Original article

Prognostic Affect of Predominant Histologic Subtypes in Resected Pulmonary Adenocarcinomas

Yaldız et al. Predominant Subtypes of Pulmonary Adenocarcinoma

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Received: 1 February 2019
Accepted: 10 September 2019

DOI: 10.4274/balkanmedj.galenos.2019.2019.1.130

Cite this article as:
Yaldız D, Örs Kaya Ş, Ceylan KC, Acar A, Aydoğdu Z, Gürsoy S, et al. Prognostic Affect of Predominant Histologic Subtypes in Resected Pulmonary Adenocarcinomas. Balkan Med J

This study has been presented as an oral presention at 'Türkiye Solunum Araştırmaları Derneği 40. Yıllık Kongresi, Antalya, Turkey'.

Background: Histologic predominant subtypes were reported as a predictor of survival in pulmonary adenocarcinoma.
Aims: To evaluate the predictive value of histologic classification in resected lung adenocarcinoma using the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS), and WHO (2015) classification system.
Study Design: Cross-sectional study.
Methods: Histologic classification of a large cohort of 491 patients with resected (stages I to III) lung adenocarcinoma was retrospectively analyzed. The tumors were classified according to their predominant component (lepidic, acinar, papillary, solid, micropapillary, and mucinous), and their predictive value were assessed for clinicopathologic characteristics, and overall survival.
Results: The patient cohort were comprised of 158 (32.2%) solid-predominant, 150 (30.5%) acinar-predominant, 80 (16.3%) papillary-predominant, 75 (15.3%) lepidic-predominant, 22 (4.5%) mucinous, 5 (1.0%) micropapillary, and 1(0.2%) adenocarcinoma in situ. Overall 5-year survival of 491 patients were found to be 51.8%. Lepidic, acinar, mucinous adenocarcinoma had 70.9%, 59.0%, and 66.6% 5-year survival, respectively and there was no statistically significant difference between them.Whereas solid, papillary and micropapillary predominant histologic pattern had 41.0%, 40.5% and 0.0% 5-year survival, respectively. Compared to other histologic subtypes; solid predominant adenocarcinoma and papillary predominant adenocarcinoma harbored significantly lower survival to lepidic ($p<0.001$, $p=0.002$), acinar ($p<0.001$, $p=0.008$), and mucinous ($p=0.048$, $p=0.048$) subtypes respectively. The survival difference between solid and papillary subtype was not found statistically significant ($p=0.67$).
Conclusion: Solid and papillary predominant adenocarcinoma was found to be poor prognostic factors in resected invasive lung adenocarcinoma.
Keywords: Pulmonary adenocarcinoma, papillary subtype, solid Subtype

Pulmonary adenocarcinoma is a heterogeneous group of tumors characterized by various predominant histological subtypes. Therefore, identification of prognostic and predictive factors in patients with resected lung adenocarcinoma is essential for stratifying higher-risk patients for further management. In 2011, the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a new classification system for lung adenocarcinoma, and major histological subtypes (acinar, lepidic, papillary, solid, and micropapillary) were defined (1). Lung adenocarcinomas should also be classified according to their predominant subtypes. Depending on this, in 2015 a new WHO classification was issued (2). Since the release of the new lung adenocarcinoma classification, many studies widely demonstrated that the solid and micropapillary predominant subtypes were associated with poorer overall survival, whereas the lepidic predominant subtype had the most favorable outcome (3,4). However, the prognostic affect of the other predominant subtypes has not been clearly described and needs further clarification.

In this study, we analyzed 491 consecutive stage I–III invasive lung adenocarcinoma patientswho underwent surgical resection between 2005 and 2016. Our aim was to explore predictive and prognostic value of predominant subtypes of lung adenocarcinoma.

MATERIALS AND METHODS

A retrospective evaluation of the clinical patient records was used to recruit patientswho had curatively resected primary lung adenocarcinoma from 2005 to 2016(n=534).Patients were excluded if they had neoadjuvant therapy, incomplete resection, metastatic disease or nodule found at the time of surgery. The participation rate of the study was 91.9% (491/534).

Before 2010, all patients were screened with contrast-enhanced chest computed tomography, and after 2010 additionally with PET-CT, due to detect unknown metastases. Patients without enlarged lymph nodes and a PET-negative mediastinum proceeded directly to surgery. However, enlarged lymph nodes on CT, independently from PET findings underwent EBUS-TBNA and/or mediastinoscopy. Patients having N2 disease had received adjuvant chemotherapy and/or radiotherapy.

From 2005 to 2010, serratus anterior muscle sparing thoracotomy was performed in all patients. Since 2010, nearly 25% of patients underwent video assisted thoracoscopic surgery (VATS).

Medical records of 491 patients were screened for age, gender, smoking history, comorbidity, type of resection, histologic subtype and, pathologic tumor-node-metastasis (TNM) stage according to the 7th edition of the lung cancer staging system. For the first 2 years, patients were followed up at 3month intervals and thereafter at 6 month intervals. Mean duration of clinical follow-up was 44.25 months (min/max: 2- 152 months). The date of death were found from the medical records and verified by a software program, linked to the national population registration system. Pathologic slides were re-reviewed by the pathologists and classified according to the predominant histologic subtype as defined by IASLC/ATS/ERS classification (1), and recently the WHO classification. In pathological examination; adenocarcinoma, showing a single-row organisation using the alveolar roof, was defined as a lepidic pattern; the ones that formed circular glandular structures including lumen as acinar pattern; structures containing fibrovascular core into the lumen as papillary pattern; those containing glandular cell groups that develop into the lumen without fibrovascular core as micropapillary pattern and those containing layered cell groups without glandular and papillary structures as solid pattern. In addition, any growth pattern containing abundant intracytoplasmic mucin was defined as mucinous adenocarcinoma.Since the majority of adenocarcinomas are heterogeneous, the dominant model is based on the proportions in the samples (Figure 1).Finally, we have compared the 5-year survival of predominant histologic subtypes in similar stages, and also in similar T and N status.

This study was approved by the Ethical Committee of the university (Date: 29.01.2018, No: 49109414-806.02.02). Written informed consent was obtained from all individuals.

Statistical analysis

Statistical evaluation was carried out with IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Patient survival was expressed by actuarial analysis according to the method of Kaplan Meier, and differences in survival were assessed by using the log-rank test in the univariate analysis. A multivariate analysis of variables was performed using the Cox proportional odds regression model. For all statistical analyses,type I error was considered as <0.005. Sample size calculations were calculated using PASS 2008 program.For the variables including age, sex, histologic type, solid and papillary component, pathologic stage, N status, T factor, pleural invasion and extent of resection, log hazard ratio in the Cox regression analysis was used. The result of power analysis for 491 patients calculated as 100% in the α=0.05 significant level.

RESULTS

Clinicopathologic Characteristics of Patients

A total of 491 resected lung adenocarcinoma patients were included in this study. There were 410 (83.5%) male patients and 81 (16.5%) female patients. The mean age was 60.2 years (range, 26-82 years). Lobectomy was performed in 77.8% of patients (*n*=382), sublobar resections in 3.7% (*n*=18), bilobectomy in 8.6% (*n*=42), and

pneumonectomy in 10% (*n*=49). The 30-day mortality for lobectomy and pneumonectomy was 1.0% (5 patients) and 1.8% (9 patients), respectively. At least one morbidity occurred in 137 (28%) of 491 patients.

Survival Analyses

Overall 5-year survival of 491 patients were found to be 51.8% (Figure 2). The number of cases in stages I, II and III were 253 (51.5%), 153 (31.2%), and 85 (17.3%). 5-year survival in stages I, II, and III were found 61.5%, 42.9%, and 39.1%, respectively (Figure 3).

Of all the patients, 158 (32.2%) were solid-predominant, 150 (30.5%) were acinar-predominant, 75 (15.3%) were lepidic-predominant, 80 (16.3%) were papillary-predominant, 22 (4.5%) were mucinous, five (1.0%) were micropapillary, and one (0.2%) was adenocarcinoma in situ. The clinicopathologic variables and their affects on survival for all 491 patients were shown in Table 1.

Univariate and Multivariate Analyses

A univariateanalysis showed that age ≥60 ($P = 0.006$), male gender ($P = 0.007$), papillary vs lepidic ($P = 0.002$), papillary vs acinar ($P = 0.008$), papillary vs mucinous ($P = 0.048$), solid vs lepidic ($P < 0.001$), solid vs acinar ($P <0.001$), solid vs mucinous ($P = 0.048$), including solid and/or papillary component (SP COM) ($P <0.001$), pathologic stage> I ($P< 0.001$), T status > T1 ($P = 0.001$), N involment ($P < 0.001$), pleural invasion ($P = 0.002$), and pneumonectomy ($P < 0.001$) were significantly associated with poor survival. On a multivariate analysis, age (OR = 1.49; % CI, 1.14-1.94; $P = 0.004$), SP COM (OR = 1.84; %CI, 1,35-2,51; $P < 0.001$), N involment (OR = 1.76; %CI, 1.21-2.56; $P =0.003$), pleural invasion (OR = 1.46; %CI, 1.04-2.06; $P = 0.029$), and pneumonectomy (OR = 1.65; %CI, 1,13-2.40; $P = 0.009$) were independent predictors of 5-year survival (Table 1).

Lepidic, acinar, and mucinous adenocarcinoma had 70.9%, 59.0%, and 66.6% 5-year survival, respectively, and there was no statistically significant difference between them. Whereas solid, papillary and micropapillary predominant histologic pattern had 41.0%, 40.5% and 0.0% 5-year survival (Figure 3). Compared to other histologic subtypes; solid predominant adenocarcinoma and papillary predominant adenocarcinoma harbored significantly lower survival to lepidic ($P < 0.001$, $P = 0.002$), acinar ($P< 0.001$, $P = 0.008$), and mucinous ($P = 0.048$, $P = 0.048$) subtypes respectively. The survival difference between solid and papillary subtypeswere not found statistically significant ($P = 0.668$). Micropapillary predominant pattern had worse prognosis and 5 year survival was nil. Lepidic predominant adenocarcinoma showed a considerably better survival than all other growth patterns (Table 2).

Overall solid and/or papillary component (SPCOM) were present in 327 patients (66.6%) and 5-year survival was 43.4%. SP COM free 164 patients (33.4%) had 67.7% 5-year survival ($P < 0.001$).

381 (77.6%) patients were found to be N0. N1 lymphatic invasion was detected in 49 (10%), and N2 lymphatic invasion in 61 (12.4%) patients. 5-year survival of N0, N1, and N2 patients were found 56.1%, 33.2%, and 38.6%, respectively (Figure 5). Correlation of subtype patterns with TNM status and 5-year survival are summarised in Table 2.

Visceral pleural invasion was observed in 103 (19%) of patients, and 5-year survival was found to be 29.5 %.

DISCUSSION

Since the IASLC/ATS/ERS classification has been proposed, many studies have investigated the correlations among the histologic subtypes and patient prognosis in pulmonary adenocarcinoma (4-6). In this study, we reviewed 491 of completely resected invasive lung adenocarcinoma patients for their clinicopathologic characteristics, prognostic factors, overall survival and survival associated histologic subtypes as well as their predictive value for the prognosis.

A variety of frequencies of the predominant subtypes of invasive adenocarcinoma were reported in the literature. In a cohort study, in stage I lung adenocarcinoma, the frequencies of lepidic, acinar, papillary, micropapillary, and solid predominant patterns were reported as5.6%, 45.1%, 27.8%, 2.3%, and 13.0%, respectively (4). Warth et al, had stated that the frequencies of lepidic, acinar, papillary, micropapillary, and solid predominant patterns were 8.1%, 42.5%, 4.7%, 6.8%, and 37.6%, respectively in stage I to IV adenocarcinoma (5). In our study, the frequenciesof predominant patterns were 15.3% for lepidic; 30.5% for acinar;16.3% for papillary; 1.0% for micropapillary;32.2% for solid and 4.5% for mucinous.

There is an increasing number of data confirming that solid subtype correlates with poor prognosis (7-10). In our series, solid and also papillary predominant adenocarcinoma had significantly worse survival compared to lepidic ($P < 0.001$, $P = 0.002$), acinar ($P < 0.001$, $P = 0.008$), and mucinous ($P = 0.048$, $P = 0.048$) subtypes respectively. The survival difference between solid and papillary subtype was not found statistically significant ($P = 0.67$). In our study solid and papillary predominant histologic pattern had 41.0%, and 40.5% 5-year survival, respectively. Although some studies have reported somewhat better survival rates for papillary predominant tumors (11), our results are consistent with that of Warth et al (5),that found similar survival rates for papillary and solid subtypes. Warth also suggested that the worse survival of the papillary subtype would probably be a result of different ethnic, and geographical patterns (5). In a study concluding stage I cases only, Yoshizawa had reported similar survival rates for lepidic, acinar and papillary predominant adenocarcinomas (4), whereas papillary subtype also had significantly worse prognosis when compared to lepidic and acinar subtypes

in stage I patients, respectively in our study (P =0.001, P =0.04). Generally, pulmonary mucinous adenocarcinoma patients are known to have poor overall survival when compared to patients with other subtypes (4,12,13). In our data, we had 22 (4.5%) mucinous adenocarcinoma patients with a 5-year survival rate of 66.6%. This survival rate is contradictory with the findings of the studies mentioned above. Recently, however, Shim et al, had shown that the survival of invasive mucinous adenocarcinomas can be compared with those of other predominant subtypes (14). And finally Warth et al, reported that invasive mucinous adenocarcinoma did better than most adenocarcinoma patients (5). We also think that these diversities are probably owing to the ethnic and geographical differences as Warth suggested (5).

We had only five patients with micropapillary adenocarcinoma and they had worse prognosis. The 5-year survival was nil. Consistent with our results Yoshizawa (15) and Tsubokawa et al (16) also reported a 0% 5-year survival. Tsubokawa et al reported micropapillary pattern as an independent predictive prognostic factor even in stage IA patients. They also suggested that these patients could require adjuvant therapy regardless of the stage (16).

Visceral pleural invasion (P = 0.002) were significantly associated with poor survival in our study. It was 10.7% in lepidic pattern whereas in papillary, acinar, solid, and micropapillary subtypes it is found 21.3%, 24%, 22.7%, and 40%, respectively. Hung et al, stated that visceral pleural invasion was more common in micropapillary and solid predominant groups and less frequent in the lepidic predominant group (9).

Nodal metastasis rates (N1+N2) vary by predominant pattern. In our study lymph node metastases was significantly associated with micropapillary subtype (40%). The other subtypes had shown similar rates of nodal metastases (solid 23.4%, acinar 22.7%, papillary 22.5%, and lepidic 18.7%). Travis et al, reported less frequent nodal metastasis in lepidic adenocarcinoma (7%) than papillary (43%); acinar (47%); solid (51%) and micropapillary adenocarcinoma (76%) (1).

Our study has some limitations due to its retrospective nature and single-center design. Secondly, we could not take EGFR or KRAS mutation status into consideration in our analyses.

In conclusion, solid and papillary predominant adenocarcinoma had significantly worse prognosis and more attention should be paid to these aggressive lung adenocarcinoma subtypes. Even the other subtypes (lepidic, acinar, and mucinous) with having a solid and/or papillary components affect survival adversely. Although stage was a powerful predictor of survival, IASLC/ATS/ERS and WHO classification is also an efficient predictor of patient survival, and should take part in the treatment planning of pulmonary adenocarcinoma. The poor prognostic group of solid, papillary and micropapillary subtypes may be candidates for adjuvant therapy even in the earlier stages of disease but future studies are needed.

Acknowledgment: We thank Hüseyin Candan from Medical Statistic for statistical evaluation.

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TABLE 1. The clinicopathologic variables and their affects on survival for 491 patients

Characteristics of patients	**Number of patients n (%)**	**Overall 5-Year survival rate**	**Univariate analysis *p*value[a]**	**Multivariate analysis**	
				Odds ratio (95% CI)	***p* value[b]**
Age mean 60.2			***0.006***	1.49 (1.14-1.94)	***0.004***
<60	235 (47.9)	55.8			
≥60	256 (52.1)	48.6			
Sex			***0.007***	1.47 (0.97-2.22)	0.071
Male	410 (83.5)	48.5			
Female	81 (16.5)	69.2			
Smoking			0.265		
Yes	362 (73.7)	51.3			
No	129 (26.3)	53.0			
Histologic type					
Acinar (1)	150 (30.6)	59.0	1-2: 0.394, ***1-3: 0.008***,	1-3: 0.58 (.39-.85),	***0.005***
Lepidic (2)	75 (15.3)	70.9	***1-4: <0.001,***1-5: 0.454,	1-4: 0.54 (.38-.76),	***<0.001***
Papillary (3)	80 (16.3)	40.5	***2-3: 0.002***, ***2-4: <0.001***, 2-	2-3: 0.57 (.36-.90),	***0.016***
Solid (4)	158 (32.2)	41.0	5: 0.834,	2-4: 0.53 (.35-.81)	***0.003***
Mucinous (5)	22 (4.5)	66.6	3-4: 0.668, ***3-5: 0.048,***		

Micropapillary**	5 (1.0)	0.0	***4-5: 0.048***		
In situ tumor**	1 (0.2)				
[c]SP COM			***<0.001***	1.84 (135-2.51)	***<0.001***
(+)	327 (66.6)	43.4			
(-)	164 (33.4)	67.7			
Pathologic stage				1.11 (0.77-1.60)	0.584
Stage I	253 (51.5)	61.5	***I-II: <0.001***		
Stage II	153 (31.2)	42.9	***I-III: <0.001***		
Stage III	85 (17.3)	39.1	II-III: 0.200		
N Status			**<0.001**	1.76 (1.21-2.56)	***0.003***
N0	381 (77.6)	56.1			
N+	110 (22.4)	36.4			
T Factor				1.32 (0.95-1.83)	0.097
T1	187 (38.1)	61.4	***1-2: 0.039***		
T2	190 (38.7)	52.9	***1-3: <0.001***		
T3	114 (23.2)	34.0	***2-3: 0.005***		
Pleural invasion			***0.002***	1.46 (1.04-2.06)	***0.029***
Yes	103 (21.0)	29.5			
No	388 (79.0)	55.9			
Extent of resection			**<0.001**	1.65 (1.13-2.40)	***0.009***
Lobectomy	442 (90.0)	54.0			
Pneumonectomy	49 (10.0)	32.4			

[a]Kaplan-Meier Log Rank (Mantel-Cox) test
[b]Cox proportional odds model
[c]SP COM: Solid and/or papillary component
*Micropapillary and in situ tumors were not included in the statistical study

TABLE 2. Correlation of subtype patterns with TNM status and 5-year survival

		Acinar (A)		**Lepidic (L)**		**Papillary (P)**		**Solid (S)**		**Mucineus (M)**		
		n	**OS[a] (%)**	**n**	**OS (%)**	**n**	**OS (%)**	**n**	**OS (%)**	**n**	**OS (%)**	**Univariate analysis *p*value[b]**
		150	59.0	75	70.9	80	40.5	158	41.0	22	66.6	A-P: 0.008 A-S: <0.001 L-P: 0.002 L-S: <0.001 P-M: 0.048 S-M: 0.048
Stage	**I**	81	69.3	44	86.9	44	47.5	71	48.4	10	90.0	A-P: 0.040 A-S: 0.012 L-P: 0.001 L-S: 0.001 P-M: 0.050
	II	45	50.7	44	46.8	22	31.2	58	36.9	6	83.3	
	III	24	45.0	12	46.7	14	36.2	29	30.1	6	22.2	A-S: 0.010
T factor	**T1**	59	62.8	28	85.8	35	49.0	50	56.9	11	77.9	L-P: 0.007 L-S: 0.046
	T2	55	65.2	37	62.3	30	46.9	62	38.5	5	75.0	A-S: 0.001 L-S: 0.033
	T3+T4	36	43.4	10	52.5	15	13.3	46	27.9	6	50.0	A-P: 0.010 A-S: 0.038 L-P: 0.050

Nodal Status	**N0**	116	61.8	61	81.6	62	41.1	121	44.4	17	80.5	A-P: 0.014 A-S: 0.002 L-P: <0.001 L-S: <0.001 P-M: 0.031 S-M: 0.048
	N1	21	55.1	4	0.0	6	33.3	15	17.3	1	-	A-S: 0.031
	N2	13	31.3	10	37.5	12	42.2	22	36.4	4	0.0	

[a]OS : Overal survival
[b]Kaplan-Meier Log Rank (Mantel-Cox) test. Only statistically significant ones were mentioned.
[*]One adenocarcinoma in situ and five micropapillary were not included

Figure legends:
FIG. 1. Microphotographs showing (a), acinar (H&E, x200), (b), lepidic (H&E, x100), (c), papillary (H&E, x200), (d), solid (H&E, x200), (e), mucinous (H&E, x200), (f), micropapillary (H&E, x200)**.**
FIG. 2. Overall survival of all patients.
FIG. 3. Overall survival of stage I, II, and III patients.
FIG. 4. Overall survival of all histologic subtypes.
FIG. 5. Overall survival of N0, N1, and N2 patients.