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Original article

Growth pattern-based grading of pulmonary adenocarcinoma—Analysis of 534 cases with comparison between observers and survival analysis

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ABSTRACT

Objectives: The 2015 WHO classification of pulmonary adenocarcinoma recommends recording observed architectural growth patterns in 5% increments for resected tumors, and determining the predominant growth pattern, which seems to be prognostic. There is debate over the best way to implement pattern-based grading, and whether such systems are reproducible.

Materials and methods: 534 resected adenocarcinomas were reviewed by 2 pulmonary pathologists to determine predominant pattern and percentages of all observed patterns. Three different grading schemes were applied based on predicted prognosis scores: score 1 (lepidic), score 2 (acinar/papillary), and score 3 (solid/micropapillary/cribriform). Mucinous tumors were separately evaluated as both scores 2 and 3 since their prognosis is more ambiguous. The first grading scheme used the score of the predominant pattern; the second used the worst observed pattern score; and the third scored tumors with ≥80% lepidic growth as 1, tumors with ≥20% of any score 3 pattern(s) as 3, and all remaining as 2.

Results: The predominant pattern assigned by each observer was an exact match in 51.7% of cases, a "close match" in 27.3% (same prognosis score), and a mismatch in 21%. Predominant pattern determined by both observers showed significant stratification of overall and progression-free survival (OS and PFS, respectively). All 3 grading schemes showed a significant difference in OS and PFS determined by both observers; but the worst score scheme provided suboptimal results, likely due to a very small score 1 group, and this scheme did not maintain significance on multivariable analysis. Survival differences for all grading schemes maintained significance whether mucinous was considered score 2 or 3, but mucinous tumors trended towards poor survival.

Conclusion: Pattern-based grading has prognostic significance in pulmonary adenocarcinoma. Interobserver variation is present, but two observers were able to predict significant differences in OS and PFS using various pattern-based grading schemes.

1. Introduction

Pulmonary adenocarcinomas are inherently very morphologically heterogeneous [1], with many architectural patterns. A growing body of evidence supports that pattern-based grading of pulmonary adenocarcinoma has great promise as a prognostic tool, especially for risk-stratifying stage I patients [2–12]. Lepidic predominant tumors have a very good outcome, especially those with minimal invasion (< 5 mm of invasion, minimally invasive adenocarcinoma, MIA) or absent invasion (adenocarcinoma in situ, AIS) [1,3–6,8–14]. In contrast, solid, micropapillary, and cribriform patterns portend a poor prognosis [1,3–13,15–22], with higher likelihood of disease progression and death from disease. Acinar and papillary patterns seem to indicate an intermediate prognosis [3,5,6,8,9,11–13,16]. The prognosis of mucinous pattern-predominant adenocarcinomas is more ambiguous, but most studies suggest an intermediate to poor prognosis [1,5,10,23,24].

Based on these data, the 2011 American Thoracic Society/European Respiratory Society/International Association for the Study of Lung Cancer (ATS/ERS/IASLC) consensus classification of pulmonary adenocarcinoma and subsequent 2015 World Health Organization (WHO) classification recommend recording invasive patterns in 5% increments, and determining the overall predominant pattern [25,26]. It is not entirely clear whether predominant pattern provides the best risk stratification, or if alternative grading systems incorporating worst pattern or reflecting the combination of patterns observed would provide superior predictive power [16]. The available data on reproducibility in determining predominant pattern has indicated moderate variability [27–32], with some suggestion that agreement may be better among experienced pulmonary pathologists [33]. Improved reproducibility is expected if the predominant patterns could be distilled into a

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grading scheme with fewer categories. In this study, we sought to use three different pattern-based grading schemes on a large group of pulmonary adenocarcinoma patients with long-term follow-up, paying particular attention to interobserver agreement between two pulmonary pathologists.

2. Materials and methods

Patients were included from the Mayo Clinic Epidemiology and Genetics of Lung Cancer Study database, who underwent surgical resection of lung adenocarcinomas at Mayo Clinic from 1997 to 2012 [34,35]. 534 cases were reviewed independently to determine largest invasive focus and percentage of all observed architectural patterns, which were recorded in 5% increments. If the tumor was composed entirely of invasive patterns, the maximum invasive size was considered equivalent to the gross tumor size. Cases were not systematically chosen (i.e. no inclusion or exclusion criteria were applied aside from available outcome data and access to histologic slides), but rather were randomly reviewed until the desired cohort size was reached. This cohort represents 30% of the adenocarcinomas surgically resected during the included time frame. When compared to the 1236 cases that were not reviewed, our cohort had a similar proportion of males and females ($p = 0.50$). The included patients were slightly older (68.2 vs. 66.8 years, $p = 0.004$), had a higher proportion of never smokers (20.8% vs. 16.7%, $p = 0.04$), and a higher proportion of stage I patients (71.0% vs. 57.8%, $p < 0.001$).

Predicted prognosis scores were assigned to each observed growth pattern: lepidic pattern (including AIS and MIA) = score 1; acinar and papillary patterns = score 2; solid, micropapillary, and cribriform patterns = score 3. Mucinous pattern tumors were separately evaluated using score 2 and score 3 to better address their ambiguous prognosis. Three different grading schemes were applied (Table 1): The score of the predominant observed pattern; the score of the worst observed pattern; and an overall pattern score, which scored tumors with > 80% lepidic growth as 1, tumors with ≥20% of any score 3 pattern(s) as 3, and all remaining as 2. The 80% and 20% cutoffs used in the overall pattern score we chosen based on the current body of literature regarding lepidic-predominant tumors and tumors with any significant component of solid, cribriform or micropapillary growth, as further discussed in introduction and discussion sections.

Descriptive statistics using Chi-square tests and Kruskal-Wallis tests were employed as appropriate. Overall and progression-free survival (OS and PFS, respectively) were evaluated with log-rank tests and Cox proportional hazards models. OS was defined as the interval from the date of diagnosis to the date of death or was censored at last known alive date. PFS was similarly defined but included deaths, lung cancer progressions, and lung cancer recurrences as events, whichever occurred first. Factors with p-values < 0.10 in univariate proportional hazards models were considered for the multivariate models which were finalized after review of several model selection processes and clinical relevance of the covariates. Survival curves were developed using the Kaplan-Meier method.

3. Results

The study included 534 patients, with an average age of 68.2 years (range 31–91). Most patients (93.7%) were Caucasian, and 300 of the patients were women (56.2%). The majority of patients were former smokers (307, 57.5%) or current smokers (116, 21.7%), and 111 were never smokers (20.8%). As expected for surgically treated patients, stage I was the most common (379, 71.0%), while 82 were stage II (15.4%), 50 were stage III (9.4%), and 23 were stage IV (4.3%). Adjuvant chemotherapy and/or radiation was received by 125 patients (23.4%), with the remaining patients having surgery alone. Lung cancer progression was experienced by 96 patients (18.0%), and 276 patients (51.7%) were alive at last follow-up. By univariable analysis, factors associated with a poorer 5-year OS included: advanced stage ($p < 0.0001$; 32.6% in stage IV, 40.1% in stage III, 57.6% in stage II, 75% in stage I); advanced age ($p < 0.0001$); former or current cigarette smoking ($p = 0.0024$; 58.4% for current smokers vs. 66.7% in former smokers vs 78% in never smokers); male gender ($p < 0.0001$; 58.6% vs 74.2% in females); requirement for adjuvant therapy ($p < 0.0001$; 57.7% vs. 71% for surgery only); originally assigned pathologic grade ($p < 0.0001$; 72.3% in well, 57.5% in moderately, and 45.8% in poorly differentiated); Caucasian race ($p = 0.0290$; 67% vs. 81.1% in other races); and lack of family history of lung cancer in a first degree relative ($p = 0.0451$; 65.8% vs 74.6% in patients with family history).

The predominant pattern was determined independently by two pathologists (lepidic, acinar, papillary, solid, micropapillary, cribriform or mucinous; Fig. 1). Predominant pattern determined by both observers showed significant stratification of OS and PFS (Fig. 2), and generally supported the risk scores assigned, with AIS and MIA having the best prognosis, and solid tumors having the worst prognosis. This stratification maintained significance for both observers when only stage I patients (n = 379) were considered (observer 1 $p = 0.0275$ for OS, $p = 0.0014$ for PFS; observer 2 $p < 0.0001$ for OS, $p = 0.0008$ for PFS). Survival data on the rare predominant patterns (cribriform and micropapillary) were limited due to the very low numbers of patients in those groups. Mucinous predominant tumors trended toward poor prognosis, with survival curve between the acinar/papillary and solid-predominant tumors, and thus it was decided to assign these as a grade 3 pattern for survival analysis. The assigned predominant pattern by each pathologist was an exact match in 51.7% of cases. If both observers assigned patterns within the same prognosis score group (i.e., acinar and papillary score 2; solid, micropapillary and cribriform score 3), it was considered a “close match”, which was observed in 27.3% of cases. If the observers assigned predominant patterns with different prognosis scores, it was considered a mismatch, which occurring in 21% of cases.

All 3 grading schemes showed a significant difference in OS (Fig. 3) and PFS (supplemental Tables 1 and 2) determined by both observers. Survival differences for all grading schemes maintained significance whether mucinous tumors were considered score 2 or 3. There was a gender difference in the predominant pattern grade for observer 1, with a trend towards more men with grade 3 tumors ($p = 0.0287$). Otherwise, no differences were observed in age, gender or race among the

Table 1
Summary of the different grade assignments used by each of the three grading schemes.

Grading Scheme	Grade 1	Grade 2[a]	Grade 3[a]
Predominant pattern	Lepidic predominant	Acinar predominant Papillary predominant	Solid predominant Micropapillary predominant Cribriform predominant
Worst pattern	Lepidic only (AIS)	Any component of acinar or papillary pattern, but no grade 3 pattern	Any component of solid, micropapillary, or cribriform growth
Overall pattern	> 80% lepidic	All tumors not fulfilling criteria for grade 1 or grade 3	≥20% composed of any combination of solid, micropapillary or cribriform growth

[a] Mucinous tumors were considered alternately as both as a grade 2 and grade 3 pattern to further investigate prognosis.