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Original contribution

Adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive pulmonary adenocarcinoma—analysis of interobserver agreement, survival, radiographic characteristics, and gross pathology in 296 nodules☆

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Summary The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society and 2015 World Health Organization classifications of lung adenocarcinoma recommend designating tumors showing entirely lepidic growth as adenocarcinoma in situ (AIS) and lepidic tumors with invasion less than or equal to 5 mm as minimally invasive adenocarcinoma (MIA), both of which have superior outcome to conventional invasive adenocarcinoma (IA). Data on interobserver variability within this classification are limited, and further validation of the superior survival of AIS and MIA is needed. A total of 296 surgically excised pulmonary adenocarcinomas were reviewed from 254 patients (1997-2009). Slides were independently reviewed by 2 pulmonary pathologists who categorized tumors as AIS, MIA, or IA. Of 296 nodules, 244 (82.4%) were agreed upon by both observers: 10 AIS, 61 MIA, and 173 IA (κ = 0.63, good agreement). In 6 cases (2%), there was disagreement between AIS and MIA; in 45 cases (15%), there was disagreement between MIA and IA; and in 1 case, there was disagreement between AIS and IA. Overall survival was significantly different among categories as determined by both observers. Cases with disagreement between MIA and IA had similar survival to agreed MIA. Disease-specific 10-year survival was 100%

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for AIS (both observers) and 97.3% and 97.6% for MIA, although this did not reach statistical significance compared to IA for either observer. Good agreement was present between observers when classifying tumors as AIS, MIA, and IA. Significant differences in overall survival were present between the 3 groups for both observers, and interobserver variability was evident. Patients with AIS and MIA experienced excellent DSS.

1. Introduction

Historically, pulmonary adenocarcinomas with lepidic growth (growth along alveolar septa) have been termed *bronchioloalveolar carcinoma* (*BAC*), a term coined by Dr Averill Liebow in 1960 [1]. He noted that BAC had an indolent clinical course compared to other aggressive types of lung cancer [1]. The definition of BAC was made more stringent over the years and was eventually defined as a tumor showing entirely lepidic growth without invasion [2-4]. Subsequent studies focused on small lepidic-predominant tumors with limited areas of invasion, which have shown that the size of invasion or scarring may be more prognostic than gross tumor size [2,3,5-8]. Tumors with less than or equal to 5 mm of invasion are associated with excellent survival and have been termed *minimally invasive adenocarcinoma* (*MIA*) [3,5]. A consensus classification was proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society in 2011, which has been adopted by the 2015 World Health Organization (WHO) classification of pulmonary adenocarcinoma [9,10]. This classification abandons the term *BAC* in favor of adenocarcinoma in situ (AIS) and formally introduces MIA as a diagnostic category, whereas tumors with greater than 5 mm invasion are classified as invasive adenocarcinoma (IA) [9,10]. AIS and MIA are limited to tumors less than or equal to 3 cm because data on larger tumors are very limited. Studies have shown that solid and micropapillary tumors are more aggressive, whereas lepidic tumors have better survival [11-19], so it is also recommended that IAs be subclassified according to the predominant histologic pattern.

The proportion of adenocarcinomas classified as AIS or MIA will likely grow in the immediate future. Because AIS/MIA are small and asymptomatic, they are the tumors most likely to be detected by imaging procedures done for other reasons. The number of detected nodules will increase due to the favorable results of the National Lung Cancer Screening Trial [20], and most screening-detected lung cancers are adenocarcinomas. These factors will lead to more incidentally discovered adenocarcinomas: some would have gone undiagnosed in the past ("overdiagnosed" cancers, indolent tumors that would not have caused the patient's death), and some may be discovered at earlier stage with a more significant lepidic component.

Little is known about interobserver agreement when classifying tumors as AIS, MIA, and IA [5,21]. Most agreement studies focus on predominant invasive pattern [18,22,23]. Preliminary validation studies of the new classification have been promising [13,15,17,24-28], but further validation of the superior survival of patients with AIS/MIA is needed. AIS/MIA are uncommon and often constitute a small minority of tumors even in large studies, especially among Western patient populations [12,13,17,28]. Furthermore, the behavior of tumors in which there is disagreement between invasive categories determined by different observers is unknown. The goal of this study is to evaluate a large number of pulmonary adenocarcinomas enriched for AIS and MIA, to compare categorization between 2 observers, and to correlate invasive group with outcome.

2. Materials and methods

The protocol was approved by the Mayo Clinic Institutional Review Board. Patients were selected from the Mayo Clinic Epidemiology and Genetics of Lung Cancer Study database, who underwent surgical resection of pulmonary adenocarcinoma (1997-2009). Cases were enriched for AIS and MIA by selecting cases to review which had the term *BAC* or *adenocarcinoma with BAC features* in the original diagnostic line. A total of 296 nodules were reviewed from 254 nonconsecutive patients. Thirty-five patients had more than 1 nodule (range, 2-5).

Pathology slides were reviewed and independently evaluated by 2 pulmonary pathologists (E. S. Y. and J. M. B.), blinded to gross size, stage, and outcome. The pathologists used published 2015 WHO/2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society criteria, applied independently by each reviewer [9,10]. Each pathologist determined foci of stromal, vascular, and pleural invasion. The largest single focus of invasion and central scar (if present) were measured with a ruler. If a tumor was entirely IA, invasive size was considered equivalent to gross size. Tumors were categorized as AIS, MIA, or IA per 2015 WHO criteria. If the patient had multiple nodules that were felt to represent independent primaries after comprehensive histologic comparison of the nodules and evaluation for extent of lepidic growth, the tumors were independently evaluated for largest invasive tumor size and included in the interobserver agreement data set.

If a tumor was categorized as AIS or MIA by one or both pathologists, residual gross pathology specimens were