Comparison of outcomes for patients with lepidic pulmonary adenocarcinoma defined by 2 staging systems: A North American experience

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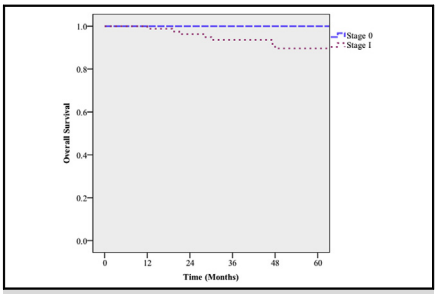
ABSTRACT

Objective: Application of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification of lepidic adenocarcinomas in conjunction with American Joint Committee on Cancer (AJCC) staging has been challenging. We aimed to compare IASLC/ATS/ERS and AJCC classifications, to determine if they could be integrated as a single staging system.

Methods: We reviewed patients from 2001-2013 who had AJCC stage I lepidic adenocarcinomas, and categorized them according to IASLC/ATS/ERS guidelines: adenocarcinoma in situ (AIS); minimally invasive adenocarcinoma (MIA); or invasive adenocarcinoma (IA). We integrated the 2 classification systems by separating AIS and MIA as being stage 0, and routinely classifying IA as stage I.

Results: Median follow-up was 52 months in 138 patients. The IASLC/ATS/ERS classification demonstrated a higher disease-free survival (DFS) in AIS (100%) and MIA (96%) versus IA (80%) ($P = .022$), and higher overall survival (OS): 100% for AIS and MIA, versus 90% for IA ($P = .049$). The AJCC classification identified a DFS of 87% and an OS of 94% for stage I patients. Integration of the 2 systems demonstrated higher DFS in stage 0 (98%) versus I (80%) ($P = .006$), and higher OS: 100% for stage 0 versus 90% for stage I ($P = .014$).

Conclusions: The IASLC/ATS/ERS classification better discriminates AIS and MIA compared with current AJCC staging; however, integration suggests that these categories may be collectively classified in AJCC staging, based on similarly favorable outcomes and distinctive survival rates. (J Thorac Cardiovasc Surg 2016;■:1-8)



Five-year overall survival of the integrated IASLC/ATS/ERS and AJCC classifications.

Central Message

Integration of IASLC/ATS/ERS and AJCC classifications suggest that AIS and MIA may be collectively classified based on favorable outcomes.

Perspective

Refining the most effective staging system is an ongoing process, requiring continuous updates. The IASLC/ATS/ERS classification better determines which patients have AIS and MIA. For future AJCC revisions, we recommend integrating them with TNM staging by separating these patients into a stage 0, which reflects indolent histology associated with superior recurrence and survival rates.

THOR

The term ''bronchioloalveolar carcinoma'' (BAC), as it was originally applied, encompassed a wide spectrum of pulmonary adenocarcinomas with lepidic features, from pure lepidic lesions to predominantly invasive adenocarcinomas with a small element of a peripheral lepidic pattern. Attempts to categorize these lesions led to the development of the Noguchi classification, and subsequently, a histologic World Health Organization classification that has undergone numerous modifications over the years, with the aim of updating the categorization of these tumors.[1-3] Despite this process, the latest 2004 World Health Organization classification offers limited clinical utility, because more

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Abbreviations and Acronyms

AIS	= adenocarcinoma in situ
AJCC	= American Joint Committee on Cancer
BAC	= bronchioloalveolar carcinoma
CI	= confidence interval
DFS	= disease-free survival
IA	= invasive adenocarcinoma
IASLC/ATS/ERS	= International Association for the Study of Lung Cancer/ American Thoracic Society/ European Respiratory Society
MIA	= minimally invasive adenocarcinoma
TNM	= tumor–nodal–metastasis

than 90% of the adenocarcinomas are classified as a mixed subtype, even though they have a variety of clinical outcomes.[1,3,4]

Publication of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification of lung adenocarcinomas in 2011 aimed to provide better stratification of these lesions by establishing that not all lesions with lepidic features have the same biology.[3] This classification was based on numerous studies showing that a greater lepidic component was associated with lower rates of recurrence and superior patient outcomes.[1,3,5-10] Although this classification offers an architectural grading of pulmonary adenocarcinomas, into low, intermediate, and high grades that correlates with clinical outcomes, the tumor–nodal–metastasis (TNM) staging currently remains the most important factor in determining the prognosis of a patient with a pulmonary adenocarcinoma.[4,11-14] However, classifying these particular patients according to American Joint Committee on Cancer (AJCC) TNM staging eliminates the distinction between those with indolent versus more-aggressive lesions, as this staging system does not take histopathology into account. For example, according to current TNM staging, a 1-cm purely lepidic lesion would be classified as a stage I lesion, and so would a 3-cm, predominantly invasive adenocarcinoma, even though these 2 lesion types have clear differences in terms of tumor biology, treatment strategy, and patient outcomes.

We aimed to compare patients categorized according to the IASLC/ATS/ERS and AJCC 7th-edition classifications, to determine if the 2 systems could be integrated as a single staging system, thus combining the advantage of the discriminating ability of the IASLC/ATS/ERS system with the simplicity and prognostic value of the AJCC system. A secondary objective is to describe our North American experience of the management of patients with stage I lepidic adenocarcinomas.

METHODS

Patients with a pure lepidic lesion or an adenocarcinoma that had lepidic features were identified from a prospectively collected pathology database. A retrospective review of patient charts and resected pathology, from August 2001 to August 2013, was performed at the Swedish Cancer Institute. Study approval was granted by the Swedish Medical Center Institutional Review Board, and individual consent for the study was waived, owing to the retrospective, observational nature of the analysis.

Study Population

We identified 187 patients who underwent resection of a dominant, primary, pure lepidic pulmonary lesion, or a dominant, primary adenocarcinoma with lepidic features on pathology. A lesion was defined as dominant if it was one of the following: (1) positive on positron emission tomography (standardized uptake value >2.5) and/or negative on positron emission tomography, but was enlarged in total size and/or size of the solid component; or (2) was clinically suspicious for malignancy, as assessed by a thoracic surgeon.[15] After careful review of all patients, the following patients were excluded: 1 who did not have pathology slides available for re-evaluation; 2 who had clinical N2 disease and had received induction chemoradiation therapy; 5 who had advanced disease at presentation; 7 who had mucinous adenocarcinoma subtype; 12 who had multiple synchronous primary tumors; and 22 who had stage II or III disease. Thus, 138 patients who had stage I lepidic-associated pulmonary lesions were included in the study.

Surgical Resection

Open and minimally invasive (video-assisted thoracoscopic or robotic) surgeries, with systematic nodal sampling or comprehensive lymphadenectomy, were performed. Prior to resection, the mediastinum was staged, using mediastinoscopy and/or endobronchial ultrasound in selected cases. The final resection that was performed to obtain a complete resection of the dominant lesion was used to define the resection type. For analysis purposes, lingula-sparing upper lobectomies were considered segmentectomies, and bilobectomies were considered lobectomies. An acceptable surgical parenchymal margin for sublobar resections was defined as a distance equal to or greater than the size of the tumor, and was estimated at the time of surgery.[16]

Pathologic Classification

The slides of the resected specimen were reviewed at 2 independent time points, the first at the time of diagnosis, after surgery by 2 separate pathologists, and the second at the time of analysis for the study. During the analysis, a dedicated pulmonary pathologist (1 of the authors), who was blinded to the patient chart and outcomes, re-evaluated all of the slides and recorded the histologic type, tumor grade, tumor location, extent of vascular and/or lymphatic invasion, histologic clearance of bronchial margins, and pleural involvement. The slides were stored in a temperature-controlled setting in cabinets, to minimize light degradation, and they were evaluated for staining and sectioning adequacy at the time of review.

To histologically categorize each lesion as adenocarcinoma in situ (AIS, ≤3 cm and comprised of pure lepidic growth), minimally invasive adenocarcinoma (MIA, ≤3 cm and comprised predominantly of lepidic growth with a ≤5-mm invasive component), or invasive adenocarcinoma (IA, >3 cm and/or >5 mm of invasion), according to the IASLC/ATS/ERS classification, the total tumor and invasive-component sizes were documented.[3] The invasive-component size was defined as the largest diameter of invasive adenocarcinoma in any 1 focus of the lesion. For