Prognosis in Resected Invasive Mucinous Adenocarcinomas of the Lung: Related Factors and Comparison with Resected Nonmucinous Adenocarcinomas

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ABSTRACT

Introduction: In the 2015 World Health Organization classification, invasive mucinous adenocarcinoma (IMA) is categorized as one of various subtypes of lung invasive adenocarcinoma (ADC). However, no comprehensive analysis regarding the clinicoradiologic and prognostic features of IMA has been reported. We aimed to report prognostic factors in IMA and to compare the prognosis of IMAs with that of nonmucinous ADCs.

Methods: We included 81 patients with a solitary IMA of the lung and analyzed them from the standpoint of clinicoradiologic presentation. Survival rates were assessed and compared with those of 646 resected solitary invasive nonmucinous ADCs.

Results: Patients with IMA showed longer disease-free survival (DFS) than did those with nonmucinous ADCs, whereas overall survival (OS) did not differ significantly ($p = 0.023$ and $p = 0.824$, respectively). The DFS of patients with IMA was between that of patients with lepidic predominant (low-grade) and acinar/papillary predominant (intermediate-grade) ADC. In terms of OS, the survival curve of IMA was similar to that of acinar/papillary predominant ADC. Multivariate analysis revealed that tumor size (hazard ratio [HR] = 1.370, 95% confidence interval [CI]: 1.141–1.645, $p = 0.001$) and maximum standardized uptake value (HR = 1.338, 95% CI: 1.160–1.544, $p < 0.001$) were independent poor prognostic predictors for DFS. Regarding OS, tumor size (HR = 1.309, 95% CI: 1.092–1.570; $p = 0.004$) was the only predictor of poor prognosis.

Conclusion: Patients with IMA demonstrate a DFS between that of patients with low-grade nonmucinous ADC and that of patients with intermediate-grade nonmucinous ADC and an OS similar to that of patients with intermediate-grade nonmucinous ADC. In IMA, tumor size and maximum standardized uptake value are the factors related to mitigating DFS and tumor size is the only predictor for reduced OS.

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Introduction

Mucinous adenocarcinoma (ADC) is characterized histopathologically by tumor cells having a goblet or columnar cell morphologic pattern with abundant intracytoplasmic mucin. In the 2011 classification system for lung ADC of the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/ European Respiratory Society (ERS), invasive mucinous adenocarcinomas (IMAs) are classified as variants of invasive ADCs. IMAs are distinguished from nonmucinous ADCs because they have major differences from nonmucinous ADCs in terms of their clinical, radiologic, pathologic, and genetic aspects.[1–10] In the 2015 World Health Organization (WHO) classification, IMA is regarded as one of the various subtypes of invasive ADC.[11]

There have been several studies indicating that patients with mucinous bronchioloalveolar carcinoma (BAC) show poorer prognosis than do those with nonmucinous BAC.[3,12] Even after proposal of the 2011 IASLC/ATS/ERS classification scheme, Russell et al.[13] and Yoshizawa et al.[14] also suggested that IMAs are usually associated with poor survival outcome. However, the prognosis of IMAs remains controversial. In contrast, Warth et al.[15] reported that IMAs show better prognosis than do conventional nonmucinous ADCs. Because of the low incidence of lung mucinous ADCs, which account for only 2% to 5 % of all lung ADCs, the numbers of patients included in most previous studies have been relatively small.[13,14,16,17] Thus, the ultimate prognosis of patients in whom IMAs were diagnosed on the basis of the 2011 IASLC/ATS/ERS[1] and 2015 WHO criteria[11] still needs to be clarified with a large sample size.

In contrast to nonmucinous ADCs, IMAs have not been the subject of any reported comprehensive studies regarding their clinicopathologic and radiologic aspects, not to mention prognostic factors. Also, limited information has been reported on the prevalence of this tumor, its radiologic presentations, and its response to surgical treatment. Therefore, the purpose of this study was twofold: (1) to review the clinicopathologic and radiologic features of patients with surgically resected IMAs and (2) to compare the prognoses of patients with IMAs with that of patients with nonmucinous invasive ADCs in a large cohort.

Patients and Methods

The institutional review board approved this retrospective study, and informed consent was waived for the use of patients' medical data.

Study Population

We reviewed the surgical database of the Department of Thoracic Surgery at Samsung Medical Center, a tertiary referral center located in Seoul, Republic of Korea, to identify patients who had undergone curative surgery for lung ADCs. All of the glass slides of resected lung ADCs from September 2003 to November 2011 in the institute were reevaluated by experienced pathologists according to the new WHO classification.[11] A total of 942 solitary lung ADCs from 942 consecutive patients were identified. Of these patients, 113 were excluded for the following reasons: (1) insufficient pathologic slides for evaluation of the whole tumor (n = 42), (2) poor quality of the computed tomography (CT) image (n = 23), and (3) concomitant presence of other malignancy (n = 48). Patients with the following types of ADC were also excluded: mixed invasive mucinous and nonmucinous ADCs (n = 10); ADC in situ or minimally invasive ADC (n = 79); and colloid, fetal, and enteric ADCs (n = 13). Ultimately, 81 patients with completely resected solitary IMAs and 646 patients with invasive nonmucinous ADCs were included in this study.

Data on clinicoradiologic presentation, tumor stage, and survival outcome were obtained from electronic medical records. Surgical treatment methods were recorded. Tumor, node, and metastasis stage for each tumor was determined according to the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer.[18] Survival and the presence of disease progression were also assessed according to the medical records and the data from the Korea National Statistical Office.

Preoperative Chest CT and Positron Emission Tomography/CT

On the basis of preoperative CT images, 81 IMAs were classified as having a nodular pattern or consolidative pattern according to the dominant presentation (Supplementary Fig. 1). The CT pattern was determined on the basis of tumor morphology. Nodular pattern was defined as a rounded opacity, whereas consolidative pattern referred to an increased parenchymal attenuation without definable shape or distribution. Other CT features such as site and number of involved lobes and tumor size were also assessed retrospectively.

For positron emission tomography (PET)/CT evaluation, regions of interest were identified in the most intense area of fludeoxyglucose F 18 (FDG) uptake in the primary tumor. FDG uptake within the regions of interest was analyzed to determine the maximum standardized uptake value (SUV_{max}).

Pathologic Evaluation

Two experienced lung pathologists (with 16 and 10 years of experience in lung pathology, respectively) interpreted all tissue sections and discussed them until