Clinicopathologic Factors Associated With Occult Lymph Node Metastasis in Patients With Clinically Diagnosed N0 Lung Adenocarcinoma

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Background. **In some patients, clinical N0 (cN0) lung adenocarcinoma diagnosed by preoperative computed tomography scanning and positron emission tomography scanning was staged as pathologic N1 (pN1) or N2 (pN2) postoperatively. The aim of this study was to determine the preoperative and postoperative clinicopathologic factors related to nodal upstaging after a surgical operation.**

Methods. **We conducted a retrospective chart review of 350 patients treated for cN0 lung adenocarcinoma by curative resection. We analyzed clinicopathologic findings, comparing pN0 patients with the nodal upstaging group.**

Results. **Of 350 patients treated for cN0 tumors, 305 (87.1%) were confirmed postoperatively as having pN0 tumors, and 45 (12.9%) were confirmed as having pN1 or pN2 tumors. The mean maximum standardized uptake value (SUVmax) was higher in the nodal upstaging group than in the pN0 group (6.9 versus 3.8, $p = 0.004$); the upstaging group also included more cases in which SUVmax was greater than 5 (70.5% versus 24.8%, $p < 0.001$). Pleural invasion, lymphatic invasion, and vascular invasion were all more frequently seen in the nodal upstaging group than in the pN0 group (all $p < 0.001$). The presence of tumors with a micropapillary component was higher in the nodal upstaging group ($p < 0.001$). Multivariate logistic regression analysis identified SUVmax greater than 5, lymphatic invasion, vascular invasion, and a micropapillary component as significant risk factors for nodal upstaging.**

Conclusions. **In lung adenocarcinoma diagnosed as clinical N0 by chest computed tomography and positron emission tomography scanning, the possibility of occult lymph node metastasis increases with SUVmax greater than 5 and when lymphatic invasion, vascular invasion, and a micropapillary component are present.**

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Adenocarcinoma is the most common histologic type of non-small cell lung cancer (NSCLC) [1]. Recently, the use of chest computed tomography (CT) for lung cancer screening and early stage adenocarcinoma detection has increased [2]. According to the National Comprehensive Cancer Network guideline for NSCLC (version 6.2015), surgery can be chosen as an initial treatment in cases of operable clinical N0 (cN0) tumors. At the time of staging workup, CT scanning of the chest and F-18-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scanning of the whole body are generally performed for lymph node (LN) staging. Surgery is often chosen as an initial treatment if both of these imaging examinations disclose an N0 tumor [3–6]. Guidelines of the European Society for Medical Oncology (2014) recommend invasive mediastinal staging (fine-needle aspiration with endobronchial ultrasonography/endoscopic ultrasonography guidance or mediastinoscopy) only if positive hilar nodes (N1 or N2 stage) are suspected or tumor is centrally located on chest CT or PET/CT scan [7]. However, patients diagnosed with cN0 tumors preoperatively are sometimes diagnosed with pathologic N1 (pN1) or N2 (pN2) tumors postoperatively. This is referred to as nodal upstaging.

Although the standard surgical treatment for NSCLC is anatomic resection (lobectomy, bilobectomy, and pneumonectomy) and systematic LN dissection [8], good results have recently been reported for limited resection of ground glass opacity nodules; randomized trials are under way [9, 10]. However, limited resection should be performed only for pN0 tumors and cannot usually be applied to all cN0 tumors. Because limited resection is contraindicated if tumors at cN0 stage require nodal upstaging, it is important to preoperatively identify patients who are at risk of such occurrence.

Adenocarcinoma is heterogeneous, existing mostly in the form of mixed subtypes [11]; therefore, its clinical course and prognosis can vary. In 2011, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society published

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Abbreviations and Acronyms

CT = computed tomography
FDG = F-18-fluorodeoxyglucose
LN = lymph node
LPA = lepidic-predominant adenocarcinoma
MPC = micropapillary component
NSCLC = non-small cell lung cancer
PET = positron emission tomography
SUVmax = maximum standardized uptake value

a new classification for adenocarcinoma [11] including five major histologic components: acinar, papillary, micropapillary, solid, and lepidic. Invasive adenocarcinoma is divided into five subtypes according to these components. Many studies have shown that the incidence of LN metastasis and prognosis differs according to the adenocarcinoma subtype [12–15]. In addition, one study showed that the incidence of LN metastasis and prognosis could depend on the individual histologic components within a tumor [16]. This histologic heterogeneity of adenocarcinoma can affect LN metastasis. Histologic component may be a factor in patients who have nodal upstaging after surgical operations for N0 tumors.

The aim of this study was to determine the number of patients who have nodal upstaging after lung resection and to identify preoperative and postoperative factors related to nodal upstaging by analyzing clinicopathologic characteristics of tumors in which postoperative nodal upstaging occurred.

Patients and Methods

Patients

Between January 2011 and December 2014, 481 patients diagnosed with lung adenocarcinoma underwent surgical resections at Seoul St. Mary's Hospital in Korea; 417 of these patients had cN0 tumors, and 350 of these were included in the retrospective chart review. Excluded were 49 patients who had not undergone LN dissection or sampling, 2 who had lung cancers of different histologic types simultaneously (squamous cell carcinoma and small-cell carcinoma), and 16 who had adenocarcinoma in situ and were not considered to be at risk for LN metastasis because of the noninvasive nature of their tumors. Patients were classified into two groups: those diagnosed with cN0 tumors before and pN0 tumors after their surgical operations (pN0 group), and those diagnosed with cN0 tumors before and pN1 or pN2 tumors after their operations (nodal upstaging group). Clinicopathologic characteristics of tumors of patients in the two groups were compared. Operative procedures included wedge resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy. Systematic LN dissection (en bloc) or sampling (partial node resection) of more than three mediastinal lymph node stations was carried out in each patient, examining all sampled LNs by frozen section. Cancer staging followed the TNM classification system defined by the American Joint Committee on Cancer [17]. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital at the Catholic University of Korea.

Preoperative Lymph Node Staging

Lymph node staging was executed by contrast-enhanced chest CT and F-18-FDG-PET/CT scanning. Lymph nodes were regarded as malignant when their short-axis diameters were greater than 10 mm on a CT scan and their FDG uptakes were greater than those of the surrounding mediastinal structures. However, high FDG in a LN was regarded as benign if the LN contained benign calcification or if unenhanced CT images showed high attenuation with a distinct margin [18, 19]. If N1 or N2 disease was suspected, based on chest CT and PET/CT images, endobronchial ultrasonography-guided or endoscopic ultrasonography-guided fine-needle aspiration was performed for accurate LN staging. In patients diagnosed with cN0 tumors by chest CT and PET/CT scanning, surgery was performed without preoperative invasive LN staging if complete resection was considered to be possible.

Histologic Evaluation

All clinical specimens were examined by pathology specialists, whose observations were recorded. Studies of tumors included histologic characteristics, size, location, differentiation, LN status, pleural invasion, lymphatic invasion, vascular invasion, and mutation studies. To describe histomorphologic patterns (histologic components) of tumors, the occupancy ratio of each component (lepidic, acinar, papillary, micropapillary, and solid) in the total tumor area was measured and recorded semiquantitatively in 5% increments, according to the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system [11].

Statistical Analysis

Clinicopathologic characteristics of pN0 tumors and tumors in the nodal upstaging group (pN1 or pN2) were compared. The Student t test or the Wilcoxon rank sum test was used for continuous variables, and the χ^2 test or Fisher's exact test was applied for categoric variables. Multivariate logistic regression was used to analyze factors influencing nodal upstaging after surgery. A value of p less than 0.05 was considered statistically significant.

Results

Of the 350 patients treated for cN0 tumors, 305 (87.1%) had pN0 tumors postoperatively and 45 (12.9%) had pN1 or pN2 tumors (nodal upstaging). The nodal upstaging group included 29 pN1 and 16 pN2 tumors. Of the patients with pN2 tumors, 11 had metastasis in both the N1 and N2 nodes and 5 had metastasis in only the N2 node. The elapsed time from clinical staging to operation was