Does Lung Adenocarcinoma Subtype Predict Patient Survival?

A Clinicopathologic Study Based on the New International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society International Multidisciplinary Lung Adenocarcinoma Classification

Prudence A. Russell, MBBS, FRCPA, Zoe Wainer, BMBS,†‡ Gavin M. Wright, MBBS, FRACS,†‡§ Marissa Daniels, MBBS,§ Matthew Conron, MBBS, FRACP,‖ and Richard A. Williams, MBBS, FRCPA, PhD**

Introduction: Lung adenocarcinoma is a heterogeneous group of tumors with a highly variable prognosis, not well predicted by the current pathologic classification system. The 2004 World Health Organization classification results in virtually all tumors encountered in clinical practice being allocated to the adenocarcinoma of mixed subtype category. A new classification developed by an international multidisciplinary expert panel sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society, is based on histomorphologic subtype and has recently been validated in a North American series of 514 stage I lung adenocarcinomas. We investigated the relationship between the new classification and patient survival in a series of Australian patients with stages I, II, and III lung adenocarcinoma.

Methods: We identified 210 patients from a surgical database who underwent resection of lung adenocarcinoma from 1996 to 2009. Two pathologists, blinded to patient outcome, independently performed histopathologic subtyping according to the new classification. Kaplan-Meier curves were used to calculate 5-year survival for each separate histopathologic subtype/variant. Univariate and multivariate analyses were undertaken to control for validated prognostic factors.

Results: We confirmed that the new subtypes of adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic-predominant adenocarcinoma had a 5-year survival approaching 100%, whereas micropapillary-predominant and solid with mucin-predominant adenocarcinomas were associated with particularly poor survival. Papillary-predominant and acinar-predominant adenocarcinomas had an intermediate prognosis. This effect persisted after controlling for stage.

Conclusions: Classification of lung adenocarcinoma according to the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification correlated with 5-year survival. These relationships persisted after controlling for known prognostic patient and tumor characteristics. The new classification has advantages not only for individual patient care but also for better selection and stratification for clinical trials and molecular studies.

Key Words: Acinar, Lepidic, Papillary, Micropapillary, Solid with mucin, Mucinous.

(*J Thorac Oncol.* 2011;6: 1496–1504)

Adenocarcinoma is the most common histopathologic type of primary lung cancer[1] and is a major focus of research to improve patient survival. Similar to other solid organ tumors, there is a wide spectrum of tumor behavior that is poorly predicted by recognized prognostic factors such as tumor node metastasis (TNM) stage at diagnosis. Although the utilization of molecular profiles to guide patient management strategies holds great promise, currently these tools are expensive and, in many settings, unavailable. Different histomorphologic patterns observed in adenocarcinoma subtypes may provide additional prognostic information, on the assumption that they are functional phenotypes reflecting an underlying genotype. The use of histopathologic features to predict tumor behavior is particularly attractive because it can be obtained quickly and cheaply at the time of diagnosis.

*Department of Anatomical Pathology, St. Vincent's Hospital, University of Melbourne; †Department of Surgery, St. Vincent's Hospital, University of Melbourne; ‡Division of Surgical Oncology, Peter MacCallum Cancer Centre; §Department of Cardiothoracic Surgery, St. Vincent's Hospital; and ‖Department of Respiratory Medicine, St. Vincent's Hospital, Melbourne, Victoria, Australia.

Disclosure: Dr. Zoe Wainer is the recipient of the 2010 Royal Australasian College of Surgeons Raelene Boyle Scholarship.

Address for correspondence: Prudence A. Russell, MBBS, FRCPA, St. Vincent's Pathology, 41 Victoria Parade, Fitzroy 3065, Melbourne, Victoria, Australia. E-mail: prue.russell@svhm.org.au

The first three authors contributed equally to this work.

ISSN: 1556-0864/11/0609-1496

The 1999 World Health Organization (WHO) classification of lung tumors introduced the adenocarcinoma of mixed subtype category,[2] partly due to a change in definition of bronchioloalveolar carcinoma (BAC).[3] Mixed subtype adenocarcinoma was retained in the 2004 WHO classification of lung tumors.[4] However, a major shortcoming of both 1999/2004 WHO classifications is that mixed subtype adenocarcinoma is the most common subtype, comprising 94% of all adenocarcinomas in one series.[5] Although pathologically accurate, it is of limited clinical utility as most adenocarcinomas will fall into this subtype despite having widely varied clinical outcomes.[6,7] Since the publication of 1999/2004 WHO classifications, there have been many advances in the practice and understanding of oncology, surgery, radiology, and molecular biology of lung adenocarcinoma. Recent work is now bringing lung cancer pathology into line with these other advances. In addition, a disconnect still exists between the strict pathologic definition of solitary BAC according to 1999/2004 WHO classifications and the clinical use of the term.[6,8–11] To address these issues, an international multidisciplinary panel of lung cancer experts including medical oncologists, respiratory physicians, pathologists, surgeons, molecular biologists, and radiologists was formed in 2008 sponsored by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS). The result of this collaboration is a new adenocarcinoma classification called the new IASLC/ATS/ERS International Multidisciplinary Lung Adenocarcinoma Classification, presented in 2009,[12] published in 2011,[13] and listed in Table 1.

Primary aims of the new classification include provision of consistent terms and diagnostic criteria for adenocarcinoma subtypes, particularly for BAC and mixed subtype adenocarcinoma, and incorporation of significant practice changing advances in the fields of pathology, molecular biology, oncology, radiology, and surgery into a classification that is still principally based on histopathologic examination.[13] Some of the most important changes include making the terms BAC and mixed subtype adenocarcinoma obsolete. In the new classification, BAC is called adenocarcinoma in situ (AIS) and describes small (<3 cm) solitary lesions with 100% lepidic growth. A related entity, previously sometimes referred to as minimally invasive BAC,[8] was not included in 1999/2004 WHO classifications but is introduced in the new classification and called minimally invasive adenocarcinoma (MIA). MIA describes small (<3 cm) solitary adenocarcinomas with predominant lepidic growth and ≤5 mm invasion. If resected, both AIS and MIA are associated with 100% or near 100% disease-free survival[3,14,15] and are usually nonmucinous, although rare examples are mucinous and called mucinous AIS and mucinous MIA in the new classification.[13]

The new classification divided mixed subtype adenocarcinoma into five invasive subtypes on the basis of comprehensive histologic subtyping.[5] Comprehensive histologic subtyping is a recently introduced process in which each histopathologic subtype present in a tumor is estimated in 5% increments followed by identification and classification of that tumor according to the predominant histologic subtype.

TABLE 1. The New IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma in Resection Specimens

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (≤3 cm, formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

Reprinted with permission from *J Thorac Oncol* 2011;6:244–285.
IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; BAC, bronchoalveolar carcinoma.

The five invasive subtypes include three present in previous WHO classifications, acinar, papillary, and solid with mucin, and two new subtypes, lepidic and micropapillary patterns.[13] Lepidic-predominant adenocarcinoma (LPA) has predominant lepidic growth with more than 5 mm of invasion and may show tumor necrosis or invasion of lymphovascular spaces or visceral pleura.[13] Micropapillary adenocarcinoma was not included in previous WHO classifications, although it was referred to in the 2004 WHO classification[4] and is a pattern of great significance because of its poor prognosis.[16–18]

Variant adenocarcinomas listed in the new classification include invasive mucinous, colloid, enteric, and fetal adenocarcinomas.[13] Mucinous BAC has been renamed invasive mucinous adenocarcinoma in recognition that these tumors have components of lepidic growth with columnar or goblet cells with abundant intracellular mucin admixed with invasive adenocarcinoma patterns with stromal invasion. In addition, invasive mucinous adenocarcinoma, when compared with AIS,[13] has different radiologic,[19] immunohistochemical,[20] and molecular features[21] as well as prognosis.[20]

Recently, Yoshizawa et al.[22] validated the new adenocarcinoma classification with a North American data set comprising 514 stage I lung adenocarcinomas. They demonstrated a correlation between adenocarcinoma subtypes, according to the new definitions, and survival, indicating a valuable prognostic role for the new classification.

Against this backdrop, we investigated the clinical utility of the new adenocarcinoma classification to determine

