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Original Article / Özgün Makale

Papillary predominant histological subtype predicts poor survival in lung adenocarcinoma

Akciğer adenokarsinomunda papiller baskın histolojik alt tip sağkalımı kötü etkiler

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ABSTRACT

Background: This study aims to investigate whether papillary predominant histological subtype can predict poor survival in lung adenocarcinoma.

Methods: Between January 2005 and December 2016, a total of 80 patients with papillary predominant subtype lung adenocarcinoma (70 males, 10 females; mean age 60.7 years; range, 42 to 79 years) operated in our clinic were included in the study. These patients were compared with those having lepidic, acinar, and mucinous subtypes. Overall and five-year survival rates were evaluated.

Results: Five-year survival was 40.5% in papillary predominant histological subtype, while this rate was 70.9%, 59.0%, and 66.6% in lepidic, acinar, and mucinous subtypes, respectively. Papillary subtype showed significantly poor survival compared to lepidic (p=0.002), acinar (p=0.008), and mucinous subtypes (p=0.048). In Stage 1 disease, it was more evident (papillary, 47.5%, lepidic 86.9% [p=0.001], acinar 69.3% [p=0.040], and mucinous 90.0% [p=0.050]).

Conclusion: Our study results suggest that papillary predominant subtype predicts poor survival in lung adenocarcinoma and these cases may be candidates for adjuvant treatment modalities even in the earlier stages of disease.

Keywords: Lung adenocarcinoma, papillary subtype, prognostic factor, survival.

ÖZ

Amaç: Bu çalışmada papiller baskın histolojik alt tipin akciğer adenokarsinomunda sağkalımı kötü etkileyip etkilemediği araştırıldı.

Çalışma planı: Ocak 2005 - Aralık 2016 tarihleri arasında kliniğimizde ameliyat olan papiller baskın alt tipli akciğer adenokarsinomlu toplam 80 hasta (70 erkek, 10 kadın; ort. yaş 60.7 yıl; dağılım 42-79 yıl) çalışmaya alındı. Bu hastalar lepidik, asiner ve müsinöz alt tipler ile karşılaştırıldı. Genel ve beş yıllık sağkalım oranları değerlendirildi.

Bulgular: Beş yıllık sağkalım papiller baskın histolojik alt tipte %40.5 iken, bu oran lepidik, asiner ve müsinöz alt tiplerde sırasıyla %70.9, %59.0 ve %66.6 idi. Papiller alt tipin sağkalımı lepidik (p=0.002), asiner (p=0.008) ve müsinöz (p=0.0048) alt tiplere kıyasla, anlamlı düzeyde daha kötü idi. Bu durum, Evre 1 hastalıkta daha belirgindi (papiller %47.5, lepidik: %86.9 [p=0.001], asiner %69.3 [p=0.040] ve müsinöz %90.0 [p=0.050]).

Sonuç: Çalışma sonuçlarımız papiller baskın alt tipin akciğer adenokarsinomunda sağkalımı kötü etkilediğini ve bu olguların, hastalığın erken evrelerinde dahi, adjuvan tedavi yöntemleri için aday olabileceğini göstermektedir.

Anahtar sözcükler: Akciğer adenokarsinomu, papiller alt tip, prognostik faktör, sağkalım.

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Lung cancer is the most common cause of cancer-related mortality worldwide, and adenocarcinoma is the leading histological type.[1,2] In 2011, the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) proposed a new classification, and major histological patterns (lepidic, acinar, papillary, solid, and micropapillary) were defined.[3] They also recommended that lung adenocarcinomas should be classified according to their predominant subtypes. Numerous studies have been published on the clinical behavior and survival effect of predominant subtypes developed based on this new classification.[4-12] These studies have often shown that patients with lepidic predominant adenocarcinomas have the most favorable outcome, and lung adenocarcinoma with solid and micropapillary predominant subtypes have a poor prognosis. However, the evaluation of patients with papillary predominant lung adenocarcinoma has not been clearly described, yet.

In the present study, we aimed to investigate whether papillary predominant histological subtype can predict poor survival in lung adenocarcinoma.

PATIENTS AND METHODS

In this retrospective study, we reviewed our thoracic surgical database of 491 lung adenocarcinoma patients who had pulmonary resection between January 2005 and December 2016. According to the IASLC/ATS/ERS lung adenocarcinoma classification, invasive adenocarcinomas formerly termed as "mixed subtype" were now classified according to their predominant subtype.[3] Using this approach, the proportions of each histological subtype were estimated in a semiquantitative manner and a predominant pattern was defined.[4] By our pathology department, 491 lung adenocarcinoma slides were re-evaluated according to this classification. In the pathological examination, adenocarcinoma, which showed a single-row organization using alveolar roof, was described as lepidic pattern; the ones which formed circular glandular structures including lumen as acinar pattern; structures containing fibrovascular core into the lumen as papillary pattern; those containing glandular cell groups developing into the lumen without fibrovascular core as micropapillary pattern; and those containing layered cell groups without glandular and papillary structures as solid pattern.[3] Due to the fact that the majority of the adenocarcinomas are heterogeneous, the predominant pattern based on the rates in the samples was indicated. Papillary pattern is shown in Figure 1.

In total, 80 (16.3%) of our 491 cases featured a papillary predominant pattern and compared with 248 (50.5%) patients having lepidic, acinar, and mucinous (LAM) predominant subtypes in terms of clinicopathological features and survival. Since the solid and micropapillary subtypes (n=163, 33.2%) were known to have poor survival, these subtypes were not used for comparison. Finally, a total of 80 papillary patients (70 males, 10 females; mean age 60.7 years; range, 42 to 79 years) were included in the study. As having the similar survival rates, lepidic, acinar,

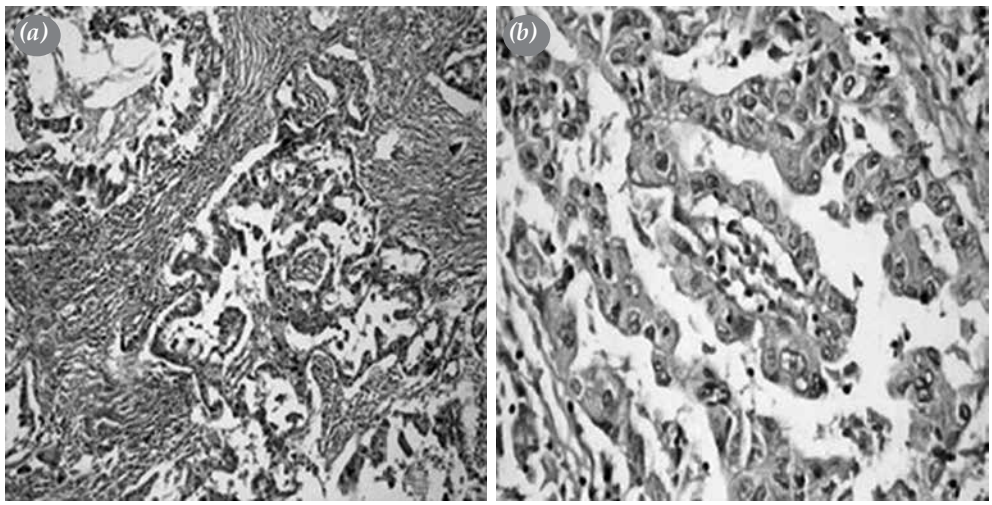

Figure 1. (a) On the inner surface of the glandular structures, atypical cell proliferation which indicated real papillary and micropapillary development containing fibrovascular core is observed that developed towards the cavity (H-E×100). **(b)** (H-E×400).

and mucinous subtypes had merged as group LAM. In our cohort, the main purpose was to evaluate the prognostic significance of papillary predominant subtype. Therefore, primary endpoint was overall survival (OS) and our study did not focus on local and distant metastasis and disease-free survival.

Patients were excluded if they had neoadjuvant therapy, incomplete resection, and metastatic disease or nodule detected at the time of surgery. Operative mortality was defined as any death occurring within 30 days after surgery and these patients were also excluded.

The patients without enlarged lymph nodes on thoracic computed tomography (CT) and a positron emission tomography (PET)-negative mediastinum proceeded directly to surgery. However, enlarged lymph nodes on CT, independently from PET findings underwent endobronchial ultrasound (EBUS)-transbronchial needle aspiration (TBNA) and/or mediastinoscopy. The patients having N2 disease received adjuvant chemotherapy and/or radiotherapy.

All patients received lung resection and mediastinal lymph node dissection. Tumor stage was determined based on the seventh edition of the Tumor, Node, Metastasis (TNM) classification of the American Joint Committee on Cancer and the International Union Against Cancer. The patients were evaluated in terms of clinical features such as age, gender, comorbid disease, smoking history, extent of resection, tumor size, visceral pleural invasion, papillary cell ratios, lymph node involvement, pathological stage, and survival.

The patients were followed quarterly for the first two years and at biannually thereafter. The date of

Table 1. Comparison of clinicopathological characteristics of the papillary with LAM

	Papillary		LAM		Chi-square test
	n	%	n	%	*p**
Age (year)					0.432
<60	35	43.8	121	48.8	
≥60	45	56.2	127	51.2	
Gender					0.080
Male	70	87.5	195	78.6	
Female	10	12.5	53	21.4	
Smoking					0.713
Yes	61	76.2	184	74.2	
No	19	23.8	64	25.8	
Comorbidity					0.734
Yes	44	55.0	131	52.8	
No	36	45.0	117	47.2	
Pathologic stage					0.980
Stage 1	44	55.0	136	54.8	
>Stage 1	36	45.0	112	45.2	
N Status					0.831
N0	62	77.5	195	78.6	
N+	18	22.5	53	21.4	
T Status					0.544
T_1	35	43.8	99	39.9	
>T_1	45	56.2	149	60.1	
Pleural invasion					0.772
Yes	17	21.3	49	19.8	
No	63	78.2	199	80.2	
Extent of resection					0.357
Lobectomy	72	90.0	231	93.1	
Pneumonectomy	8	10.0	17	6.9	

LAM: Lepidic, acinar, mucinous; * Pearson chi-square test.

death was reached from the medical records and verified by a software program linked to the national population registration system.

A written informed consent was obtained from each participant. The study protocol was approved by the Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) values, or number and frequency. Overall survival was estimated using the Kaplan-Meier method, with patients followed from time of surgery until death from any cause, and with a log-rank test to probe for significance. A multivariate analysis of variables was performed using the Cox proportional odds regression model. The correlation between the histological subtypes and patient characteristics was analyzed using the Pearson chi-square test. A p value of <0.05 was considered statistically significant.

RESULTS

Of all papillary cases, 61 (76.3%) were smokers with a mean tobacco use of 45.6 (range, 17 to 120) pack years and 44 (55%) had at least one comorbidity (i.e., chronic obstructive pulmonary disease, coronary heart disease, hypertension, and diabetes mellitus). Lobectomy was performed in 64 (80.0%), bilobectomy in eight (10.0%), pneumonectomy in eight patients (10.0%). Baseline demographic and clinicopathological characteristics of papillary cases are shown in Table 1.

The median size of tumors was 3.6 (range, 0.4 to 10.0) cm. Visceral pleural invasion was present in 17 patients (21.3%) and, in nine of these patients (53%), parietal pleural and/or chest wall invasion were present. Nodal involvement was identified in 22.5% (N1=6 patients; N2=12 patients) of the papillary, 18.4% of lepidic, 22.7% of acinar, and 22.7% of mucinous predominant subtypes (LAM=21.4%, chi-square test, p=0.831). According to the T status, T1 was found in 43.8% of papillary, and 38.2%, 39.3%, and 50.0% of lepidic, acinar, and mucinous subtypes, respectively (LAM=39.9%, chi-square test, p=0.544). A total of 44 patients (55.0%) were in Stage 1, 22 (27.5%) were in Stage 2, and 14 (17.5%) were in Stage 3. Among the patients with Stage 1 disease, five-year survival rate was 47.5% in the papillary predominant subtype and 75.7% in the LAM group (p=0.001).

Five-year survival was 40.5% in papillary predominant histological pattern, while this rate was 70.9%, 59.0%, and 66.6% in LAM, respectively. Papillary subtype showed significantly poor survival compared to lepidic (p=0.002), acinar (p=0.008), and mucinous subtypes (p=0.048) (Table 2).

In the univariate analysis, the papillary subtype was compared with LAM and, irrespective of gender, comorbidity, size of tumor, and pleural invasion; age ≥60 years (p=0.001), smoking history (p=0.001), Stage 1A disease (p=0.002), N0 disease (p<0.001), and lobectomy (p=0.001) were found to be significantly associated with poor five-year survival in papillary subtype. In multivariate analysis, papillary subtype (Odds ratio [OR]=1.647; 95% confidence interval [CI], 1.155-2.348; p=0.006), N+ disease (OR=1.848; 95% CI: 1.255-2.720; p=0.002), pleural invasion (OR=1.933; 95% CI: 1.249-2.991; p=0.003), and extent of resection (OR=2.096; 95% CI: 1.240-3.544; p=0.006) were

Table 2. Five-year survival of predominant subtypes

			Five-year survival	Univariate analysis
Predominant subtypes	n	%	%	*p**
Papillary	80	16.3	40.5	Lepidic: 0.002 Acinar: 0.008 Mucinous: 0.048
Lepidic	76	15.5	70.9	Acinar: 0.394 Mucinous: 0.834
Acinar	150	30.5	59.0	Mucinous: 0.454
Mucinous	22	4.5	66.6	

Kaplan-Meier Log Rank (Mantel-Cox) test.

Table 3. Comparison of clinicopathological characteristics of the papillary with LAM

	Papillary		LAM		Papillary	LAM	Univariate analysis	Multivariate analysis		
Characteristics of patients	n	%	n	%	%	%	*p**	*p***	OR	CI 95%
Age (mean)		60.7		60.2				0.805	1.046	0.732-1.495
<60	35	43.8	121	48.8	40.7	59.7	0.104			
≥60	45	56.2	127	51.2	40.3	69.7	0.001			
Gender								0.093	1.555	0.928-2.605
Male	70	87.5	195	78.6	41.9	59.7	0.027			
Female	10	12.5	53	21.4	27.8	80.8	0.002			
Smoking								0.259	1.253	0.847-1.853
Yes	61	76.2	184	74.2	39.0	64.0	0.001			
No	19	23.8	64	25.8	44.4	64.0	0.115			
Comorbidity								0.845	1.037	0.721-1.492
Yes	44	55.0	131	52.8	41.0	61.4	0.038			
No	36	45.0	117	47.2	39.9	67.5	0.005			
N Status								0.002	1.848	1.255-2.720
N0	62	77.5	195	78.6	41.1	70.8	<0.001			
N+	18	22.5	53	21.4	40.4	36.2	0.797			
T Status								0.630	1.098	0.750-1.607
T_1	35	43.8	99	39.9	49.0	71.3	0.012			
>T_1	45	56.2	149	60.1	34.1	59.4	0.010			
Pathologic stage								0.230	1.328	0.484-1.169
Stage 1A	28	35.0	85	34.3	48.6	77.2	0.002			
Stage 1B	16	20.0	51	20.6	46.9	73.4	0.137			
>Stage 1	36	45.0	112	45.1	31.9	49.6	0.107			
Pleural invasion								0.003	1.933	1.249-2.991
Yes	17	21.3	49	19.8	07.1	35.7	0.010			
No	63	78.7	199	80.2	49.3	67.8	0.018			
Extent of resection								0.006	2.096	1.240-3.544
Lobectomy	72	90.0	231	93.2	40.9	66.2	0.001			
Pneumonectomy	8	10.0	17	6.8	37.5	37.1	0.616			

LAM: Lepidic, acinar, mucinous; * Kaplan-Meier Log Rank (Mantel-Cox) test; ** Cox regression-Enter method; OR: Odds ratio; CI: Confidence interval.

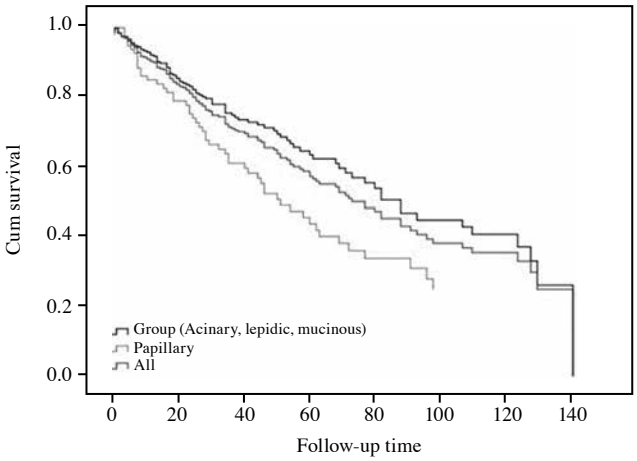

Figure 2. Survival function at mean of covariates (Cox regression-Enter method, p=0.006).

independent predictors of five-year survival (Table 3, Figure 2).

The mean papillary pattern ratio in these 80 predominant papillary patients was 94.0±14.1% with a median value of 100% (range, 40 to 100%). Of 248 patients in the LAM group, 51 had a mean papillary pattern of 7.8±11.4% with a median value of 0.0% (range, 0 to 45%). In the LAM group, patients with and without papillary component had a five-year survival rate of 47.4% and 66.1%, respectively, although it did not reach statistical significance (p=0.408).

The mean follow-up was 46.5 (range, 2 to 138) months. The mean survival for papillary predominant and LAM patients were found to be 61.2±5.9 and 86.3±4.2 months, respectively. Overall five- and 10-year survival rates were 40.5%, and 22.7% for papillary and 64.1% and 44.1% for LAM cases, respectively.

DISCUSSION

In an international multidisciplinary panel in 2011, the IASCL/ATS/ERS developed a classification which recommended that resected lung adenocarcinoma should be classified according to the predominant histological subtype.[3] Since its publication, the prognostic value and clinical relevance of this classification have been validated in multiple independent studies worldwide.[6,7,11] These studies have confirmed a 100% survival outcome of adenocarcinoma *in situ* with 100% lepidic growth pattern and have consistently reported that the worst survival outcomes are seen in patients with invasive adenocarcinoma with predominately micropapillary and solid patterns.[6,9,11] However, specifically for the papillary pattern, confusing data with respect to incidence, clinical associations, and prognostic impact have been reported.[12] The incidence of papillary predominant cases has been estimated ranging from 5% up to one-third of adenocarcinoma cases.[6,13] In our study, this rate was 16.3%.

Another controversy is the prognostic impact of the papillary pattern. Previous studies reported that papillary predominant cases had an intermediate OS.[8,11] However, the others suggested a compromised survival for papillary predominant adenocarcinoma similar to patients with micropapillary and solid predominant subtypes.[7,14,15] Consistent with these findings, papillary, solid, and micropapillary predominant histological pattern had 40.5%, 40.6%, and 0.0% five-year survival rate, respectively, while lepidic, acinar, and mucinous predominant histological pattern had 70.9%, 59.0%, and 66.6% five-year survival rate, respectively in our study.

Jemal et al.[1] showed that disease stage was a highly significant predictor of survival. Yoshizawa et al.[6] and Tsubokawa et al.[16] also found that lepidic, acinar, and papillary predominant adenocarcinomas had an intermediate clinical behavior in Stage 1. Controversially, in our study, there was a significant difference in five-year survival rates; as such papillary predominant subtype adenocarcinoma patients in Stage 1 (n=44; 55%) had a five-year survival rate of 47.5%, while the LAM group (n=136; 54.8%) had a rate of 75.7% (p=0.001). Comparing the papillary with the LAM group which were beyond Stage 1, the five-year survival rates were 31.9% and 49.6%, respectively; however, it did not reach statistical significance (p=0.107).

The rates of nodal metastasis vary by predominant pattern. In our study, all subtypes showed similar results (papillary 22.5%, lepidic 18.7%, acinar 22.7%, and mucinous 22.7%). Travis et al.[3] reported that lepidic adenocarcinoma was node-positive in 7% of the cases, in contrast to papillary, acinar, solid and micropapillary adenocarcinoma which were node-positive in 43%, 47%, 51%, and 76% of the cases, respectively.

Although disease stage is a powerful predictor of survival, the IASLC/ATS/ERS classification is also a useful predictor of survival and should take part in the treatment planning of lung adenocarcinoma. In our study, besides histological subtype, the presence of papillary cell component also affected the prognosis adversely.

The main limitations of the present study are its retrospective nature and single-center design.

Therefore, further prospective, multi-center studies are needed to evaluate the prognostic value of papillary predominant adenocarcinoma of the lung. In addition, our survival analysis did not record epidermal growth factor receptor or Kirsten rat sarcoma mutations and vascular and/or lymphatic invasion of the tumor.

In conclusion, papillary predominant subtype predicts poor survival and these patients may be candidates for adjuvant treatment modalities even in the earlier stages of disease. However, this should be clearly confirmed in further large-scale adenocarcinoma cohorts.

Declaration of conflicting interests

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