Relevance Between Programmed Death Ligand 1 and Radiologic Invasiveness in Pathologic Stage I Lung Adenocarcinoma

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Background. **Programmed death ligand 1 (PD-L1) was reported to predict the response of immunotherapy; however, the association between PD-L1 expression and radiologic and pathologic features has yet to be elucidated.**

Methods. **In all, 292 patients with resected pathologic stage I adenocarcinoma were analyzed for PD-L1 expression by immunohistochemistry and evaluated to determine the association between PD-L1 expression and the radiologic/pathologic invasiveness. Specifically, the radiologic invasiveness and noninvasiveness were determined based on the consolidation/tumor ratio, with a cutoff value of 0.25 by thin-section computed tomography.**

Results. **Among 292 patients, 47 (16.1%) were positive for PD-L1 expression; the remaining 245 patients (83.9%) were negative for PD-L1 expression. Fisher's exact test demonstrated that PD-L1 expression was significantly associated with a higher consolidation/tumor ratio ($p = 0.029$) and higher maximum standardized uptake value ($p = 0.004$). The mean values of consolidation/tumor ratio and maximum standardized uptake in patients with and without PD-L1 expression were 0.845 ± 0.052 and 7.241 ± 0.795, and 0.607 ± 0.023 and 3.60 ± 0.364, respectively ($p < 0.001$ and $p < 0.001$, respectively). Among 47 adenocarcinomas harboring PD-L1 expression, the frequencies of PD-L1 expression for consolidation/tumor ratios of 0, 0.1 to 0.25, 0.26 to 0.5, and 0.51 or more were 6.4%, 2.1%, 4.3%, and 87.2%, respectively ($p = 0.007$). Pathologically, PD-L1 was identified exclusively only in more invasive subtypes, not in less invasive ones, such as atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant ones ($p < 0.001$).**

Conclusions. **Expression of PD-L1 was significantly associated with radiologic/pathologic invasive adenocarcinomas. This study provides the first evidence of the radiologic and pathologic invasiveness in resected pathologic stage I adenocarcinoma with PD-L1 expression.**

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Immune checkpoint inhibition against programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) has recently demonstrated a benefit in the survival of various types of cancer, such as melanoma and lung cancer [1]. The PD-1 is expressed on the surface of T cells and manipulates their activity through interaction with its ligands PD-L1 and PD-L2 [1]. The interaction between PD-1 and PD-L1 or PD-L2 attenuates the T-cell activity, which results in the downregulation of the immune response against cancer cells [2]. Inhibition of such interactions with PD-1 or PD-L1 blocking antibodies induces immune response in T cells against cancer cells [1]. Recent clinical trials have demonstrated that PD-1 inhibitors exhibited a survival benefit in comparison with conventional standard therapy in non-small cell lung cancer (NSCLC) [3, 4]. Therefore, immune checkpoint inhibition has emerged as a novel and promising therapeutic option in the treatment of lung cancer.

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Abbreviations and Acronyms

CT = computed tomography
C/T = consolidation/tumor
EGFR = epidermal growth factor receptor
GGO = ground-glass opacity
NSCLC = non-small cell lung cancer
PD-1 = programmed death 1
PD-L1 = programmed death ligand 1
SUVmax = maximum standardized uptake value

Despite this era of newly emerging and promising immunotherapies for lung cancer, however, surgical resection remains the most curable treatment option for patients with early stage NSCLC, and specifically, stage I NSCLC can be curatively treated by lobar resection combined with nodal dissection [5]. Radiologically, the small nodules in patients with stage I adenocarcinoma often present as ground-glass opacity (GGO) mixed with some extent of consolidation, which indicates pathologically invasive portions. It is therefore important to predict pathologic noninvasiveness precisely by using a preoperative radiologic test to determine the appropriate surgical procedures, such as lobectomy or limited resection [6]. A prospective study conducted by the Japan Clinical Oncology Group (JCOG) revealed that small nodules 2.0 cm or less in diameter with 25% or less consolidation detected by thin-section computed tomography (CT) can be defined as radiologic noninvasive lung adenocarcinoma, because such nodules correspond to pathologically noninvasive adenocarcinomas with very high sensitivity [6]. Given these findings, several prospective studies have been conducted to investigate the significance of limited resection for patients with small lung adenocarcinomas with some consolidation [7, 8].

A line of reports have demonstrated associations between radiologic features and genetic alterations, such as epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase rearrangement [9, 10]. For instance, *EGFR* L858R was reported to be associated with radiologically dominant GGO, whereas tumors harboring an anaplastic lymphoma kinase rearrangement often exhibit a solid pattern [9, 10]. However, there are no reports showing the relationship between the expression of immune checkpoint factors, such as PD-L1, and radiologic features, specifically radiologic invasiveness in patients with stage I adenocarcinoma.

In the present study, we evaluated the relationship between PD-L1 expression and radiologic and pathologic invasive features in patients with pathologic stage I lung adenocarcinoma.

Patients and Methods

Study Patients

Among 417 patients with lung adenocarcinoma who underwent surgery at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, between January 2003 and December 2012, 292 patients with pathologic stage I adenocarcinoma were included in this study. Tissue specimens from the enrolled patients were retrieved from the registry of the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University. The clinicopathologic features, including age at surgery, sex, smoking history, tumor differentiation (seventh edition, General Rule for Clinical and Pathological Record of Lung Cancer, Japan), pathologic tumor-node-metastasis (TNM) stage (seventh edition, Lung Cancer Staging, American Joint Committee on Cancer), pleural or lymphovascular invasion, histologic subtype (World Health Organization classification 2015), surgical procedure, and *EGFR* mutation status, were examined. The *EGFR* status was determined in tumor tissue using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (Mitsubishi Chemical Medience, Tokyo, Japan) in 176 specimens [11]. Briefly, systemic dissection of the hilar and mediastinal lymph nodes was performed at the same time as pulmonary lobectomy. After surgery, routine checkups, including a physical examination, blood tests (including serum tumor markers), and chest radiograph, were performed at 3-month intervals for the first 3 years and at 6-month intervals thereafter. Computed tomography was performed twice a year for the first 3 years and then at least annually thereafter. Clinical information and follow-up data were obtained from the medical records. This study was approved by our Institutional Review Board.

Chest Computed Tomography

Chest CT was performed in the supine position during inspiratory breath-hold using various multi-detector row scanners: Aquilion 4, Aquilion 64, Aquilion ONE, and Aquilion ONE VISION (Toshiba Medical Systems, Tochigi, Japan); Somatom Plus 4 Volume Zoom (Siemens Medical Solutions, Malvern, PA); and Brilliance CT and Brilliance iCT (Philips, Amsterdam, Netherlands). The imaging parameters for thin-section CT were as follows: peak tube voltage 120 kVp, tube current 100 to 500 mA; scan field of view 320 to 360 mm; and slice thickness 2 mm. A real exposure control (Toshiba) or automatic exposure control (Siemens and Phillips) was added in each study. All of the CT data sets were transferred to a Picture Archiving and Communication System (PACS), which was accessible by the workstations (Volume Analyzer, Synapse-Vincent; Fujifilm, Tokyo, Japan) with a specialized application for the lungs. The diameter of consolidation in each tumor (C) and the diameter of the whole tumor (T) including GGO were measured manually with axial two-dimensional CT data at a 2-mm slice section; the C/T ratio was then calculated. All CT images were evaluated by the authors (G.T., M.K., S.K.), and any discrepancies in their evaluations were resolved by averaging.

Positron Emission Tomography/Computed Tomography

The 18F-fluorodeoxyglucose positron emission tomography (PET)/CT scanning was performed using various