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Title: Prognostic impact of nestin expression in resected large cell neuroendocrine carcinoma of the lung

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Body: Large cell neuroendocrine carcinoma (LCNEC) of the lung is categorized as a high-grade neuroendocrine carcinoma with an aggressive clinical behavior. Nestin is a class VI intermediate filament protein expressed in stem/progenitor cells during central nervous system development. Recently, we reported that nestin expression is a prognostic indicator of a poorer survival probability in patients with resected NSCLC. In the present study, we aimed to determine its prognostic significance concerning survival in patients with resected LCNEC. Nestin expression in tumor cells was immunohistochemically studied in 30 patients with resected LCNEC, and its associations with clinicopathologic parameters were evaluated. Kaplan-Meier survival analysis and Cox proportional hazards models were used to estimate the effect of nestin expression on survival. Nestin expression was observed in 8 of the 30 (26.7%) LCNECs. Clinicopathologically, no significant association between nestin expression and age, gender, smoking habits, p-TNM stage, tumor size, or nodal status was observed. On survival analysis, nestin expression was significantly associated with a poorer prognosis in patients with LCNEC (P = 0.016). Multivariable analysis confirmed that nestin expression increased the hazard of death after adjusting for other clinicopathologic factors (HR= 3.53; 95% CI, 1.21-10.3). The present study suggests that nestin expression is a prognostic indicator of a poorer survival probability in patients with resected LCNEC, although its prognostic significance still requires confirmation with larger patient populations. This study was approved by Kitasato university human ethics comittee.