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Original article

Matched-pair analysis of a multi-institutional cohort reveals that epidermal growth factor receptor mutation is not a risk factor for postoperative recurrence of lung adenocarcinoma

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ABSTRACT

Objective: It is unclear whether epidermal growth factor receptor (EGFR) mutation status is a risk factor for postoperative recurrence of surgically resected lung adenocarcinoma (ADC). Therefore, we conducted a multi-institutional study employing matched-pair analysis to compare recurrence-free survival (RFS) and overall survival (OS) of patients with lung ADC according to EGFR mutation status.

Methods: We collected the records of 909 patients who underwent surgical resection for lung ADC between 2005 and 2012 at five participating institutions and were also examined their EGFR mutation status. For each patient with an EGFR mutation, we selected one with the wild-type EGFR sequence and matched them according to institution, age, gender, smoking history, pathological stage (pStage), and adjuvant treatment. We compared RFS and OS of the matched cohort.

Results: The patients were allocated into groups (n = 181 each) with mutated or wild-type EGFR sequences. Both cohorts had identical characteristics as follows: institution, median age (68 years), men (85, 47%), ever smokers (77, 43%), and pStage (IA, 108, 60%; IB, 48, 27%; II, 14, 8%; III, 11, 6%). The 3- and 5-year RFS rates of patients with mutated or wild-type EGFR sequence were 79%, 68% and 77%, 68%, respectively ($p = 0.557$). The respective OS rates were 92%, 81%, and 89%, 79% ($p = 0.574$).

Conclusion: Matched-pair and multi-institutional analysis reveals that an EGFR mutation was not a significant risk factor for recurrence of patients with surgically resected lung adenocarcinoma.

1. Introduction

Harboring epidermal growth factor receptor (EGFR) mutation is a robust prognostic factor for patients with advanced or recurrent lung adenocarcinoma (ADC) [1,2], and certain randomized phase III trials demonstrate that the longer survival of patients harboring EGFR mutations is mainly associated with the dramatic effect of treatment using EGFR tyrosine kinase inhibitors (EGFR-TKIs) [3,4]. However, it is unknown whether an EGFR mutation *itself* influences a patient's survival [5–7]. Kim et al. suggest that age, pStage and smoking status, but not EGFR mutation status, are significant prognostic factors for the overall survival (OS) and recurrence-free survival (RFS) of 636 patients with ADC [6].

According to a review of EGFR mutations as prognostic and predictive markers, some investigators suggest that EGFR mutation is a prognostic factor of OS and RFS, although others disagree [5]. To resolve this clinical question, we conducted a pilot study [8], that compared the RFS of patients with mutated and wild-type EGFR sequences, because EGFR-TKIs are not usually administered to patients who undergo surgical resection until the tumors recur [1,9]. Further, we

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conducted a matched-pair analysis [8] to reduce the potential bias introduced because of patients' backgrounds of those with EGFR mutant or wild type sequences, because we expected that such bias likely influences patients' survival. This pilot study suggests that patients harboring an EGFR mutation may experience longer RFS. However, a review of the data suggested that the study had insufficient statistical power because of the small number of patients included in the matched cohort. Therefore, we conducted the current multi-institutional study of a matched cohort to determine whether an EGFR mutation is a risk factor for recurrence of patients with surgically resected lung ADCs.

2. Patients and methods

2.1. Study design

According to the results of our pilot study [8], we calculated the sample size required for sufficient statistical power. Considering the difference between the RFS curves of the EGFR mutant (EGFR-M) and wild-type (EGFR-WT) groups among pair-matched patients in the pilot study, and a statistical power of 80% (two-sided significance, $p = 0.05$), we found that 179 patients were required for each group. Estimating that the matching process would reduce the number of patients by approximately 50% with 10% inaccurate data, we planned to enroll at least 788 patients. For this purpose, we retrospectively collected patients' medical records from five institutions.

According to the protocol depicted in Fig. 1, we collected the information of patients who underwent complete surgical resection for treating lung ADC between January 2005 and December 2012, and their tumors were analyzed for EGFR mutations. The primary endpoint of this study was the RFS of the EGFR-M and EGFR-WT groups after pair matching. The staff of each institution included at least two thoracic surgeons certified by The Japanese Association for Chest Surgery. Regarding pathological diagnosis, we asked each institution to classify adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IA), and to diagnose pathological stage (pStage) according to the TNM classification of malignant tumors of the Union for International Cancer Control (UICC, 7th Edition) [10] and the World Health Organization (WHO) classification [11]. We directly incorporated the data from each institution into the analysis and did not perform a central review of pathological findings such as pleural invasion, vascular invasion, lymphatic permeation, and WHO classification.

2.2. Patient selection

The medical information of 1463 patients was collected from the five participating institutions. We excluded patients when their information was inconsistent with the protocol and excluded patients with anaplastic lymphoma kinase (ALK) fusion genes [12–14]. Further, excluding patients harboring minor EGFR mutations as defined below and patients who underwent limited resections, we finally enrolled 909 patients (Fig. 1).

2.3. Analysis and evaluation of EGFR mutations

Each institution adopted its own commercial method to identify EGFR mutations. Fukushima Medical University used the PCR-Invader method (BML, Tokyo, Japan) according to the manufacturer's protocol [15]. Similarly, Kanazawa Medical University and Miyagi Cancer Center used a direct sequencing method (SRL, Tokyo, Japan). Tohoku University employed the PNA-LNA PCR Clamp method (LSI Medience Corporation, Tokyo, Japan). Yamagata Prefectural Central Hospital

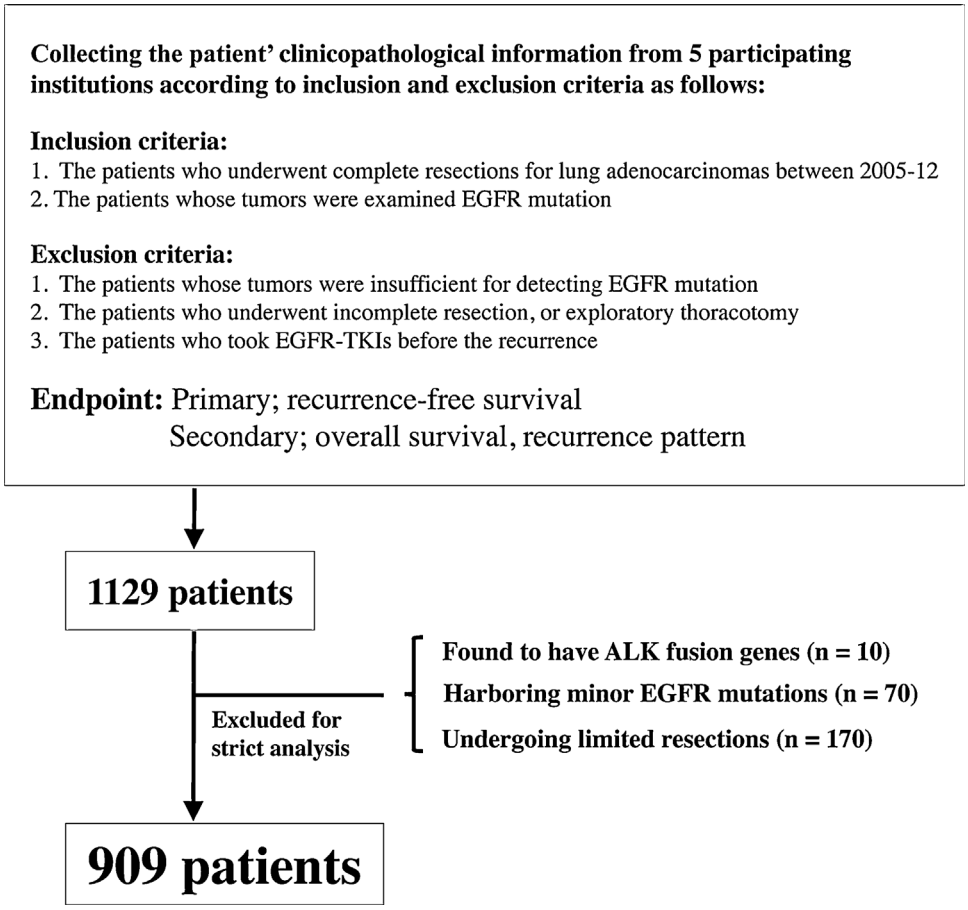

Fig. 1. Study design and enrolled patients. Five institutions participated in this research, and medical records were collected to determine patients' eligibility for the study. The inclusion criteria were complete resection for lung adenocarcinomas between 2005 and 2012, and the tumors analyzed for EGFR mutations. The exclusion criteria were as follows: tumors insufficient for detecting EGFR mutation, incomplete resection, exploratory thoracotomy, EGFR-TKIs administered before recurrence, or detection of ALK fusion genes. The primary endpoint was recurrence-free survival (RFS), and secondary endpoints were overall survival (OS) and recurrence pattern. The patients who underwent limited resection (segmentectomy or wedge resection) and whose tumors harbored minor mutations such as exon 18 G719A, exon 20 T790M, exon 21 L861Q were initially enrolled, but subsequently excluded later for detailed analysis. Finally, 909 patients were enrolled in this study.