Prognostic impact of stathmin 1 expression in patients with lung adenocarcinoma

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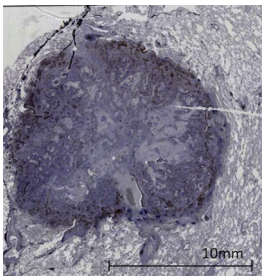
ABSTRACT

Objective: Stathmin 1 is a major cytosolic phosphoprotein that regulates microtubule dynamics and is associated with malignant phenotypes in various cancers, including non–small cell lung cancer. We aimed to determine differences in overall survival and disease-free proportion in patients with lung adenocarcinoma stratified by stathmin 1 tumor expression.

Methods: With the use of immunohistochemistry, stathmin 1 expression was determined in resection specimens from 303 patients with adenocarcinoma. Associations between stathmin 1 protein expression and overall and disease-free proportion were assessed (Kaplan–Meier survival curves compared with log-rank statistics). Cox proportional hazards regression determined the hazard for death stratified by stathmin 1, adjusting for clinicopathologic characteristics.

Results: During follow-up, 74 (24.4%) recurrences and 73 (24.1%) all-cause deaths were recorded. Expressed in 53.8% of adenocarcinoma cases, overall survival and disease-free proportion were significantly worse in stathmin 1–positive patients (log-rank $P < .001$ and $P < .001$, respectively). When adjusted for clinical and pathologic factors, stathmin 1 expression was an independent prognostic variable for both overall survival (hazard ratio, 2.21; 95% confidence interval, 1.28-3.80) and disease-free proportion (hazard ratio, 2.02; 95% confidence interval, 1.13-3.63) and for disease-free proportion even in the subset of patients with stage I (hazard ratio, 2.79; 95% confidence interval, 1.07-7.27). There was no significant difference between the stathmin 1–positive patients with stage IA and patients with stage IB in overall survival ($P = .975$) and disease-free proportion ($P = .490$), respectively.

Conclusions: Stathmin 1 expression was an independent prognostic factor for adenocarcinoma, even when restricted to patients with early-stage cancer. (J Thorac Cardiovasc Surg 2017;154:1406-17)



Positive staining of STMN1 in lung adenocarcinoma.

Central Message

STMN1 expression was an independent unfavorable prognostic factor for lung adenocarcinoma.

Perspective

Our study demonstrated that STMN1 expression was associated with an unfavorable OS and DFP, and was an independent unfavorable prognostic factor for lung adenocarcinoma, even when restricted to stage I.

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In recent years, efforts to improve survival have focused on the identification of targetable molecular changes within the tumor. The identification of the *EGFR* gene mutation in patients with lung adenocarcinoma and subsequent development of therapies targeted toward the mutation have resulted in significantly reduced hazard of death and notable survival for *EGFR*-gene mutation–positive patients.[1-4] Efforts to improve survival in patients with *EGFR* wild-type gene status have been less successful. Thus, there is a continuing need to identify new and targetable molecular alterations in these patients.

Stathmin 1 (STMN1) is a cytosolic phosphoprotein that plays a crucial role in the control of cellular division and proliferation by regulating microtubule dynamics.[5] STMN1 plays an important role in a variety of biological processes,

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Abbreviations and Acronyms

CEA = carcinoembryonic antigen
CI = confidence interval
DFP = disease-free proportion
HR = hazard ratio
LI = labeling index
NSCLC = non–small cell lung cancer
OS = overall survival
STMN1 = stathmin 1

including carcinogenesis. STMN1 is highly expressed in various types of human malignancies and is also known as oncoprotein 18. Moreover, STMN1 expression correlates with tumor progression and poor prognosis in the following cancers: gastric cancer, colorectal cancer, endometrial carcinoma, and non–small cell lung cancer (NSCLC).[6-10] Thus, STMN1 is a fundamental cancer-associated gene and a potential target for diagnosis and treatment. The relationship between STMN1 and survival in patients with NSCLC has been assessed in 2 prior studies, and STMN1 expression was found to be associated with poor differentiation, large tumor size, advanced N and TNM classification stages, and worse survival.[9,10] However, these studies included only small numbers of patients, and the true impact of STMN1 expression on survival in patients with adenocarcinoma, especially in early stages, and its relationship with clinicopathologic features remain unclear.

The aim of this study is to determine the differences in overall survival (OS) and disease-free proportion (DFP) in patients with adenocarcinoma, especially in early stages, stratified by STMN1 expression and the relationship among STMN1 protein expression, clinicopathologic characteristics, mRNA expression, and driver gene mutation status.

PATIENTS AND METHODS

Patients and Specimens

We analyzed 303 consecutive patients with lung adenocarcinoma who underwent complete resection with pathologically confirmed negative margins with mediastinal lymph node dissection at Gunma University Hospital (Maebashi, Gunma, Japan) between June 2003 and April 2013. No patients received chemotherapy or radiotherapy before surgery. Histologic diagnoses were made on the basis of the 4th edition of the World Health Organization criteria, and disease stage was determined according to the TNM Classification of Malignant Tumors, 7th edition.[11] The study protocol was approved by the institutional review board. All samples were used in accordance with the Helsinki Declaration after obtaining written informed consent.

We examined the patients at 3-month intervals for the first 3 years and at 3- to 6-month intervals thereafter on an outpatient basis. The follow-up duration ranged from 1 month to 12.5 years (median, 47 months). The follow-up evaluation included a physical examination, chest radiography, and blood analysis, including analysis of pertinent tumor markers. Computed tomography scans of the chest and abdomen or positron emission tomography and computed tomography were performed at least every year. Whenever any symptoms or signs of recurrence were detected, further evaluations were performed. We diagnosed recurrence on the basis of compatible physical examination and diagnostic imaging findings, and confirmed the diagnosis histologically when clinically feasible.

Immunohistochemical Staining

A 4-μm section was cut from formalin-fixed and paraffin-embedded blocks of samples. Each section was mounted on a Silane-coated glass slide, deparaffinized, and soaked for 30 minutes at room temperature in 0.3% H_2O_2/methanol to block endogenous peroxidases. The sections were then heated in boiled water and Immunosaver (Nishin EM, Tokyo, Japan) at 98°C for 45 minutes. Nonspecific binding sites were blocked by incubating with Protein Block Serum-Free (DAKO, Carpinteria, Calif) for 30 minutes. A mouse monoclonal anti-STMN1 (OP18) antibody (Santa Cruz

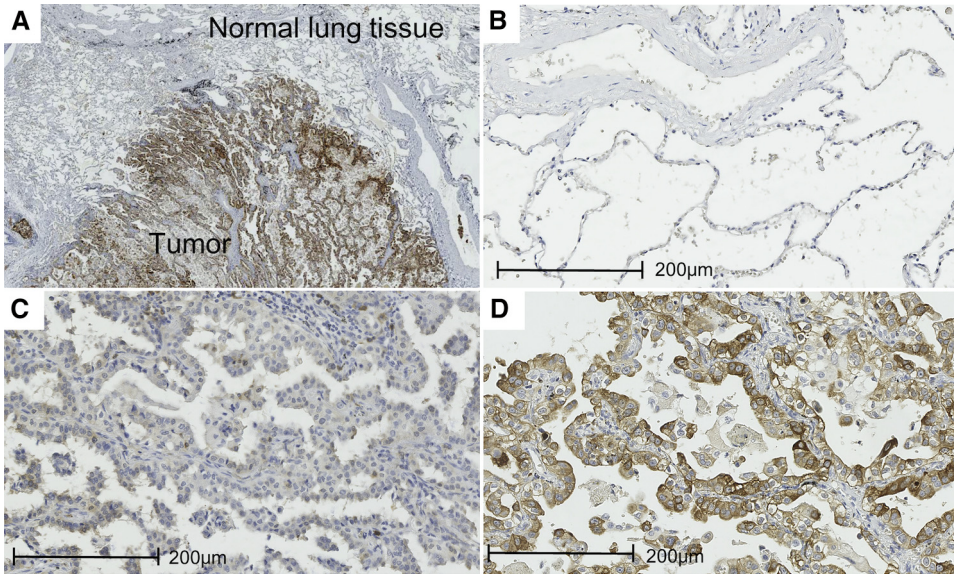

FIGURE 1. Negative and positive staining of STMN1 protein expression. A, STMN1 expression in tumor and adjacent normal lung tissue (×3.2). B, No STMN1 expression in normal lung tissue (×200). C, Weak STMN1 expression in tumor tissue (×200). D, Strong STMN1 expression in tumor tissue (×200).