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Original Article

Relationship between Lung Adenocarcinoma Histological Subtype and Patient Prognosis

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Purpose: Lung adenocarcinoma (AC) demonstrates various histological subtypes within the tumour tissue. A panel established jointly by the IASLC, ATS and ERS classified invasive lung ACs based on the predominant histological subtype. We examined the distribution of tumours in lung AC patients according to histological subtype and analysed the effects of this classification on survival.
Methods: The records of patients who had pulmonary resection for lung cancer between January 2000 and December 2009 were reviewed and 226 lung AC patients who fulfilled the inclusion criteria were identified. Histological subtypes of the ACs and their ratios in the tumour tissue were determined. Tumours were classified according to the predominant histological subtype and subsequently graded. The relationship between the predominant histological subtype, grade and survival were analysed.
Results: Tumours were predominantly acinar in 99 cases (43.8%), solid in 89 (39.3%), lepidic in 20 (8.8%), and papillary in 11 (4.8%), whereas 7 tumours (3%) were variants of AC. Stage significantly affected survival (p = 0.001); however, the predominant histological subtype had no significant effect. The 5-year survival rate for patients with histologically grade II tumours was 48.6%, whereas that in patients with grade III tumours was 56%. (p = 0.69).
Conclusion: Invasive lung ACs may be defined by their predominant histological subtype. However, it is not yet possible to conclude that this classification is related to survival.

Keywords: lung adenocarcinoma, histological classification, lepidic, acinar, solid, papillary

Introduction

Lung adenocarcinoma (AC) is one of the most common histopathological types among non-small cell lung cancers (NSCLCs). Lung ACs show different histopathological and clinical features as compared with ACs of other organs.[1–5)]

Recently, the identification AC subtypes and the effects of subtype on survival have been studied extensively.[6–11)] It has been argued that the histological subtypes of these tumours affect survival.[12–14)] Based on this hypothesis and recent findings, a panel formed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) published a consensus report in 2011 entitled "Multidisciplinary Classification of Lung Adenocarcinoma".[15)] The aims of this classification were to gather data for future TNM systems through comprehensive histological subtyping for lung AC, provide a

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guide for effective treatment and better prognosis, and facilitate differentiation of primary and metastatic tumours when multiple tumours are present.[16,17]

In the present study, we classified lung AC patients who had pulmonary resection based on the most recent consensus report and explored the relationship between predominant subtype and survival.

Material and Methods

Patients

A total of 1,560 cases that underwent pulmonary resection for NSCLC between January 1, 2000 and December 31, 2009 were identified in the database of the second and third Thoracic Surgery Clinics of our hospital. Of these, we retrospectively reviewed 466 cases whose postoperative histopathological diagnosis was lung AC, bronchioloalveolar carcinoma (BAC), or AC with BAC components. A total of 240 patients had neoadjuvant therapy during the preoperative period. Patients were excluded from the study if any of the following criteria were met, even if the tumours were histologically determined to be AC: the presence of an extrapulmonary metastasis, stage T4 tumour, mediastinal lymphatic metastasis, satellite tumour, or synchronous multiple primary or metachronous lung cancer; underwent a sublobar resection; did not undergo an excision of at least three mediastinal and two hilar-interlobar lymph nodes; presence of an incompletely resected tumour; and died during surgery (within 30 days after the procedure). The remaining 226 cases comprised the study group. Ethics approval was obtained from the Hospital Ethics Board for this retrospective study.

TNM stage was determined according to the 7th edition of the Cancer Staging Manual of the American Joint Committee on Cancer.

Patients were assessed radiologically during the preoperative period by chest x-ray, thoracic computed tomography (CT), and upper abdominal CT. Routine biochemical and pulmonary function tests were performed. Patients with borderline pulmonary function tests had second- and third-level tests and echocardiography. All patients were assessed by fiberoptic bronchoscopy. Cranial CT or magnetic resonance imaging (MRI) was performed to exclude cranial metastasis. One hundred and sixty-five cases (73%) had positron emission tomography-CT while 138 cases (61%) had mediastinoscopy. All patients were operated via a thoracotomy approach.

All cases were followed up radiologically by chest x-ray and clinically by physical examination once every 3 months during the first 2 years, bi-annually between years 3 to 5, and annually thereafter. Additional laboratory tests and advanced radiological imaging studies were ordered when necessary. All patients were contacted over the phone and information was gathered regarding their most recent states.

Histological examination

Lung specimens were fixed in 10% buffered formalin for 24 hours. Tumour tissues were sampled and at least two specimens for each centimetre of the tumour diameter were embedded in paraffin. Three-micron thick sections were obtained for microscopic examination.

During the course of the study, haematoxylin and eosin (H&E) and periodic acid-Schiff (PAS)-stained (if available) tumour sections [mean number of slides = 11 (range, 2–37)] were re-examined under a light microscope by two pathologists (HNU and NA). Histopathological definitions and assessments were based on the 2011 IASLC/ATS/ERS multidisciplinary classification of lung ACs. The ratios of histological subtypes present in the tumour were evaluated semi-quantitatively and expressed as multiples of 5%. Both pathologists performed their assessments independently and their results were subsequently compared. Predominant subtypes were determined and graded according to the recommendations of Yoshizawa. (**Table 1**)

In addition to the predominant histological subtypes, the extent of invasion and presence of pleural invasion, lympho-vascular invasion (LVI), and perineural invasion were also noted. Pleural invasion was examined by elastic Van Gieson (EVG) staining.

Statistical analysis

Data were analysed using SPSS statistical software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Illinois, USA). Spearman's test, Chi-square or Fisher's Exact test, Student's *t*-test, and one-way analysis of variance (ANOVA) were used for correlations, comparison of frequencies, comparison of means, and comparison of medians, respectively. Survival time was calculated as the time between the day of the operation and the day of death or last follow-up visit, if the patient was alive. The survival rate was computed using the Kaplan–Meier method, while the log-rank or Cox proportional hazards model was used to compare survival rates. The level of significance was set at $p < 0.05$.

Table 1 Grade of adenocarcinoma according to histological subtypes[18)]

Low grade
Adenocarcinoma in situ
Minimally invasive adenocarcinoma
Intermediate grade
Lepidic predominant
Acinar predominant
Papillary predominant
High grade
Sold predominant
Micropapillary predominant
Invasive mucinous adenocarcinoma, mixed mucinous/ non-mucinous
Colloid predominant

Table 2 Characteristics of patients

	Total	Male	Female
Location of tuomur			
Right upper lobe	105 (46,4)	98 (43,3)	7 (3.1)
Right middle lobe	4 (1,7)	3 (1,3)	1 (0,4)
Right lower lobe	32 (14.1)	24 (10,6)	8 (3,5)
Left upper lobe	64 (28,3)	59 (26,1)	5 (2,2)
Left lower lobe	21 (9,2)	11 (4,8)	10 (4,4)
Operative mode			
Lobectomy	184 (81,4)	155 (68,5)	29 (12,8)
Blobectomy	6 (2,6)	5 (2,2)	1 (0,4)
Pneumonectomy	36 (15,3)	35 (15,4)	1 (0,4)
Pathological Stage			
IA	39 (17,2)	25 (12,8)	14 (45,1)
IB	48 (21,2)	46 (3,5)	2 (6,4)
IIA	53 (23,4)	47 (20,8)	7 (3,0)
IIB	57 (25,2)	51 (22,5)	6 (2,6)
IIIA	28 (12,3)	26 (11,5)	2 (0,8)

Results

There were 195 males (86.3%) and 31 (13.7%) females included in the study, with a male-to-female ratio of 6.2. The mean patient age was 57.6 years (range, 37–79 years). No significant differences were noted in the predominant histological subtype, subtype ratio, pleural invasion, lympho-vascular invasion, or perineural invasion, as assessed by two independent pathologists.

Patient demographics, tumour localisations, types of lung resections, and pathological tumour stages are summarised in **Table 2**. The patients in Stage III had T3N1M0 disease.

Tumours were examined with respect to adenocarcinoma subtypes and variants, based on the IASLC/ATS/ERS consensus report. Two tumours that were previously reported to be non-mucinous BAC were considered to be lepidic predominant AC due to the presence of pleural invasion, despite a tumour smaller than 3 cm in diameter. One of the two tumours that was previously reported to be mucinous BAC was diagnosed as mucinous AC due to being 13 cm in diameter and showing pneumonic dissemination. The other tumour was considered to be lepidic predominant AC because of mucin within the alveoli in the absence of typical goblet or columnar cells.

Most of the tumours (N = 207, 91.5%) contained more than one subtype, whereas only 12 tumours were pure and contained only one subtype (seven lepidic, three solid, and two acinar). Seven tumours were variants of AC (three colloid and four mucinous). No ACs *in situ* or microinvasive, pure papillary, or predominantly micropapillary ACs were identified in the study group. When cases with AC variants were excluded, which resulted in 219 cases, the acinar subtype (**Fig. 1a**) was predominant in 99 cases (43.8%), solid subtype (**Fig. 1b**) was predominant in 89 (39.3%), lepidic subtype (**Fig. 1c**) was predominant in 20 (8.8%), and papillary subtype (**Fig. 1d**) was predominant in 11 (4.8%). The micropapillary subtype was observed in low ratios (5%–30%) in 71 cases. Only seven of the lepidic predominant tumours contained this subtype, whereas the remaining 13 cases contained more than one subtype, with the lepidic subtype ranging between 45 and 90%. A tumour larger than 3 cm in diameter was identified in two cases that contained the pure single subtype. Although the tumour was smaller than 3 cm in diameter in five cases, one or more cases of visceral pleural invasion, LVI, and stromal invasion >5 mm was present. Thus, none of these tumours was considered to be AC *in situ* or microinvasive AC.

Tumours were classified according to the predominant histological subtype. Distributions of the pathological stages for each subtype group, mean tumour size, presence of lymph node metastasis, presence of pleural invasion, lympho-vascular invasion, and perineural invasion were noted (**Table 3**). Histologic subtype groups were compared with each other regarding the above variables. No statistically significant differences were noted in the distribution of pathological stage or type of lung resection between histologically predominant subtypes ($p = 0.12$ and $p = 0.84$, respectively).

When the tumours were graded according to the predominant subtype, 130 tumours were grade II and 96 tumours were grade III. T stage in grade III tumours was greater than that in grade II tumours ($p = 0.043$). The mean tumour size was greater in tumours with a mucinous

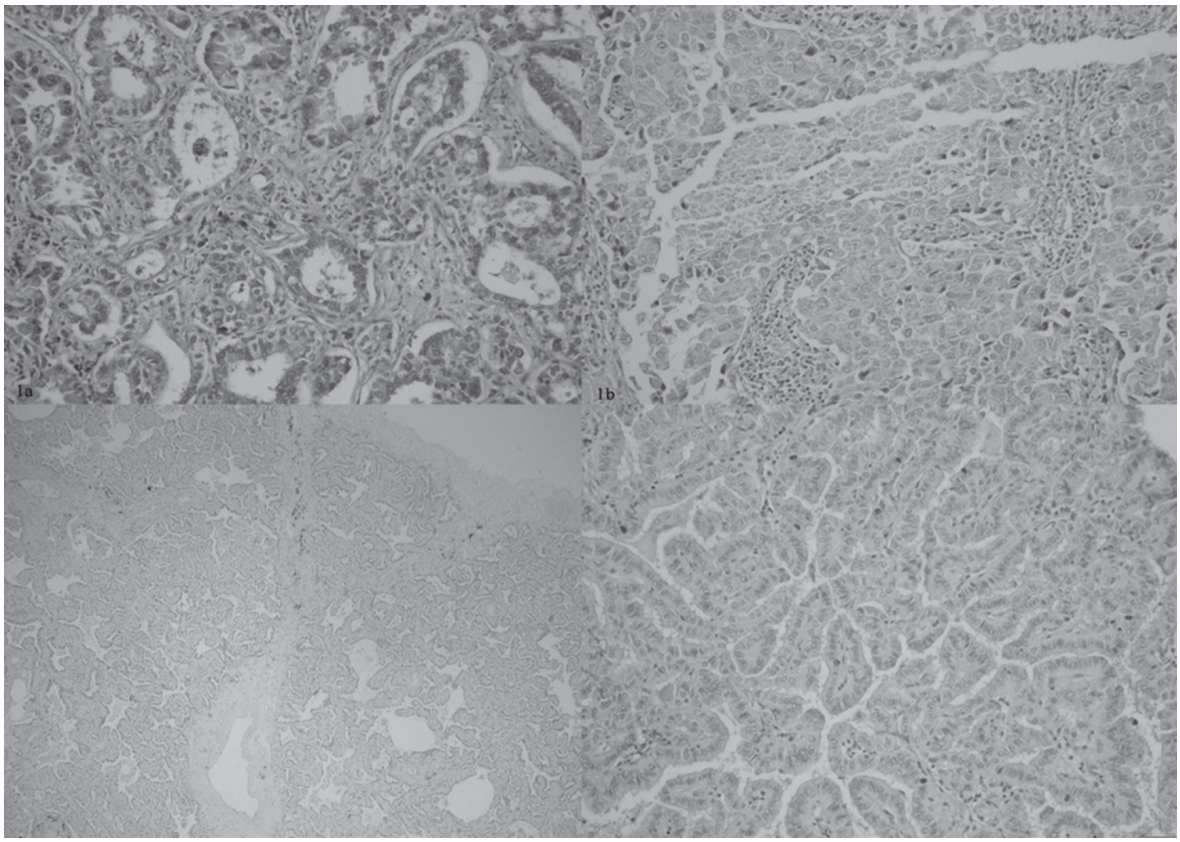

Fig. 1 (**a**) Acinar patern shows irregular-shaped glands that spread neoplastic cells, H&E × 200; (**b**) The tumor shows predominantly solid growth, PAS. × 200; (**c**) Lepidic patern consists of growth of neoplastic cells along the surface of alveolar walls that show fibrous thickening, H&E, × 100; (**d**) Papillary patern, tumor cells are growing along the surface of papillary structures with fibrovascular cores, H&E, × 100.

Table 3 Distribution of predominant histological subtypes and characteristics of tumour

Predominant histological subtypes	Pathological Stage			Mean gross size (range)	Nodal status (%)	Pleural invasion (%)	LVI (%)	Perineural invasion (%)
	IA/IB	IIA/IIB	IIIA					
Lepidic (n = 20)	8/5	4/2	1	3.5 (1.5–9)	4 (20)	6 (30)	14 (70)	3 (15)
Acinar (n = 99)	17/23	24/23	12	5 (1–13)	32 (32.3)	33 (33.33)	94 (94.95)	23 (23.23)
Papillary (n = 11)	4/2	3/2	0	4 (1–9)	4 (36.3)	3 (27.2)	8 (72.7)	2 (18.1)
Solid (n = 89)	10/18	22/25	14	5.8 (2–15)	36 (40.4)	37 (41.5)	84 (94.3)	17 (19.1)
Colloid (n = 3)	0/0	0/2	1	7.4 (7.5–10)	1 (33.3)	0 (0)	1 (33.3)	0 (0)
Mucinous (n = 4)	0/0	1/3	0	6.9 (3.5–13)	0 (0)	1 (25)	1 (25)	1 (25)
Total (n = 226)	39/48	54/57	28	5.2 (1–15)	77 (37)	80 (35.4)	202 (88.5)	46 (20.35)
P				p = 0.0001	p = 0.34	p = 0.56	p = 0.0001	p = 0.88

or colloid pattern (p = 0.0001). In addition, the lymphovascular invasion ratio was significantly lower in tumours with a mucinous or colloid pattern as compared with other tumours (p = 0.0001).

Patients were followed up for a median of 37 months (range, 2–139 months). The 5-year survival rate was calculated to be 52.3%. Further, the survival rates in Stage IA, IB, IIA, IIB, and IIIA patients were 81.2%, 61.2%, 42.3%, 46.9%, and 37.1%, respectively. In addition, the survival rate was significantly affected by Stage (p = 0.001).

When the relationship between predominant histological subtype and survival was examined, the 5-year survival in patients with a grade II tumour was 48.6%,

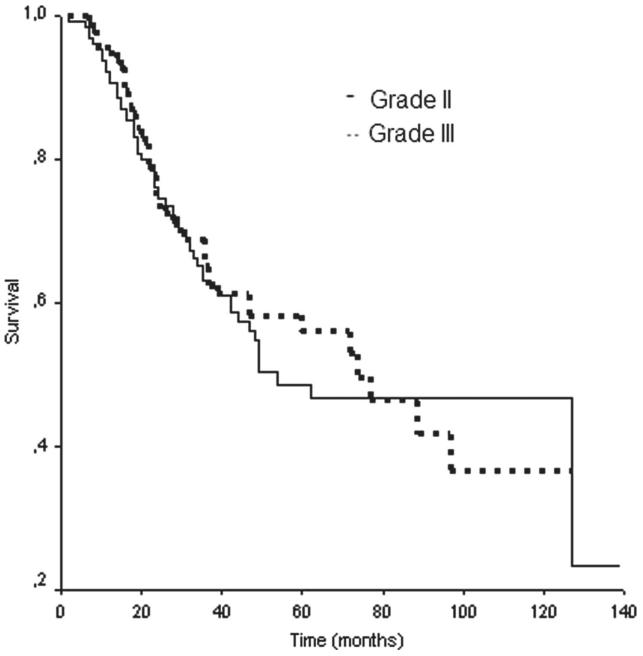

Fig. 2 Survival curves of the Grade II and Grade III adenocarcinoma patients.

whereas that in patients with a grade III tumour was 56%. The difference between the two groups was not statistically significant (p = 0.69) (**Fig. 2**). Grade was also not a significant prognostic factor when the patients were classified according to tumour stage (**Table 4**).

Table 4 **Overall survival according to combined grade and pathological stage**

	Survival in grade II %	Survival in grade III %	p =
Stage I (68.6)	69.3	64.1	0.36
Stage II (44.4)	37.3	51.2	0.16
Stage III (37.1)	NC	53.3	0.12

Discussion

Previous studies classified lung ACs according to their histological characteristics, which are known to influence survival.[19–22] However, a universally recognized classification system has not been constructed. Further, there is not sufficient evidence to indicate that existing classifications are effective for predicting survival.[23]

A panel of international experts reached a consensus regarding lung AC classification and published their recommendations in 2011.[15] This consensus report presented standardised terminology, clarified the histological diagnostic criteria of ACs, and determined the predominant subtypes of invasive ACs, thus facilitating the examination of possible effects of these subtypes on disease prognosis.[24]

Significant changes, particularly regarding the diagnosis of BAC, have been introduced with this new classification system and certain BACs that were previously classified as grade I are now classified as grade III. These changes resulted in an understanding of why patients that were previously classified with low-grade BAC exhibited poor prognosis.

One of the principal aims of this classification was to determine the effects of AC subtypes on survival. Using this classification system, Yoshizawa, et al. performed a study on 514 patients with Stage I AC and reported the prognostic outcomes of determining the predominant subtype.[18] Other researchers have also reported similar results.[25–27] Additionally, Russell, et al. argued that histological subtyping was as powerful an indicator of survival as TNM.[28]

In the present study, we found no significant relationship between survival and invasive AC subtypes. Studies in the literature that reported an effect of AC subtype on survival based their conclusions on data that were generally obtained from early-stage AC cases.[18,29] Additionally, the effects on survival were limited to disease-free survival and do not reflect overall survival.[18] Similarly, Ebright, et al. found no relationship between histological subtype and survival. These criticisms are consistent with the results of the present study.[30]

Male sex was argued to be an independent factor affecting survival in AC patients.[9,18] The male-to-female ratio in the present study was higher than that reported in other studies in the literature. However, lung cancer distributions among males and females in our country are similar and the ratio of male patients is higher. This might have obscured the effects of histological subtype on survival.

The present study possessed limitations, one of which is the bias introduced by conducting a retrospective study. The insufficient number of patients is another limitation. Furthermore, patients were allocated not only into histological subtype groups, but also into five pathological stage groups. This resulted in an uneven distribution and fewer subjects in each of the subtype-stage groups, reducing the power of the survival analysis.

In conclusion, the new classification system reported by the IASLC/ATS/ETS enables more detailed classification and reporting of histological subtypes of resected

lung ACs. Conversely, we failed to identify a significant relationship between survival and the histologically predominant subtype of invasive AC based on this classification. The nature of this relationship requires further elucidation through advanced studies with a larger sample size and molecular evidence. Until the results of such studies are made available, it would be misleading to conclude that histological subtypes of lung ACs have an effect on patient survival.

Disclosure Statement

I hereby declare that the authors have no financial or other interest in the study or manufacture of the paper. ICMJE form for disclosure of potential conflicts of interest is added file.

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