Original Study

Factors Influencing the Diagnostic Accuracy of Identifying the Histologic Type of Non–Small-Lung Cancer With Small Samples

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Abstract

The pathologic diagnosis of the histologic type is critical to decision-making regarding the treatment options for lung cancer. However, a greater risk of misdiagnosis exists with smaller tissue samples. We found that the non–small-cell lung cancer tumor differentiation grade and tumor diameter were associated with the diagnostic accuracy of the preoperative transbronchoscopic examination findings.

Background: The pathologic diagnosis has become a greater consideration in decision-making regarding the treatment options for lung cancer. Therefore, the accurate diagnosis of the tumor histologic type is essential, even when only small biopsy or cytology samples are available. However, the risk of a misdiagnosis with smaller biopsy samples is greater. The factors underlying the increased risk of a misdiagnosis in small samples are unknown. The aim of the present study was to identify the clinical and pathologic factors (other than immunohistochemical staining) that influence the pathologic diagnostic accuracy in small biopsy and cytological lung samples obtained by bronchoscopy.

Patients and Methods: We performed transbronchial lung biopsy or brushing and lavage to determine the preoperative diagnosis of 126 of 299 surgically resected lung cancer specimens. We assessed the diagnostic accuracy of the preoperative transbronchoscopic examination findings against that of the surgically resected lung specimens.

Results: On univariate analysis, the mean pathologic tumor size in the noncorresponding cases was larger than that in corresponding cases. Vascular invasion was also more prevalent in the noncorresponding cases. The tumor differentiation grade in the noncorresponding cases was poorer than in the corresponding cases. The noncorresponding cases were at a more progressed stage. On multivariate analysis, the pathologic tumor size and tumor differentiation grade were associated with the noncorresponding cases. **Conclusion:** We found a larger tumor size and poor differentiation grade were indicative of lung cancer tissue with a greater content of heterogeneous cells. Therefore, a possibility exists of a false diagnosis using only these factors. Thus, treatment decisions should be made considering the pathologic diagnosis and other relevant factors.

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Keywords: Large tumor size, Poor differentiation grade, Postoperative diagnosis, Preoperative diagnosis, Risk factor

Introduction

In the early 2000s, non–small-cell lung cancer (NSCLC) typing was not considered relevant to treatment planning. Therefore, a significant proportion of NSCLC cases at that time were reported as NSCLC not otherwise specified (NSCLC-NOS) on small biopsy and cytologic samples. However, tumor histologic typing is now considered important in the decisions regarding the clinical treatment options.[1] Several prospective randomized studies have shown that new chemotherapeutic (ie, pemetrexed) and molecular-targeted (eg, gefitinib, erlotinib, and bevacizumab) agents can lead to improved results compared with previous standard therapeutic options for nonsquamous advanced lung carcinoma.[2-9] Therefore, the demand for pathologists to differentiate between squamous and nonsquamous NSCLC is increasing. The pathologic diagnosis has become more important for making treatment decisions.

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For most patients with lung cancer diagnosed at an advanced unresectable stage, small biopsy or cytologic tissues samples are frequently the only resource available for diagnosis. However, the histologic type often cannot be diagnosed owing to the limited availability of the tissue samples.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology reported that the generic term "NSCLC" should be avoided as a single diagnostic term. Conventionally, immunohistochemical analysis of small biopsy samples of poorly differentiated carcinoma cases is used to arrive at a diagnosis. Therefore, the following terms are more appropriate for differentiation: "NSCLC, favor adenocarcinoma" and "NSCLC, favor squamous cell carcinoma." Furthermore, "mutation analysis" (eg, epidermal growth factor receptor) should be performed in this setting.[10] However, in clinical practice, small biopsy or cytologic samples are occasionally encountered that are unsuitable for diagnosis using immunohistochemical staining because the samples are too small or misdiagnosed even after immunohistochemical analysis.

The aim of the present study was to identify the clinical and pathologic (other than immunohistochemical staining) factors influencing the accuracy of the NSCLC histologic type diagnosis in small biopsy and cytology samples obtained by bronchoscopy.

Patients and Methods

Patients

We performed transbronchial lung biopsy or brushing and lavage on surgically resected samples collected from 126 of 229 patients with lung cancer from January 2011 to December 2012 at Tokyo Medical University (Tokyo, Japan) to arrive at a preoperative diagnosis. The patients included 74 men and 52 women, aged 37 to 87 years (median age, 68.0 years). All the patients provided informed consent for clinical research before study initiation.

Methods

The samples were collected using either transbronchial lung biopsy or brushing and lavage by forceps or brush and isotonic sodium chloride solution using a bronchoscope, respectively from radiographically confirmed tumors. We assessed the diagnostic accuracy of preoperative transbronchoscopic examination findings compared with the diagnosis of the surgically resected specimens. Cases in which the histologic diagnosis was determined from the small biopsy and cytological tissue samples differed from the diagnosis from the surgically resected specimens were classified as "noncorresponding cases." Cases in which the same diagnosis was reached from the small biopsy and cytologic tissue samples and surgically resected specimens were classified as "corresponding cases." We assessed the accuracy of the diagnosis of malignancy using the small biopsy and cytologic tissue samples without a specific histologic type compared with the corresponding cases when a different area of interest was clearly extracted in the noncorresponding cases. All samples were independently reviewed by $\geq$ 2 experienced pathologists. The samples underwent immunohistochemical analysis if possible.

Statistical Analysis

The statistical software used to conduct the factor analysis was SPSS for Windows. The Pearson χ^2 test and/or Fisher's exact test were used to compare sex, tumor location, histologic type, tumor differentiation grade, and pathologic stage. Age, tumor size, bronchoscopy using a guide sheath, and lymphatic and vascular invasion were compared using Welch's t test. All P values were 2 sided. The associations were considered statistically significant at $P < .05$. We calculated the odds ratios and 95% confidence intervals using unconditional logistic regression analysis. The logistic regression model was developed as a multivariate model. On multivariate analysis, the following variables were included in the model: sex, tumor location, histologic type, tumor differentiation grade, pathologic stage, patient age, tumor size, bronchoscopic findings using a guide sheath, and lymphatic and vascular invasion.

Results

Corresponding Cases

The preoperative and postoperative diagnoses corresponded in 107 patients (60 men and 47 women; median age, 69 years; age range, 37-87 years). In the surgical specimens, 86 cases were adenocarcinoma, 19 were squamous cell carcinoma, and 2 were small cell carcinoma. The median pathologic tumor size in the resected specimens was 30 mm (range, 10-70 mm). The tumor was located in the right upper lobe in 39 cases, right middle lobe in 5, right lower lobe in 28, left upper lobe in 26, and left lower lobe in 9 cases. Bronchoscopy with a guide sheath was performed in 51 patients. Lymphatic and vascular invasion was observed in 64 and 60 cases, respectively. Tumor differentiation grade 1 or 2 and pathologic stage I were diagnosed in 81 and 72 cases, respectively.

Noncorresponding Cases

The preoperative and postoperative diagnoses conflicted in 19 cases (14 men and 5 women; median age, 68 years; age range,

Table 1 Pre- and Postoperative Diagnosis in Noncorresponding Cases

Pt. No.	Small Biopsy or Cytology Specimen	Surgical Specimen
1	Adenocarcinoma	LCNEC
2	Adenocarcinoma	LCNEC
3	Adenocarcinoma	Pleomorphic carcinoma
4	Adenocarcinoma	Pleomorphic carcinoma
5	Adenocarcinoma	LCNEC
6	Adenocarcinoma	Squamous cell carcinoma
7	Adenocarcinoma	Squamous cell carcinoma
8	Adenocarcinoma	Squamous cell carcinoma
9	Adenocarcinoma	LCC without LCNEC
10	Adenocarcinoma	LCC without LCNEC
11	Adenocarcinoma	Squamous cell carcinoma
12	Squamous cell carcinoma	Pleomorphic carcinoma
13	Squamous cell carcinoma	Pleomorphic carcinoma
14	Squamous cell carcinoma	Adenosquamous cell carcinoma
15	Squamous cell carcinoma	LCNEC
16	Squamous cell carcinoma	LCNEC
17	Squamous cell carcinoma	Adenocarcinoma
18	Squamous cell carcinoma	Adenocarcinoma
19	Adenosquamous cell carcinoma	Pleomorphic carcinoma

Abbreviations: LCC = large cell carcinoma; LCNEC = large cell neuroendocrine carcinoma; Pt. No. = patient number.