Impact of Solid Minor Histologic Subtype in Postsurgical Prognosis of Stage I Lung Adenocarcinoma

Tianxiang Chen, MD, PhD,* Jizhuang Luo, MD,* Haiyong Gu, MD, Yu Gu, MD, Qingyuan Huang, MD, Yiyang Wang, MD, Jiajie Zheng, MD, Yunhai Yang, MD, and Haiquan Chen, MD

Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai; Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai; and Departments of Radiation Oncology and Thoracic Surgery, Shanghai Cancer Center, Fudan University, Shanghai, China

Background. **Few studies focus on the outcome and effect of a postsurgical treatment strategy for early stage patients with minor solid components pattern. This study investigated the prognosis and the adjuvant chemotherapy benefit among stage I invasive lung adenocarcinoma patients with minor solid components pattern according to the eighth TNM staging classification.**

Methods. **A total of 3,308 lung adenocarcinoma patients with mixed histologic components was divided into three groups: solid predominant, solid minor, and solid absent pattern. Disease-free survival and overall survival were analyzed to evaluate survival difference among patients in the different groups using the Kaplan-Meier approach and multivariable Cox models.**

Results. **Both solid predominant and solid minor groups showed significantly worse disease-free survival ($p < 0.001$) and overall survival ($p < 0.001$) compared with the solid absent group. There were no significant disease-free survival (hazard ratio [HR] 1.41, 95% confidence interval [CI]: 0.87 to 2.30, $p = 0.161$) or overall survival (HR 1.60, 95% CI: 0.83 to 3.09, $p = 0.159$) difference between the former two groups. For patients in stage IB, adjuvant chemotherapy improves disease-free survival (HR 0.33, 95% CI: 0.11 to 1.02, $p = 0.044$) but not overall survival (HR 0.61, 95% CI: 0.21 to 1.77, $p = 0.360$) in the solid predominant group. No adjuvant chemotherapy benefits for disease-free survival (HR 1.04, 95% CI: 0.49 to 2.22; $p = 0.922$) and overall survival (HR 0.49, 95% CI: 0.13 to 1.90; $p = 0.291$) were seen for the solid minor group.**

Conclusions. **Solid minor components predict a significantly worse prognosis compared with the solid absent pattern. However, adjuvant chemotherapy may be unhelpful to improve outcomes for stage IB patients with solid minor components after surgery.**

(Ann Thorac Surg 2018;105:302–8)

Lung cancer continues to be a leading cause of cancer-related death worldwide [1]. Since low-dose computed tomography has been used in China, the incidence of early stage lung adenocarcinoma has dramatically increased [2, 3]. Adenocarcinoma is becoming the most common histologic subtype, more than 80% to 90% of which presented as heterogeneous histologic patterns [4]. The recommended standard therapy for early stage lung adenocarcinoma was surgical resection with mediastinal lymph node dissection or systematic sampling [5]. Unfortunately, 30% to 40% of these patients still would have tumor relapse [6], and the risk of recurrences peaked within the first 2 years after surgery [7, 8].

In 2011, a new lung adenocarcinoma classification system was proposed by the International Association Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) [9]. Classification of individual tumors according to the most predominant subtype and the percentages of the subtypes was also reported. Previous studies [10–12] widely demonstrated that the solid predominant subtype was associated with poorer disease-free survival (DFS) and overall survival (OS), whereas the lepidic predominant subtype was believed to predict an excellent survival rate in most publications. Ujiie and colleagues [13] demonstrated that lung adenocarcinoma patients with stage I solid predominant pattern had earlier, more extrathoracic, and more multisite recurrences. The median postrecurrence survival for solid pattern patient was only 8.7 months, whereas the postrecurrence survival was 30.1 months for nonsolid pattern patients. This result provided a rationale for investigating adjuvant therapy among stage I solid pattern patients. To date, the prognoses of patients with solid minor components still have not been thoroughly studied.

According to the IASLC staging project, the eighth TNM classification for lung cancer was enacted January 2017 [14]; however, the adjuvant chemotherapy strategy

Accepted for publication Aug 7, 2017.

*Drs Tianxiang Chen and Jizhuang Luo contributed equally to this work.

Address correspondence to Dr Haiquan Chen, Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, 270 Dong-An Rd, Shanghai 200032, China; email: hqchen1@yahoo.com.

Published by Elsevier Inc.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2017.08.018

for stage I patients according to the eighth TNM staging classification remains unclear. In this study, we carried out a study of a large cohort based on the eighth TNM staging classification, to evaluate the value of solid minor components in predicting the prognosis, and to study adjuvant chemotherapy benefit for patients with stage I lung adenocarcinoma. Our conclusions help to guide the postsurgical management of patients with resected early stage invasive lung adenocarcinoma.

Patients and Methods

Patient Cohort

The Institutional Review Board from Shanghai Chest Hospital, Shanghai Jiao Tong University, approved of the retrospective study. We reviewed the medical records of all surgical patients who were diagnosed as having pathologic stage I adenocarcinoma at Shanghai Chest Hospital between January 2010 and March 2015. The inclusion criteria was single nodule, postsurgical TNM stage I, no lymph nodes or organ metastasis. The exclusion criteria included patients who had multiple nodules, malignancy history, adenocarcinomas in situ, minimally invasive adenocarcinoma, invasive adenocarcinoma variants (including mucinous, enteric, or fetal morphologies), or who received neoadjuvant chemotherapies. Finally, a total of 3,308 patients were included in this study.

Clinicopathologic Evaluation

For the patients who received surgery before the new IASLC/ATS/ERS classification of lung adenocarcinoma conducted in the department of pathology of our hospital, two pathologists independently reviewed all hematoxylin-and-eosin stained slides of the surgically resected specimens to reevaluate the histologic classification. According to the criteria of the new IASLC/ATS/ERS classification, the percentage of each histologic component in 5% increments was recorded. Invasive adenocarcinomas were classified into five major subtypes according to the predominant pattern: lepidic, acinar, papillary, micropapillary, and solid predominant. To determine the impact of solid component on a patient's prognosis, patients were grouped as follows based on the percentages of solid components in tumor: solid predominant group, solid minor (lepidic, acinar, papillary, or micropapillary predominant pattern, containing solid component) group; and solid absent group.

The clinicopathologic features, including sex, age, tumor size, surgical procedure, visceral pleural invasion, lymphovascular invasion, chemotherapy and radiotherapy history, and recurrence patterns were obtained from patients' medical records. The TNM staging was based on the eighth edition of the American Joint Committee on Cancer cancer staging manual [14].

Adjuvant Chemotherapy

For stage IB adenocarcinoma patients with tumor size greater than 4 cm, solid or micropapillary predominant pattern, wedge resection Nx or R1/R2 resection, age less than 80 years, we would consider adjuvant chemotherapy. The recommended time for the first cycle of adjuvant chemotherapy is 1 month after surgery. The recommended adjuvant chemotherapy regimens were four-cycle platinum-based regimens, regardless of EGFR and ALK mutation status.

Surveillance Protocol

Overall survival was defined as the period between surgery and the date of death resulting from any cause. Disease-free survival was defined as time from surgery to the date the first event (recurrence or metastasis) occurred. Patients with no event were censored at the date of the last follow-up. We obtained OS and DFS status from clinical medical records or telephone follow-up.

The routine preoperative examination in Shanghai Chest Hospital includes head and chest computed tomography scan and upper abdomen sonography to exclude multiple nodules and distant metastasis; we also perform pulmonary function testing, heart sonography, and some necessary blood tests to evaluate the patient's performance status. For some patients with suspicious lymph node enlargement, we also advise performing a positron emission tomography examination to exclude distant metastasis.

The postoperative lung cancer surveillance, described in our previous publications [15, 16], consisted of physical examination, blood tests, chest computed tomography, neck and upper abdominal ultrasound examination, and were performed every 3 months for the first year after surgery and at 6-month intervals thereafter. Whole-body bone scanning and brain magnetic resonance imaging were performed annually. Additional imaging studies were performed if patients had any symptoms or signs of recurrence, regardless of the follow-up schedule. For patients who did not follow up in out hospital regularly, telephone follow-up was conducted to record the survival status.

Statistical Methods

The χ^2 test was used to compare categoric variables between groups. The Cochran-Mantel-Haenszel test was used to estimate the correlation between the histologic subtypes and covariates. The log rank test was used to compare the differences in DFS and OS between histologic groups for univariable analysis. Multivariable Cox models stratified by trial and adjusted for sex, age, visceral pleural invasion, lymphovascular invasion, tumor size, histologic subtypes, adjuvant chemotherapy, and surgical procedure were used to measure the predictive value for patient survival. The value of statistical significance was set to 0.05 (pooled analysis). Statistical analyses were performed using IBM SPSS Statistics 19 (IBM Corporation, Armonk, NY) and Prism 5 (GraphPad Software, San Diego, CA).

Results

Among the 3,308 patients in our study cohort, there were 1,368 men (41.8%) and 1,940 women (58.6%); 915 patients