Lung Cancer 118 (2018) 13–19

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

# High expression of P-cadherin is significantly associated with poor prognosis in patients with non-small-cell lung cancer

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ARTICLE INFO

*Keywords:*
P-cadherin
E-cadherin
Cadherin switch
Tumor progression
Prognosis
Non-small-cell lung cancer

ABSTRACT

*Objectives:* Placental (P)-cadherin expression is associated with malignant phenotype of cancer cell. The loss of E-cadherin has been thought to play a key role in tumor progression in several cancers. In this study, we aimed to clarify the role of P-cadherin expression in non-small-cell lung cancer (NSCLC).

*Materials and methods:* NSCLC patients ($n$ = 172) were enrolled in this study; among them, 107 harbored adenocarcinomas, and 65 had squamous cell carcinomas. We examined P-cadherin and E-cadherin expression by immunohistochemical analysis and assessed the associations between each cadherin expression and both cadherin expression patterns with clinicopathological factors and prognosis. To investigate the pathway to acquire tumor progression associated with P-cadherin and E-cadherin, we examined p120 catenin localization by immunohistochemical analysis.

*Results:* High P-cadherin expression was significantly associated with lymphatic metastasis, pathological stage, and Ki-67 proliferation index ($P < .05$, respectively). Low E-cadherin expression was significantly associated with maximum standardized uptake value, lymphatic metastasis, and pathological stage ($P < .05$, respectively). The cytoplasmic p120 catenin localization was associated with the low E-cadherin and high P-cadherin expression group ($P < .001$). High P-cadherin expression was associated with shorter disease-free survival ($P = .044$) and shorter overall survival (OS; $P = .044$). The low E-cadherin and high P-cadherin expression group was associated with shorter OS ($P = .024$).

*Conclusions:* High P-cadherin expression was associated with tumor progression and poor patient survival in NSCLC. In these patients, the low E-cadherin expression might be associated with tumor progression involving cytoplasmic p120 catenin.

## 1. Introduction

Lung cancer is the main cause of cancer-related death worldwide [1], despite considerable progress in diagnostic and therapeutic approaches, including molecular-targeted therapies and cancer immunotherapy [2]. Many oncogenes related to the development of lung cancer have been identified; however, the precise mechanisms that related to tumor progression of non-small-cell lung cancer (NSCLC) remain unclear.

Cadherin is an adhesion molecule reportedly involved in the malignant phenotype of cancer [3]. Cadherin is linked to the actin cytoskeleton through catenins, such as α-, β-, and p120 catenin, and it establishes the cadherin–catenin complex, which regulates cell–cell adhesion, cell sorting, and tissue morphogenesis [4,5]. Classical cadherins are a subfamily of the cadherin superfamily and were originally named according to their prominent tissue of their specific expression, including epithelial (E)-cadherin and placental (P)-cadherin, which are expressed in epithelial cells, whereas neural (N)-cadherin is expressed in the nervous system [4–6].

During tumor progression in cancer, the cancer cells lose E-cadherin membrane expression and exhibit a non-polarized, motile, and invasive mesenchymal phenotype known as epithelial-to-mesenchymal transition (EMT) [3]. Catenin migration from the juxta membrane domain to the cytoplasm and nucleus occurs by the loss of E-cadherin expression, which also promotes tumor progression [6]. Many studies on lung cancer have explored the relationships between the loss of E-cadherin

*Abbreviations:* BI, Brinkman index; DFS, disease recurrence free survival; E-cadherin, epithelial cadherin; EhPh, E-cadherin-high/P-cadherin-high; EhPl, E-cadherin-high/P-cadherin-low; ElPh, E-cadherin-low/P-cadherin-high; ElPl, E-cadherin-low/P-cadherin-low; EMT, epithelial-to-mesenchymal transition; GGO, ground glass opacity; HRCT, high-resolution computed tomography; N-cadherin, neural cadherin; NSCLC, non-small-cell lung cancer; OS, overall survival P-cadherin placental cadherin; PET, positron emission tomography; SUV max, maximum standardized uptake value

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https://doi.org/10.1016/j.lungcan.2018.01.018
Received 5 September 2017; Received in revised form 9 January 2018; Accepted 23 January 2018

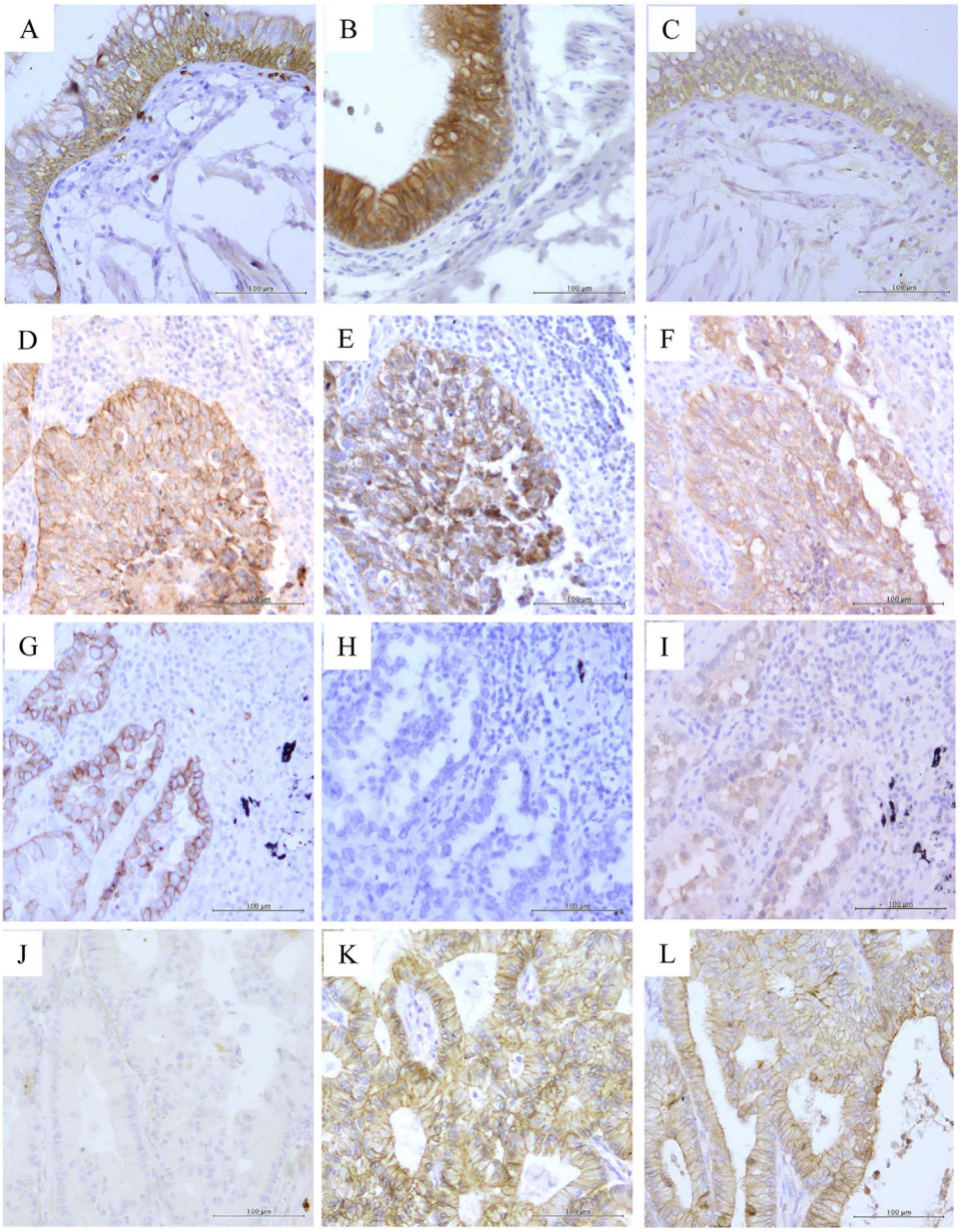


**Fig. 1.** Representative immunohistochemistry findings for normal lung tissue and lung tumors. A normal bronchial epithelium with staining for (A) P-cadherin, (B) E-cadherin and (C) p120 catenin. A squamous cell carcinoma with (D) strong and moderate staining for P-cadherin, (E) moderate staining for E-cadherin and (F) membranous staining for p120 catenin. A micropapillary predominant adenocarcinoma with (G) strong staining for P-cadherin, (H) negative staining for E-cadherin and (I) cytoplasmic staining for p120 catenin. An acinar predominant adenocarcinoma with (J) negative staining for P-cadherin, (K) strong and moderate staining for E-cadherin and (L) membranous staining for p120 catenin.

expression and clinicopathological features, showing that loss of E-cadherin expression is associated with malignant phenotype, although the prognostic associations remain debated [7–10]. Because tumor progression is a complex and multi-step process, elucidation of other biomarkers related to E-cadherin expression or repression is pivotal.

Upregulated P-cadherin expression is reportedly associated with tumor progression and poor patient survival in some invasive epithelial tumors, including breast [11] and pancreatic cancer [12]. P-cadherin upregulation is also known to result from cadherin switch from E-cadherin expression [13]; however, the recent studies in breast cancer showed that cells co-expressing E-cadherin and P-cadherin increased migration and invasion and showed resistance to apoptosis and that tumors co-expressing E-cadherin and P-cadherin are associated with high histological grade and poor prognosis [14,15]. Elucidating the role of P-cadherin expression and the relationship between E-cadherin and P-cadherin expression in cancer offer important insights into malignant phenotype.

In non-small-cell lung cancer (NSCLC), the expression and role of P-cadherin remain incompletely understood. In this study, we clarified the role of P-cadherin expression in NSCLC. We undertook a comprehensive clinicopathological investigation of E-cadherin and P-cadherin expression by immunohistochemical staining and assessed its association with clinicopathological factors and patient prognosis in NSCLC. Moreover, to investigate the pathway to acquire tumor progression, we examined the associations between p120 catenin localization and E-cadherin and P-cadherin expression pattern.

## 2. Materials and methods

### 2.1. Patients and specimens

Patients ($n$ = 172), including 107 with invasive adenocarcinoma (62.2%) and 65 with squamous cell carcinoma (37.8%), who had undergone radical lung resection at Tokyo Medical and Dental University Hospital (Tokyo, Japan) between April 2010 and March 2013 were enrolled in this study. Patients who received preoperative treatment, including chemotherapy or radiotherapy, were excluded. Expression of E-cadherin and P-cadherin was evaluated by immunohistochemical staining of 172 primary tumors. Additionally, expressions of P-cadherin in 47 metastatic lymph nodes; 30 samples of N1 and 17 samples of N2