論　文　内　容　要　旨

Prognostic Impact of Programmed Death-ligand 1 and Surrounding Immune Status on Stage I Lung Cancer.

(PD-L1 発現と周囲免疫状態が I 期肺癌の予後に与える影響)

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Programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1) pathway have now attracted increasing attention because many studies have demonstrated that positive PD-L1 expression was correlated with favourable clinical benefits achieved with anti–PD-1/PD-L1 antibodies. However, the prognostic impact of PD-L1 expression itself remains controversial, and the presence of PD-L1 positivity in cohorts of patients has been reported to be related from a poor prognosis to better locoregional control and prognosis. Briefly, tumor cells that express PD-L1 may survive immune regulation by binding to PD-1 on CD8+ cytotoxic T cells (CTLs) thereby downregulating CTL function, which otherwise would have attacked and killed the tumor cells. Thus, the PD-1/PD-L1 pathway shows their effects by interaction with the surrounding immune microenvironment. Moreover, cancer immunity itself consists of various immune cells. So far, few studies have evaluated the relationship between PD-1/PD-L1 pathway and the surrounding immune microenvironment. We hypothesized that the prognostic impact of the PD-1/PD-L1 pathway may be affected by the status of other biological factors involved in cancer immunity, such as CD4, CD8, regulatory T cells (Tregs) and human leukocyte antigen (HLA) class I molecules, which have critical roles in cancer immunity as well. Therefore, we conducted this translational study.

We retrospectively reviewed 126 patients with pathologic stage I non-small cell lung cancer who underwent complete resection without induction therapy between April 2013 and December 2015. PD-L1 expression was evaluated with immunohistochemistry in correlation with clinicopathologic features and surrounding immune microenvironment status, including CD4, CD8, Tregs and HLA class I. Factors affecting prognosis were assessed by the Kaplan–Meier method and Cox regression analyses.

Analysis of 126 lung cancer patients revealed that positive PD-L1 expression status on tumor cells was a potential factor to predict poor prognosis, which may depend on concurrent CD8 status, especially existing in the intratumoral compartment in lung cancer. A total of 23 patients (18.3%) were positive for PD-L1 expression. No significant correlation was observed between PD-L1 expression and the surrounding immune microenvironment status. The PD-L1–positive group had a worse prognosis than the PD-L1–negative group (5-year recurrence-free survival [RFS] rates, 63.4% vs. 81.0%; P=0.061). Among surrounding immune cells, intratumoral CD8 status had an impact on prognosis most strongly (P=0.12). In the intratumoral CD8–high group, PD-L1 expression demonstrated no significant prognostic impact, whereas in the intratumoral CD8–low group, patients positive for PD-L1 demonstrated a significantly worse prognosis than those negative for PD-L1 (5-year RFS rates, 41.7% vs. 78.6%; P=0.034). Multivariable Cox regression analysis revealed that 'PD-L1–positive and intratumoral CD8–low' status was an independent prognostic factor (hazard ratio, 3.80; 95% confidence interval, 1.22–10.5; P=0.023).

We concluded that the prognostic impact of the PD-1/PD-L1 pathway may be distinct according to concurrent intratumoral CD8 status.