients were N0, 9 (22%) patients were N1 and 2 (4.9%) patients were N2 in the solid group; whereas, 22 (71%) patients were N0, 3 (9.7%) patients were N1 and 6 (19.4%) patients were N2 in the acinar group. N2 was more numerically observed in the acinar group, but it was not statistically significant (Table 2).

T factor according to histopathological subtype

Median tumor diameter was 5 cm in the group whose predominant pattern was solid and 3 cm in the acinar group. TNM staging was IA in 7 (17.1%) patients, IB in 12 (29.3%) patients, IIA in 6 (14.6%) patients, IIB in 9 (22%) patients in the solid group, whereas it was IIIA in 7 (17.1%) patients, IA in 8 (25.8%) patients, IB in 10 (32.3%) patients, IIA in 4 (12.9%) patients, IIB in 3 (9.7%) patients, and IIIA in 6 (19.4%) patients in the acinar group.

No difference was observed between the groups in terms of T, N, and M factors (Table 2).

Mortality and survival by histopathological subtype

In the female sex, acinar-type adenocarcinoma was most frequently observed in 10 patients (32.3%). Concerning the pattern, 23 (56.1%) patients survived and 18 (14.6%) patients died in the solid group; 21 (67.7%) patients survived and 10 (32.2%) died in the acinar group; 5 (55.6%) patients survived and 4 (44.4%) patients died in the lepidic group; 7 (70%) patients survived and 3 (30%) patients passed away in the papillary group, and 2 (66.7%) patients survived and 1 (33.3%) patient passed away in the micropapillary group (Table 3). There was no difference in survival between the groups (Figure 1, p=0.834). In addition, no significant difference was observed between the subtypes in terms of mortality (p>0.05).

Table 2. TNM characteristics of the tumor according to the predominant patterns and statistically differences between the groups

	Predominant pattern					
	Lepidic	**Acinar**	**Papillary**	**Micropapillary**	**Solid**	**P değeri**
Tumour diameter (cm) (Median, CAF)	2.5 (2)	3 (3)	2.6 (4)	2nd	5 (3)	P>0.005
VP invasion (n, %)						
PL0	6 (66.7)	18 (58.1)	4 (40)	2 (66.7)	20 (48.8)	P>0.005
PL1	3 (33.3)	8 (25.8)	5 (50)	1 (33.3)	14 (34.1)	
PL2	0 (0)	3 (9.7)	1 (10)	0 (0)	2 (4.9)	
PL3	0 (0)	2 (6.5)	0 (0)	0 (0)	5 (12.2)	
pT (n, %)						
T1	4 (44.4)	10 (32.3)	3 (30)	2 (66.7)	8 (19.5)	P>0.005
T2	3 (33.3)	15 (48.4)	3 (30)	1 (33.3)	14 (34.1)	
T3	2 (22.2)	5 (16.1)	3 (30)	0 (0)	15 (36.6)	
T4	0 (0)	1 (3.2)	1 (10)	0 (0)	4 (9.8)	
N (n, %)						
N0	6 (66.7)	22 (71)	8 (80)	2 (66.7)	30 (73.2)	P>0.005
N1	2 (22.2)	3 (9.7)	0 (0)	1 (33.3)	9 (22)	
N2	1 (11.1)	6 (19.4)	2 (20)	0 (0)	2 (4.9)	
TNM (n,%)						
IA	2 (22.2)	8 (25.8)	3 (30)	1 (33.3)	7 (17.1)	P>0.005
IB	3 (33.3)	10 (32.3)	2 (20)	1 (33.3)	12 (29.3)	
IIA	1 (11.1)	4 (12.9)	0 (0)	1 (33.3)	6 (14.6)	
IIB	1 (11.1)	3 (9.7)	3 (30)	0 (0)	9 (22)	
IIIA	2 (22.2)	6 (19.4)	2 (20)	0 (0)	7 (17.1)	

Table 3. Mortality and survival by mean follow-up duration according to predominant patterns

	Predominant pattern				
	Lepidic	**Acinar**	**Papillary**	**Micropapillary**	**Solid**
Age (Mean ± SD)	56.9±10.0	62.1±8.6	59.1±8.4	54.3±6.8	60.4±10.2
Gender (n, %)					
Male	7 (77.8)	21 (67.7)	9 (90)	2 (66.7)	35 (85.4)
Female	2 (22.2)	10 (32.3)	1 (10)	1 (33.3)	6 (14.6)
Status (n, %)					
Survived	5 (55.6)	21 (67.7)	7 (70)	2 (66.7)	23 (56.1)
Exitus	4 (44.4)	10 (32.3)	3 (30)	1 (33.3)	18 (43.9)
Follow-up (months) (Median, NAF)	31 (14.5)	34 (18)	33 (11)	34	30 (24)

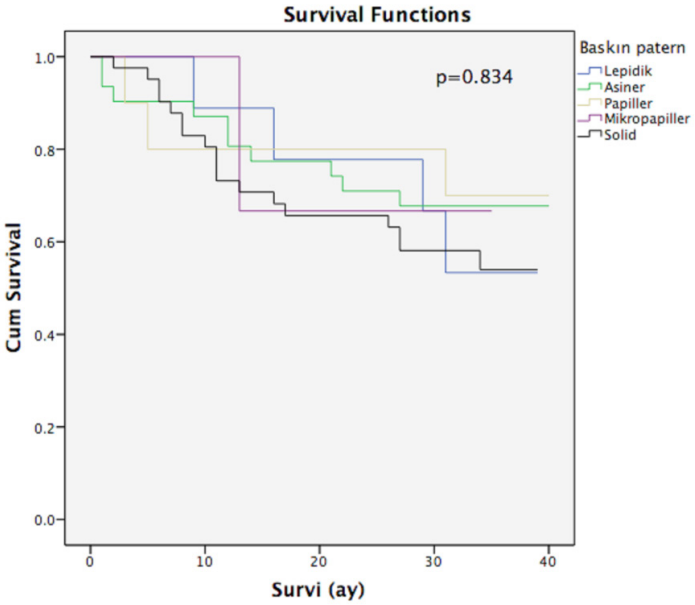

Figure 2. Survival curve relative to predominant subtypes. Concerning the predominant pattern, 23 (56.1%) patients survived in the solid group, 21 (67.7%) patients survived in the acinar group, 5 (55.6%) patients survived in the lepidic group survived, 7 (70%) patients survived in the papillary group and 2 (66.7%) patients survived in the micropapillary group

Discussion

In our study, the acinar type was the second common predominant pattern after solid type adenocarcinomas. N2 involvement in the patients with acinar type pattern was more than the solid pattern; however, the difference between them was not statistically significant. The advanced pathological stage was higher in the solid pattern due to the T factor compared with the acinar pattern. Although the number of acinar-type patients was lower than the solid-type patients, Stage IIIA frequency was similar because of N2 involvement. In this cross-sectional study, the pattern with the worst prognosis and the highest incidence among subtypes after the solid pattern in adenocarcinomas was the acinar type. The acinar predominant pattern was believed to have an intermediate prognosis. It has been reported to have a worse prognosis in those with a lepidic predominant pattern and a better prognosis in those with micropapillary, mucinous/colloid, and solid patterns [7,8]. In our study, a comparison could not be made because of the inefficient number of subtypes other than acinar and solid patterns.

Acinar, solid, and lepidic patterns are both common and difficult to distinguish from each other. While solid and lepidic patterns can be classified more reliably, the diagnosis of acinar pattern presents moderate diagnostic difficulty [9]. The frequent observation of the acinar pattern after the solid pattern in this study is also associated with the complete examination of the resected tumor.

Some studies indicate that invasive mucinous adenocarcinoma has a good prognosis and is not aggressive. These contradictory results are associated with a small number of patients [10]. The inability to determine subtypes in small biopsy materials also plays a role in the inability to determine the prognosis. Matsuzawa et al. stated that if the biopsy material is larger than ≥0.7 mm², a more accurate result is obtained in pathological diagnosis [11]. When larger samples were taken in their studies, the compliance was low in acinar-type adenocarcinoma in comparison with other types of adenocarcinoma. This discrepancy has been attributed to the difficulty of distinguishing pre-existing thickened septal alveolar structures from neoplastic cells in acinar adenocarcinoma with desmoplastic stroma [12].

Invasive mucinous adenocarcinoma (IMA) is a clinically and genetically distinct subtype of invasive lung adenocarcinoma [13]. Five-year survival is 50% in patients with acinar predominant pattern IMA, and the survival at 7-year follow-up is down to 25% in this predominant pattern. Acinar predominant pattern is observed to have a poor prognosis in both mucinous and non-mucinous lung adenocarcinomas in some studies [14]. Similarly, our study shows that patients with acinar-type adenocarcinoma show a prognosis like those with a solid pattern. Mortality was observed in 18 (14.6%) of 41 patients in the solid group and 10 (32.2%) of 31 patients in the acinar group. The difference between them was not statistically significant; however, more studies are required on this subject.

The limitation of this study is that it was conducted at a single center and there was an insufficient number of subtype patients. However, it is important that the study is cross-sectional, allows us to evaluate all the material in patients with surgical resection, and gives results closer to the results that may be followed in practice.

Conclusion

In conclusion, the acinar pattern shows poor prognostic characteristics like the solid pattern.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethics committee approval numbered 116.2017.041 was obtained by the SUAM Clinical Research Ethics Committee.

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