Nonpredominant lepidic pattern correlates with better outcome in invasive lung adenocarcinoma

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ABSTRACT

Objectives: Histologic heterogeneity is a typical feature of pulmonary adenocarcinoma. This study aimed to deconstruct the intratumoral growth pattern composition and to examine the prognostic relevance of the current lung adenocarcinoma classification in a series of Finnish lung cancer patients.

Materials and methods: A cohort of 112 patients with surgically operated stage I–IV lung adenocarcinoma was retrospectively reviewed. Histologic subtyping was performed according to the classification system established by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS). Systematically collected clinical information including survival data was correlated with the subtype status. In addition, emphasis was placed on the nonpredominant histologic patterns, gender and smoking history.

Results: The most common subtype was acinar predominant adenocarcinoma with 56 cases (50%). Most tumors were composed of a mixture of two or more growth patterns, and single pattern tumors were rare (9.8%). Micropapillary predominant adenocarcinoma and solid predominant adenocarcinoma were the subtypes with the lowest disease-specific survival rates (5-year DSS 21.4% and 30.4%; shared mean DSS 46.3 months, $p = 0.040$). A nonpredominant lepidic component was observed in 24 (21.4%) tumors, and its presence predicted a better outcome (mean DSS 127.4 months vs. 55.7 months, $p = 0.001$). This association was confirmed by multivariate analysis ($p = 0.004$). Solid pattern and solid, papillary, micropapillary and cribriform predominant histology associated with smoking ($p < 0.001$), while mucinous pattern was more common in nonsmokers ($p < 0.001$) and in women ($p = 0.050$).

Conclusions: Micropapillary and solid predominant adenocarcinomas showed significantly lower survival rate than other major subtypes, yet the prognostic value of the current lung adenocarcinoma classification is not limited only to the predominant growth patterns. The more favorable outcome associated with the nonpredominant lepidic pattern further emphasizes the importance of histologic subtyping and assessment of tumor heterogeneity in the diagnostics of lung adenocarcinoma.

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1. Introduction

Lung cancer remains the leading cause of global cancer incidence and mortality [1]. In most countries, adenocarcinoma has become the most predominant histologic subtype accounting for approximately a half of all lung cancers [2]. Primary lung adenocarcinoma is known to be a very heterogeneous tumor in many aspects, and both its histopathology and the course of the disease

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are diverse. Acknowledging this, a proposal for a multidisciplinary lung adenocarcinoma classification was established in 2011 [3]. To date, the validity of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification has been tested in multiple independent studies beginning from the early reports by Yoshizawa et al. [4] and Russell et al. [5], and most recently, the classification was adopted by the World Health Organization (WHO) [6].

In 2011, Yoshizawa et al. reported that the IASLC/ATS/ERS classification identified histologic subsets with significant prognostic differences in a series of stage I lung adenocarcinomas [4]. Subsequently, Russell et al. reported that subtyping according to the IASLC/ATS/ERS displayed a significant correlation with the 5-year survival in stage I–III lung adenocarcinomas, and in fact, the classification was the strongest predictor of patient survival, independent of the TNM stage [5]. In both studies, patients with adenocarcinoma in situ and microinvasive adenocarcinoma showed excellent 5-year survival, followed by lepidic predominant adenocarcinoma. Acinar predominant and papillary predominant adenocarcinomas shared an intermediate prognosis, while micropapillary predominant and solid predominant adenocarcinomas were associated with high-grade clinical behavior and a dismal prognosis.

In 2012, the studies by Thunnissen et al. [7] and Warth et al. [8] validated the reproducibility of the IASLC/ATS/ERS classification, and they have been followed by several reports further validating its prognostic value [9–12]. Histologic subtyping has been proposed as being a potential screening method with which to identify the lung cancer patients at high risk of recurrent disease [11]. In these pioneering studies, micropapillary predominant and solid predominant adenocarcinomas are repeatedly identified as high-grade tumors. Currently, also the nonpredominant micropapillary and solid patterns are recognized as markers of unfavorable prognosis [9,13–15].

The aim of the present study was to investigate the correlation between the IASLC/ATS/ERS classification and patient outcome and clinical characteristics in a series of patients with surgically operated lung adenocarcinoma, assessing both the predominant and nonpredominant histologic patterns.

2. Materials and methods

2.1. Patients

A retrospective analysis was conducted on 112 lung adenocarcinoma patients who underwent a complete surgical resection with curative intent in the Oulu University Hospital between January 1998 and December 2007. None of the patients had received preoperative chemotherapy or radiotherapy. The clinical and histologic data were re-evaluated by two clinicians and two pulmonary pathologists. Clinical information including age, sex, smoking history and follow-up data was collected systematically from the medical records using a specific formula planned for the study. A nonsmoker was defined as a person whose lifetime tobacco consumption equaled fewer than 100 cigarettes. Other relevant data, such as the location and the size of tumor, were traced from the original pathology reports (Table 1).

Ethical approval for the study was obtained from the Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu (statement 2/2008), and from the National Supervisory Authority for Welfare and Health (former National Authority of Medicolegal Affairs, Reg. no. 863/04/047/08). For the retrospective histologic material, informed consent permission was given by the National Supervisory Authority for Welfare and Health, the national licensing authority.

2.2. Histopathologic evaluation

Surgical specimens had been routinely formalin fixed, paraffin embedded, sectioned, and stained with hematoxylin and eosin. Additionally, at least one representative tumor slide was stained with Alcian Blue PAS to evaluate the presence of intracytoplasmic mucin. One pathologist (JMM) reviewed all available histologic material from 112 cases, and all available tumor slides from each case were independently re-evaluated by two pathologists (JMM and ELB) according to the IASLC/ATS/ERS classification [3,16], blinded to clinical data. An average of 5 tumor slides (ranging from 1 to 16 slides) was processed per case.

Five major growth patterns were defined: lepidic, acinar (including acinar and/or cribriform pattern), papillary, micropapillary and solid (Fig. 1A–F). Patterns were assessed semiquantitatively in 5% increments, and a predominant pattern was designated for each tumor. All tumors were confirmed invasive (no microinvasive adenocarcinoma or adenocarcinoma in situ included), and reclassified as either lepidic, acinar, papillary, micropapillary or solid predominant adenocarcinoma. Tumors with a single growth pattern were referred to as pure tumors. In addition, tumors exhibiting mucinous pattern were divided into invasive mucinous adenocarcinoma, mixed mucinous and nonmucinous adenocarcinoma, and colloid adenocarcinoma (Fig. 1G–H).

2.3. Pathological staging

All tumors were restaged according to the TNM classification of malignant tumors (Union for International Cancer Control/American Joint Committee on Cancer, 7th edition) [17].

2.4. Statistical analyses

Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Interobserver agreement over the histologic growth patterns was verified using Cohen's kappa statistics. Associations between clinicopathologic and histologic parameters were analyzed using χ^2 test and Fisher's exact test (categorical variables), and one-way analysis of variance. Survival analyses were performed using the Kaplan–Meier method with log-rank test and the Cox proportional hazard regression model. All tests were two sided, and p-values less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Out of the 112 patients, 71 were men (63.4%) and 41 were women (36.6%). Their age ranged from 41 to 82 years, with a median of 66.0 years. The majority, 88 patients (78.6%) were current or ex-smokers, while 20 patients (17.9%) were nonsmokers. No smoking data was available from four patients (3.6%). Nineteen patients underwent pneumonectomy (17%), nine bilobectomy (8%), 73 lobectomy (65.2%), and 11 sublobar resection (segmentectomy or wedge resection, 9.8%) (Table 1). The postoperative 30-day mortality was 0.9% (1/112 patients).

3.2. Distribution of growth patterns

According to the IASLC/ATS/ERS classification, the most frequent subtype in our study was acinar predominant adenocarcinoma (50%), followed by solid predominant adenocarcinoma (22.3%), invasive mucinous adenocarcinoma (8.9%), papillary predominant