Significance of Lymphadenectomy in Part-Solid Lung Adenocarcinoma: Propensity Score Matched Analysis

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Background. It is evident that the frequency of nodal metastasis in part-solid lung adenocarcinoma is significantly low. For those cases, the prognostic impact of the lymph node dissection (LND) is highly controversial.

Methods. We reviewed 462 clinical stage I radiologic part-solid lung adenocarcinoma patients who underwent lobectomy or segmentectomy with lymphadenectomy. Consolidation tumor ratio was evaluated for all patients. Extent of LND was classified into systematic/lobe-specific mediastinal LND (m-LND) and hilar LND only (h-LND). Prognostic significance of LND was assessed by a multivariable analysis using propensity score matching. Survival was calculated by the Kaplan-Meier method using the log rank test.

Results. The m-LND was performed in 314 patients (68%), and h-LND in 148 (32%). Overall survival (OS) was not significantly different between m-LND and h-LND (5-year OS, 94.2% versus 92.8%, $p = 0.585$), as shown in 92 matched pairs (5-year OS, 94.0% versus 93.2%, $p = 0.845$). Cox proportional hazards model revealed maximum standardized uptake value as an independently significant oncologic prognosticator ($p = 0.003$), but extent of LND was not ($p = 0.997$). Nodal involvement was found in 16 patients, and was exclusive in solid-dominant lesions (ie, 0.5 less than consolidation tumor ratio of 1.0 or less; 4.9%). Multivariable analysis revealed carcinoembryonic antigen and maximum standardized uptake value as significant predictors of nodal metastasis among solid-dominant lesions (0.001, 0.002). For 329 solid-dominant lesions (71%), however, survival was similar between m-LND and h-LND (5-year OS, 93.2% versus 87.1%, $p = 0.097$), and was proven in 58 matched pairs (5-year OS, 82.9% versus 82.9%, $p = 0.822$).

Conclusions. Extent of LND was not associated with survival outcome of part-solid lung adenocarcinoma. Furthermore, it had no influence on the prognosis even for solid-dominant lesions by propensity score analysis, which could be selectively omitted based on both preoperative variables including carcinoembryonic antigen or maximum standardized uptake value.

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Since reported by Cahan [1] in 1960, complete hilar and mediastinal lymphadenectomy have been widely recognized as essential local management strategies for lymph node dissection (LND) in surgically resected non-small cell lung cancer (NSCLC). In general, complete hilar and mediastinal lymphadenectomy require en bloc resection of the lymph nodes based on the established anatomic boundaries. Patients with positive lymph nodal metastases could have a potential risk for locoregional or distant recurrence of lung cancer. Hence, complete lymphadenectomy for NSCLC plays a pivotal role in that it provides the most reliable information regarding cancer staging and prognosis. In addition, anatomic lymphadenectomy could reduce the risk of undetected positive lymph nodes, which may result in a thorough retrieval of remnants and proper delivery of optimal postoperative treatment, and that may influence survival outcomes [2, 3].

However, there is still plenty of room for argument regarding the actual oncologic benefit that radical lymphadenectomy could provide. Recently, we could predict tumor invasiveness and probability of pathologic lymph nodal involvement more precisely on the basis of preoperative radiologic features of the main tumor [4–6]. According to the numerous studies that investigated the radiologic and pathologic correlations of lung cancers, radiologic part-solid tumors with a ground glass opacity (GGO) component denote a favorable prognosis, which would represent adenocarcinoma of the lung almost for all, and their pathologic features are less invasive in most cases [4, 7, 8]. Furthermore, unlike radiologic pure-solid tumor without any GGO component, which demonstrates an oncologically invasive nature, the estimated rate of lymph node metastasis in part-solid lung

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Abbreviations and Acronyms

CEA = carcinoembryonic antigen
CT = computed tomography
CTR = consolidation tumor ratio
GGO = ground glass opacity
h-LND = hilar lymph node dissection
LND = lymph node dissection
m-LND = mediastinal lymph node dissection
NSCLC = non-small cell lung cancer
OS = overall survival
RFS = recurrence-free survival
SUVmax = maximum standardized uptake value

adenocarcinoma is approximately less than 5% [5–8]. For those cases, the prognostic impact of the nodal dissection is highly controversial.

To resolve this problem, this study aimed to investigate the prognostic impact of the extent of LND in patients with clinical stage I radiologic part-solid lung adenocarcinoma.

Material and Methods

Study Population

Between 2008 and 2015, we retrospectively evaluated 462 consecutive surgical patients with clinical stage I radiologic part-solid lung adenocarcinomas who underwent lobectomy or segmentectomy with lymphadenectomy. Clinical stage was based on the eighth edition of the TNM classification in our surgically resected series [9, 10], and there were no missing data for the variables used in this study. The inclusion criteria were preoperative staging determined by thin-section computed tomography (CT), and complete resection without preoperative chemotherapy or radiotherapy. With regard to the clinical nodal assessment, clinical-N0 meant not enlarged lymph nodes less than 10 mm in short axis on CT scan or negative 18F-fluorodeoxyglucose uptake by lymph nodes on positron emission tomography. Invasive modalities for mediastinal lymph node staging, such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration, were not routinely used preoperatively if they did not fit the size criteria for clinical nodal involvement. The medical record of each patient was reviewed retrospectively under a waiver of authorization approved by the Institutional Review Board of Juntendo University School of Medicine, Tokyo, Japan.

Radiologic Evaluations on Thin-Section CT Scan

Tumor size was reviewed in detail by the authors preoperatively based on thin-section CT findings. In addition, all tumors were subsequently evaluated to estimate the extent of GGO using the same thin-section CT scan with a 2-mm collimation. The lung was photographed with a window level of −500 to −700 H and a window depth of 1,000 to 2,000 H as the "lung window," and a window level of 30 to 60 H and a window depth of 350 to 600 H as the "mediastinal window." The consolidation tumor ratio (CTR) was defined as the ratio of the maximum size of consolidation to the maximum tumor size on thin-section CT scan. Based on a CTR, part-solid tumor was defined as a tumor with both a focal nodular opacity and a GGO (0 less than CTR $\leq$1.0), which were divided into two groups: GGO-dominant (0 less than CTR $\leq$0.5); and solid-dominant (0.5 less than CTR $\leq$1.0) [7, 11]. This lesion (ie, pure GGO) or radiologic pure-solid tumors without a GGO were excluded from this study to investigate the prognostic relevance between part-solid tumors and the extent of lymph node dissection.

Operation Policy

Anatomic lung resection is essential for radiologic invasive lung cancers with a solid-dominant appearance, and such patients are candidates for limited surgical resection including segmentectomy, especially if the tumor shows a radiologically noninvasive appearance (ie, CTR $\leq$0.5). With regard to the extent of lymph nodal dissection, systematic or lobe-specific lymph nodal dissection is warranted as a standard surgical policy for lymph node management [12, 13]. However, considering the intraoperative frozen section diagnosis of the lymph node, hilar node dissection without any mediastinal explorations was indicated for some patients. The extent of nodal dissection was decided based on the several radiologic findings of the tumor including size, location, maximum standardized uptake value (SUVmax), GGO dominance, or patient comorbidities including being elderly or at high cardiopulmonary risk, including severely poor pulmonary function due to chronic obstructive pulmonary disease or intestinal pneumonia, severe chronic cardiac diseases due to angina treated by coronary artery bypass graft or coronary artery stent, or chronic arrhythmia with a low ejection function. According to the criteria, the extent of LND was classified into systematic/lobe-specific mediastinal-LND (m-LND) and hilar-LND only (h-LND) in this study.

Statistics

The χ^2 test was used to compare the factors. An unpaired Student's t test was used if continuous variables were normally distributed, and if not, the Wilcoxon rank sum test was used. Cox proportional hazards model was fit to assess whether the extent of the LND was a prognostic variable in clinical stage I radiologic part-solid lung adenocarcinoma using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY). Forward and backward stepwise procedures were used to determine the combination of factors that were essential for the survival outcomes. Survival was estimated using the Kaplan-Meier method and compared by log rank test across the different groups. The date of surgical resection was set as the starting point, and the date of death or survival at follow-up was set as the endpoint of overall survival (OS). The date of occurrence of the first event including relapse, death or survival at follow-up was set as the endpoint of the recurrence-free survival (RFS). Continuous variables that were normally