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Clinical and Pathologic Prognostic Factors That Are Influential in the Survival and Prognosis of Lung Adenocarcinomas and Invasive Predominant Subtypes

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Therapeutic approaches to lung adenocarcinomas differ because of their heterogeneous morphologies, prognoses, and clinical features. For this reason, new histopathologic classifications for lung adenocarcinomas were done by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society to form subtypes with homogeneous prognoses. There are limited clinical data in the literature on the prognosis of the subgroups formed according to the new classification. A total of 86 patients with adenocarcinoma who had undergone pathologic stages I and II curative resection and mediastinal lymph node dissection were retrospectively analyzed according to the seventh TNM staging system revised by the Union for International Cancer Control/American Joint Committee on Cancer. Histologic subtyping was reassessed according to the dominant histopathologic morphology. When survival rates of lung adenocarcinomas were compared according to their localizations, it was observed that adenocarcinomas localized to the right hemithorax had a longer survival than the ones with left hemithorax localization ($P = 0.026$). When necrosis was taken into account,

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it was seen that necrosis rate was higher in solid predominant type compared with other types, whereas it was lower in acinary type ($P = 0.046$). When peritumoral lymphovascular invasion data were assessed, it was observed that disease-free survival was influenced in a negative fashion ($P = 0.018$). New histopathologic classification of adenocarcinomas has been a step forward to attaining homogeneous groups, but when the biologic heterogeneity of the adenocarcinomas is taken into account, the authors believe that considering the peritumoral lymphatic vascular invasion, left hemithorax localization, and tumoral necrosis entities in the upcoming TNM classification will contribute to evaluating the prognosis.

Key words: Adenocarcinoma – Invasive adenocarcinoma – Solid – Recurrence

Lung cancers are the leading cause of cancer-related deaths worldwide.[1] The most common type of lung cancer is adenocarcinoma (30%–50%). The incidence of lung adenocarcinomas is continually rising.[2]

Yesner and Carter[3] long ago reported a 7% increase in lung adenocarcinomas, 4% decrease in squamous cell carcinoma, and a 3% decrease in small-cell cancers in second-decade male populations.

In 2011, it was reported that a total of 40% of lung cancers are adenocarcinomas; of the remaining lung cancers, 30% are squamous cell carcinomas, 20% are small-cell carcinomas, and 10% are large-cell carcinomas.[4]

Adenocarcinomas are heterogeneous in pathologic, clinical, radiologic, and surgical features and clinical prognosis. Adenocarcinomas were divided into 4 subtypes according to their predominant morphologic structure by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS).[4]

1. Preinvasive lesions: atypical adenomatous hyperplasia; adenocarcinoma *in situ* (mixed, nonmucinous, mucinous)
2. Minimally invasive adenocarcinoma (nonmucinous, mucinous, mixed)
3. Invasive adenocarcinoma (lepidic, acinar, solid, papillary, micropapillary)
4. Variants (invasive mucinous, colloid, fetal, enteric)

According to the histologic classifications of adenocarcinomas according to dominant morphologic structure, the clinical prognoses of the subtypes are not clearly expressed in the literature. Providing the homogeneity within the subtypes with regard to clinical prognosis is important in approaches during presurgical, surgical, and postsurgical intervals.

Patients and Methods

Medical records were retrospectively assessed for adenocarcinoma patients between the years 2000 and 2010 who previously had neither preoperative neoadjuvant therapy nor adjuvant therapy and who had stages Ia, Ib, IIa, and IIb resection according to the revised seventh TNM classification. Between the years 2000 and 2010, resection was performed on 487 non–small-cell lung cancer patients, and 86 of these patients were found to have either stage I or II adenocarcinomas. Slides of the patients were reviewed and reevaluated according to the new histologic staging. Patients were evaluated according to age, sex, tumor size (T size), tumor localization, surgical procedure, subtypes, recurrence, and survival. Clinical outcomes were determined according to survival, disease-free survival, and recurrence period.

All patients underwent preoperative routine thorax–upper abdomen and brain computed tomography (CT), and bone scintigraphy. After clinical staging, endobronchial lesions were excluded via bronchoscopy in centrally located lesions. In patients with pathologic-size mediastinal lymphadenopathies in thorax positron emission tomography–CTs, N_2 was assessed from 3 to 4 mediastinal lymph node levels of upper and lower paratracheal, pretracheal, and anterior subcarinal nodes obtained by routine mediastinoscopy before resection.

During operation, 87.2% of the patients had lobectomies, a minimum of 3 to 4 lymph nodes were dissected from N_1 and N_2 stations for sampling, and median clinical follow-up was 4 years (range, 2–13.1 years).

Pathologic assessment

All biopsy and resection materials for the 86 patients were reevaluated by light microscopy and reclassified according to the new IASLC/ATS/ERS classification of lung adenocarcinomas.[4] Moreover, tumor sizes were microscopically measured and reassessed with regard to lymphovascular invasion of peritumoral tissue in lung and metastatic lymph nodes.

Statistical assessment

The SPSS 20 program and Kaplan-Meier method–log-rank test were used to analyze the recurrence and disease-free survival rates for patients with adenocarcinomas according to tumor size, adenocarcinoma subtypes, and predominant structures of invasive adenocarcinoma (SPSS, IBM software). Four-cell χ^2 test was used for binary comparisons. The time interval between the patient's operation and his or her last available follow-up date or exit date for any reason was accepted as overall survival, and the time from his or her operation to the first clinically determined recurrence date or non–cancer-related exit date was considered to be disease-free survival. $P < 0.05$ was considered to be statistically significant.

Results

Adenocarcinoma subtypes were evaluated according to age, sex, localization, stage, size, nodal invasion, recurrence, and survival.

A total of 69.8% of the patients were older than 60 years, 83.7% were male, and 16.3% were female (Table 1).

Histologically, 70 patients (81.4%) had invasive subtype, 11 patients (12.8%) had variant subtype, and 5 patients (5.8%) had preinvasive adenocarcinoma subtypes (Table 1).

Table 1 Clinical features and histologic distribution of the patients

	No. of patients (%)
Age, y	
60 and over	60 (69.8)
Between 50–60	16 (18.6)
Between 40–50	9 (10.5)
Between 30–40	1 (1.2)
Total	86 (100)
Sex	
Male	72 (83.7)
Female	14 (16.3)
Subtypes	
Preinvasive type	5 (5.8)
Variant type	11 (12.8)
Invasive type	70 (81.4)
Acinar	33 (38.4)
Solid	27 (31.4)
Lepidic	5 (5.8)
Papillary	3 (3.5)
Micropapillary	2 (2.3)
Stage	
Ia	21 (24.4)
Ib	17 (19.8)
IIa	27 (31.4)
IIb	21 (24.4)
Localization	
Right	57 (66.3)
Left	29 (33.7)
Surgical procedure	
Segmentectomy	6 (7)
Lobectomy	75 (87.2)
Bilobectomy	5 (5.9)

1. Assessment of lung adenocarcinomas with regard to tumor localizations

A total of 57 of the adenocarcinomas (66.3%) were in the right hemithorax, and 29 (33.7%) were in the left hemithorax. There were no statistically significant differences with regard to right/left lung localization between adenocarcinoma histologic subtypes and invasive adenocarcinoma predominant subtypes. However, survival was found to be statistically longer in types with right hemithorax localization ($P = 0.026$; Table 2).

Invasive adenocarcinomas had a tendency to locate more in the superior lobe localizations compared with the other 2 subtypes, and this was found to be statistically significant ($P = 0.008$; Table 3). Although it was determined that superior lobe localization did not contribute to survival compared with other localizations, survival rate was significantly lower in left superior lobe lesions compared with right superior lobe lesions ($P = 0.039$; Table 2).

2. Assessment of adenocarcinomas with regard to stage

In our series, 21 patients (24.4%) were stage Ia, 17 patients (19.8%) were stage Ib, 27 patients (31.4%) were stage IIa, and 21 patients (24.4%) were stage IIb. In 13 patients with stage II there was N_1 and in 4 patients there was 1 lymph node invasion, 3 patients had 2 invasions, and 2 patients had 4 to 5 invasions.

There was a statistically significant difference between the disease-free survival intervals of stages Ia and Ib (log-rank, $P = 0.030$; Table 2).

Table 2 Clinical-pathologic data influential on survival

	No. (%)	Five-year disease-free survival, %	*P* value
Stage			
Ia	21 (24.4)	90.5	Between Ia and
Ib	17 (19.8)	58.8	Ib: 0.030*
IIa	27 (31.4)	73.1	Between IIa
IIb	21 (24.4)	47.6	and IIb: 0.041*
Lymph node			0.001*
Positive	13 (15.1)	46.2	
Negative	73 (84.9)	72.2	
PLI			0.018*
Positive	27 (31.4)	51.9	
Negative	59 (68.6)	75.9	
Superior lobe localization			0.039*
Right superior	32 (63.5)	75	
Left superior	19 (36.5)	47.4	
Invasive predominant types			0.4
Acinar	33 (38.4)	65.6	
Solid	27 (31.4)	59.3	
Lepidic	5 (5.8)	100	
Localization			0.026*
Right	57 (66.3)	73.2	
Left	29 (33.7)	58.6	
VPI			
Positive	36 (41.9)	60—N_1 (36/9)	0.035*
Negative	50 (58.1)	78—N_1 (50/4)	0.032*

PLI, peritumoral lymphovascular invasion; VPI, visceral pleura invasion.

Table 3 Comparison of the invasive type with the other types

	Invasive/ other type, No.	*P* value
T marker		0.047*
Less than 3 cm	25/10	
More than 3 cm	45/6	
N marker		0.272
N_0	58/15	
N_1	12/1	
M marker		0.244
M_0	51/13	
M_1	20/2	
Localization		0.008*
Superior lobe	47/5	
Other lobe	23/11	
Recurrence		0.016*
Positive	26/1	
Negative	44/15	
Peritumoral lymphovascular invasion		0.016*
Positive	26/1	
Negative	44/15	
Necrosis		0.410
Positive	19/6	
Negative	51/10	
Survival at 5 y		0.022*
Invasive and others	70/16	

M marker, metastasis; N marker, lymph node involvement; T marker, tumor.

*$P < 0.05$.

Stage Ia comprised a patient group that included 5 patients with preinvasive adenocarcinoma, 14 patients with invasive adenocarcinoma (2 lepidic, 5 acinar, 2 papillary, and 5 solid), and 2 patients with variant-type adenocarcinoma.

Stage Ib comprised 14 patients with invasive adenocarcinoma (1 lepidic, 6 acinar, 1 micropapillary, and 6 solid) and 3 patients with variant-type adenocarcinoma.

There was a statistically significant difference between the disease-free survival intervals of stages IIa and IIb as well (log-rank, $P = 0.040$; Table 2). The stage IIa group had 24 patients with invasive adenocarcinoma (14 acinar, 1 papillary, and 9 solid) and 3 patients with variant type. Stage IIb had 18 patients with invasive adenocarcinoma (2 lepidic, 8 acinar, 7 solid, and 1 micropapillary) and 3 patients with variant type.

Our series was classified according to the seventh TNM classification, and when the disease-free survival rates between stages Ia-Ib-IIa and IIb were compared it was seen that stage IIb had the shortest survival period and the difference was statistically significant (Table 2 and Fig. 1).

There were no statistically significant differences between stages Ib and IIa when disease-free survivals were compared (log-rank, $P = 0.4$; data not shown).

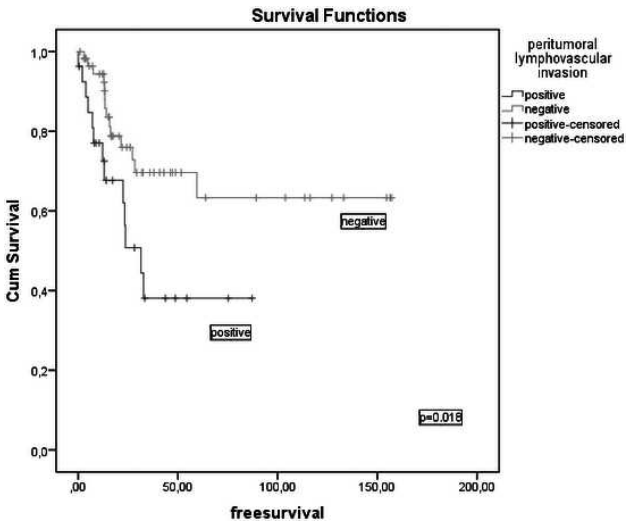

Fig. 1 Kaplan-Meier analysis of recurrence-free disease survival according to stages.

Table 4 Comparison of the adenocarcinomas with T size more and less than 3 cm

	T size marker, No. (%)		
	Less than 3 cm	More than 3 cm	*P* value
Necrosis			0.003*
Positive	4	21	
Negative	31	30	
PLI			0.04*
Positive	7	20	
Negative	28	31	
Lymph node involvement			0.039*
Positive	2	11	
Negative	33	40	
Recurrence			0.001*
Positive	4	23	
Negative	31	28	
Disease-free survival at 5 y	35 (88.2)	51 (54.9)	0.006*

PLI, peritumoral lymphovascular invasion.

3. Assessment of T size of adenocarcinoma cases

In 29 cases (33.7%) tumor sizes were ≥3 cm and <5 cm, in 21 cases (24.4%) tumor sizes were ≥2 cm and <3 cm, in 16 cases (18.6%) tumor sizes were ≥5 cm and <7 cm, and in 11 cases (12.8%) tumor sizes were ≤2 cm.

Of the adenocarcinomas, tumor size was smaller than 3 cm for 51 cases (59.3%), and 35 cases (40.7%) were larger than 3 cm. Tumor necrosis, lymph node invasion (N_1), and peritumoral lymphatic invasion were all found to be statistically higher in tumors larger than 3 cm ($P = 0.003/0.039/0.04$; Table 4).

When cases with T size larger than 3 cm were compared with cases with a T size smaller than 3 cm, recurrence rate was found to be significantly higher ($P = 0.001$). Five-year disease-free survival rate was 54.9% in tumors larger than 3 cm, whereas it was 88.2% in tumors smaller than 3 cm (log-rank, $P = 0.006$; Table 4).

In invasive adenocarcinomas and solid predominant subtypes, T size was larger than 3 cm in most cases, and this ratio was found to be significantly high ($P = 0.047/0.020$; data not shown).

4. Assessment of pleural involvement of adenocarcinomas

In 35 cases (41.9%) visceral pleural involvement was seen, and in 51 cases (58.1%) no pleural involvement was seen. It was determined that pleural involvement had no effect on disease-free survival, but it had an effect on overall survival (log-rank, $P = 0.035$; Table 2).

A total of 9 of the 36 patients who had pleural involvement had N_1, and 4 of the 50 patients who did not have pleural involvement had N_1. N_1 was found to be statistically higher in patients with pleural involvement ($P = 0.037$; data not shown). In 19 of the 36 patients with pleural involvement and in 8 of the 50 patients who did not have pleural involvement, there was peritumoral lymphatic invasion. Pleural involvement rate was statistically significant in patients with peritumoral lymphatic invasion ($P < 0.001$; data not shown).

There was no difference with regard to pleural involvement between invasive adenocarcinoma predominant subtypes and adenocarcinoma subtypes.

5. Assessment of nodal involvement of adenocarcinomas

In our series, 73 patients (84.9%) had no lymph node involvement, whereas 13 patients (15.1%) had lymph node involvement. Survival rate was 61.5% in those patients with nodal involvement and 72.2% in the patients without nodal involvement. Disease-free survival rate was found to be low in patients with nodal involvement ($P = 0.001$; Table 2).

In tumors larger than 3 cm, incidence of N_1 and peritumoral lymphatic invasion was determined to be high ($P = 0.039/0.048$; Table 4). In 27 of the patients (31.4%), there was peritumoral lymphatic invasion and in the remaining 59 (68.6%) there were no signs of peritumoral lymphatic invasion.

In patients with peritumoral lymphatic invasion, the survival rate was found to be 51.9%, and it was 75.9% in the patients who did not have such an invasion (log-rank, $P = 0.018$). The significant unfavorable effect of peritumoral lymphovascular invasion on disease-free survival has been determined (Table 2).

In our series, there was no significant difference between invasive adenocarcinomas and other types according to lymph node involvement; however, peritumoral lymphovascular invasion was determined to be significantly higher in invasive adenocarcinomas ($P = 0.016$; Table 3).

6. Assessment of tumoral necrosis of adenocarcinomas

In 25 patients (29.1%) tumoral necrosis was seen, but in 61 patients (70.9%) there was no tumoral necrosis. In tumors larger than 3 cm, tumoral necrosis rate was significantly high ($P = 0.003$; Table 4).

The necrosis ratio in solid predominant invasive subtype showed major differences compared with other types. Although the necrosis ratio was high in

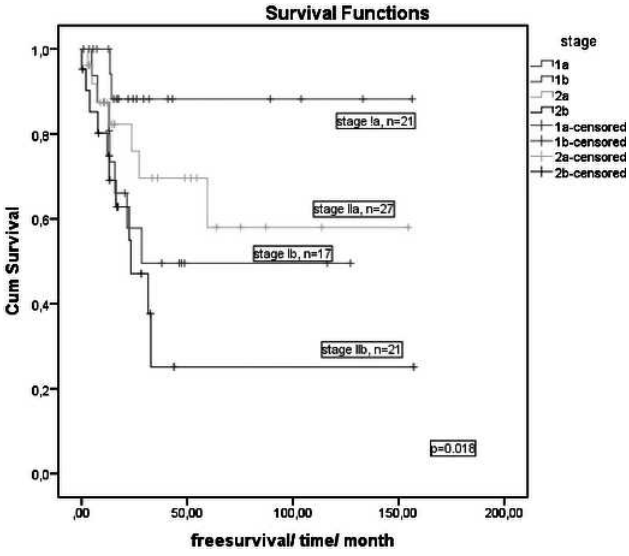

Fig. 2 Lymphovascular invasion's effect on disease-free survival adenocarcinomas.

the solid type, it was low in the acinar type ($P = 0.043$).

In our series, we did not determine any effect of tumoral necrosis on general survival and disease-free survival.

Assessment of peritumoral lymphovascular invasion

It was observed that peritumoral lymphovascular invasion affects disease-free survival. When 27 patients (31.4%) with lymphovascular invasion and 59 patients (68.6%) with no reports of lymphovascular invasion were compared with regard to disease-free survival, survival rate was found to be 51.9% in the group with lymphovascular invasion and 75.9% in the group without the invasion (log-rank, $P = 0.018$; Table 2 and Fig. 2). Recurrence rate was calculated to be significantly higher in the group with lymphovascular invasion ($P = 0.014$). A total of 13 of the 27 patients with lymphovascular invasion had N_1, whereas none of the 59 patients without lymphovascular invasion had N_1 ($P = 0.000$).

Surgical procedures and complications

A total of 75 of the patients (87.2%) underwent lobectomy, whereas 6 patients (7%) had segmentectomy and 5 patients (5.9%) had bilobectomy and systematic lymph node dissection. The most common complication in the postoperative period was persistent air leak (8.1%) and empyema (3.5%).

Rate of recurrence and mortality

A total of 27 patients (31.4%) had recurrence during follow-up, and there was no recurrence in 59 patients (68.6%). Recurrence rate was higher in invasive adenocarcinomas both in stage I and stage II compared with the other 2 subtypes ($P = 0.016$). There were no significant differences in recurrence rate between invasive adenocarcinoma predominant subtypes.

In our series, 61 patients (70.9%) were alive at the last visit, whereas 25 patients were dead. A total of 22 patients (25.6%) died because of a cancer-related reason and 3 had non–cancer-related mortalities.

Discussion

A total of 86 patients who underwent resection and systematic lymph node dissection because of stages I and II adenocarcinoma were separated into types and stages according to the seventh TNM classification and new lung adenocarcinoma histomorphologic classification. Five-year survival following resection in the preinvasive type was 100% and in accordance with literature data.[5]

In our series, adenocarcinoma types known as mixed adenocarcinomas were overly composed in number, but because the mixed types were considered to be an invasive adenocarcinoma group according to the new classification, our series ended up including mostly invasive adenocarcinomas.

In tumors larger than 3 cm, peritumoral lymphovascular invasion, lymph node involvement, recurrence rate, and necrosis rate were all higher compared with tumors smaller than 3 cm. It has been observed that a T size exceeding 3 cm is a marker of poor prognosis. In the literature, the number of reports dealing with tumors exceeding 3 cm is limited.

In the invasive adenocarcinoma type and especially in the solid predominant type, the tumor size was larger than 3 cm compared with other types. Rate of necrosis is significantly higher in solid invasive types compared with other types. Current literature data accept the presence of necrosis as a sign of poor prognosis, along with recurrence rate.[6]

In our series, necrosis did not have a significant effect on overall survival and disease-free survival. Solid predominant invasive type was assigned to the high-grade malignant potential group in the literature.[5,7–11]

In our series, it was seen that malignity criteria and aggressivity were high in cases with a tumor

size larger than 3 cm. Solid-type tumors had more necrosis and were mostly tumors exceeding 3 cm. Survival was also shorter in solid predominant type compared with other types. Taking all of these observations and the literature data into account, solid predominant type was assessed to be a high-grade invasive adenocarcinoma.

There were a lot of studies that reported a 5-year survival rate of close to 100% in the lepidic predominant type.[15,19–21] In our study, because the survival ratio of lepidic predominant invasive type was high, it was accepted as the type with the least malignant aggressivity potential.

Necrosis rate was statistically low in acinar predominant type compared with all other invasive predominant types, and the tumor size was not larger than 3 cm in these tumors, unlike in solid types. The survival rate was between 65.6% and 69%. For these reasons, this type of tumor was evaluated as predominant invasive type with moderate malignant aggressivity.

The number of papillary predominant invasive type was limited ın our study, and there was no reliable survival analysis. However, there are many reports in the literature that describe papillary predominant type as an adenocarcinoma with moderate malignant aggressivity.[6,16] Kadota *et al*[16] have calculated the maximum standardized uptake values in a fluorodeoxyglucose–positron emission tomography study of 222 adenocarcinoma cases with stage I disease. From the highest to the lowest values, they were defined in this particular order: solid, micropapillary, acinar, papillary, lepidic, and predominant invasive adenocarcinoma types. The authors have stated that the relationship between histologic type and recurrence rate was correlated. Our clinical-pathologic data seem to be parallel (solid-acinar–lepidic) with the study data of Kadota *et al*.[16]

In our study group the number of micropapillary predominant invasive type was limited; therefore, a reliable survival analysis was not performed for this entity. In the literature, micropapillary predominant type is reported as predominant invasive tumor with high malignant aggressivity.[12,17–21]

In another study, these tumors were classified into 3 grades depending on their clinical behavior and prognosis. Lepidic type was accepted as grade 1, acinar and papillary types were grade 2, and solid and micropapillary types were assessed to be grade 3.[6] In our series, acinar predominant invasive type was statistically more prevalent in males. This finding is contrary to previous literature data. Male sex, along with solid predominant type, was regarded as a bad prognosis factor in some studies.[7]

Invasive adenocarcinomas tend to be in the superior lobes compared with the 2 other types, and the difference is statistically significant. Superior lobe localization did not have any impact on survival when survival rates for other localizations were taken into account. However, mortality rate was found to be significantly higher in adenocarcinomas with left hemithorax localization.

In invasive adenocarcinomas with stages I and II, the recurrence rate was higher than the other types, and the survival was lower in a significant fashion.

In our series, it was observed that peritumoral lymphovascular invasion had a negative effect on disease-free survival, in parallel with results of a study by Kato *et al*.[22]

In a study conducted by Kato *et al*,[22] the presence of angiolymphatic invasion was not found to have a major impact on patients with tumors larger than 3 cm, but angiolymphatic invasion was found to have a clinical impact in the same patient group if those patients also had accompanying pleural involvement. In our study group, peritumoral lymphovascular invasion was determined to be statistically higher in patients with tumors larger than 3 cm, contrary to the findings by Kato *et al*.[22] On the other hand, peritumoral lymphovascular invasion was found to be significantly higher in patients with pleural involvement, similar to findings by Kato *et al*.[22]

In the patient group with lymphovascular invasion, N_1 was found to be significantly high, and there were no patients with N_1 in the group without lymphovascular invasion. Presence of lymphovascular invasion in patients with pleural involvement and no pathologic lymph node involvement should lead the physician to think of the possibility of occult lymph node positivity. In such cases, early additional treatment plans should be considered.

There were no differences between invasive adenocarcinoma predominant types with regard to peritumoral lymphatic involvement.

Patients were staged according to the TNM classification revised by IASLC/ATS/ERS. In our series, it was determined that disease-free survival between stages Ia-Ib and IIa-IIb was different in a statistically significant fashion.

It is worth pointing out that disease-free survival was not homogeneous between stages I and II, but that there was not such a difference between stages Ib and IIa. In our series, disease-free survival rates between all stages (Ia-Ib–IIa-IIb) were evaluated

with Kaplan-Meier and log-rank tests, and it was determined that survival ratio was significantly lower in stage IIb patients. The fact that these stages had different survival periods within themselves and were actually heterogeneous in this aspect was attributed to the notion that adenocarcinomas had biologic heterogeneity.[7–9]

The reasons that survival periods were long in stage Ia were that they had 5 preinvasive lesions, they had an absence of micropapillary type, and solid and acinar types had the same ratio within the stage.

Kadota *et al*[16] and Goldstraw *et al*[23] have reported the survival percentage to be 73% in stage Ia patients and 58% in stage Ib patients. The reason that the survival rate was higher in stage Ia was attributed to the fact that early-stage adenocarcinomas showed biologic heterogeneity. It was pointed out that adjuvant therapy protocols had to be applied to this subset of patients in whom recurrences could be seen.

Limitations

As a retrospective study and one with a small sample size, limitations are inevitable. However, this study had the inherent limitations of all observational studies.

As a result, the new histologic classification of adenocarcinomas has been a step forward in identifying groups with homogeneous prognosis. However, when the heterogeneity of the adenocarcinomas is taken into account, the authors believe that more entities that will affect the prognosis, such as peritumoral lymphatic invasion, left hemithorax localization, and tumor necrosis rate, should be considered in TNM classification.

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