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Tumor histology affects the accuracy of clinical evaluative staging in primary lung cancer

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ABSTRACT

Objective: Pathological examination of lung cancer often reveals a more advanced stage than clinical stage. The objective of this study was to evaluate whether the association between clinical and pathologic stages depends on tumor histology.
Methods: This retrospective study enrolled patients who had undergone major lung resections and systemic lymph node dissections (1990–2004). In total, 483 patients had adenocarcinoma and 225 had squamous cell carcinoma.
Results: Clinical and pathologic N-status were significantly different in patients with adenocarcinoma ($p < 0.0001$) but not in those with squamous cell carcinoma. Patients with adenocarcinoma were more likely to be upstaged from clinical N0 disease to pathologic N2 disease than those with squamous cell carcinoma ($p = 0.04$). Of those patients with adenocarcinoma, surgical procedure, clinical N-status, metastatic pathologic N2 stations and curability were significant prognostic factors. It is of interest, however, that a similar statistically significant difference could not be shown in patients with squamous cell carcinoma. Furthermore, multivariate analysis demonstrated that clinically detectable N2 disease and multiple pathologic N2 stations significantly affected the poorer prognosis in adenocarcinoma. Adenocarcinoma patients with clinically undetectable N2 disease had significantly better 5-year survival than those with clinically detectable N2 disease ($p < 0.0001$), although this was not the case for patients with squamous cell carcinoma ($p = 0.81$).
Conclusion: In adenocarcinoma patients with pathologic N2 disease, clinical N-status and metastatic pathologic N2 stations were significant prognostic factors. A similar difference was not found in patients with squamous cell carcinoma. Adenocarcinoma and squamous cell carcinoma appear to have different tendencies for lymph node metastasis.

1. Introduction

The optimal treatment of lung cancer relies on proper staging of the disease. The stage of lung cancer patients not only guides the decision-making process with regard to choosing the optimal treatment modality, but also provides important prognostic information with regard to survival. Clinical stage is based on information provided by any method before thoracotomy, while pathologic stage is based on information obtained during the surgical procedure and after pathologic analysis of the excised surgical specimen.

Nodal status is a strong predictor of the effectiveness of surgical intervention for non-small cell lung carcinoma (NSCLC). Accurate staging of N2 disease has become particularly important. Computed tomography (CT) scans are widely available and the most commonly used noninvasive imaging modality for the evaluation of the mediastinum in patients with NSCLC. Unfortunately, the accuracy of the chest CT scans in differentiating benign from malignant lymph nodes in the mediastinum is unacceptably poor and has not improved over the past decade, despite improvements in CT scan resolution [1]. In recent years, numerous clinical staging modalities have become increasingly available [1,2]. In particular, positron emission tomography (PET) with fluorodeoxyglucose has emerged as an important imaging modality in the evaluation of distant metastases as well as the primary tumor [1,3]. However, CT scans and bronchoscopy have been systematically used in clinical staging. Contrast enhanced CT scans remain the standard imaging modality to define the extent and location of the primary tumor and detect metastases, although size criteria of CT scans have been reported to yield lower accuracy in the diagnosis of mediastinal lymph node involvement [1,2,4].

Although there have been many reports comparing clinical and pathologic stages, little is known about the relationship

Abbreviations: NSCLC, non-small cell carcinoma; CT, computed tomography; PET, positron emission tomography; CEA, carcinoembryonic antigen.

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between these two staging methods according to tumor histology [5]. The objectives of this study were to compare the two staging methods according to tumor histology to evaluate the reliability of CT analysis, and analyze whether the upstaging affects the prognosis in patients with pathologic N2 disease.

2. Patients and methods

2.1. Patients selection

This retrospective analysis was based on data collected in a database of patients with primary lung cancer, who had been histologically diagnosed and had received thoracotomy at National Hospital Organization Toneyama Hospital in Japan. Between 1990 and 2004, 1046 consecutive patients underwent thoracotomy for primary lung cancer, 944 of whom had adenocarcinoma or squamous cell carcinoma. Excluding 95 patients with limited resections, 102 patients with preoperative treatments, and 39 patients with bronchiolo-alveolar carcinoma, 708 patients (adenocarcinoma; 483, squamous cell carcinoma; 225) were enrolled in this study. These patients had initially undergone lobectomy or pneumonectomy with systemic nodal dissection of the mediastinum and hilum, and had no history of chemotherapy or thoracic radiotherapy.

2.2. Methods

Clinical stage is based on the size of the lymph node as determined by CT scan. All patients had thoracic CT scans preoperatively, with 10 mm thick contiguous sections to evaluate nodal status. If lymph nodes were detected, 2 mm thick sections were further assessed to detect lymph node involvement. All CT scans were reviewed by a radiologist, thoracic surgeons, and pulmonologists preoperatively. Mediastinal or hilar lymph nodes 1 cm or larger in their shortest axis were diagnosed as metastatic [1,6]. When an enlarged mediastinal lymph node was detected on preoperative CT scan, mediastinoscopy was performed in 115 patients and transbronchial fine needle aspiration was performed in 105 patients during this period. Among them, 52 patients undergoing mediastinoscopy and 47 patients undergoing transbronchial fine needle aspiration who were actually diagnosed to have pathologic N2 disease were excluded. PET was employed toward the end of the study (from 2002). However, these results were not reflected in clinical N-status. All patients underwent staging according to the 1997 TNM classification criteria [7]. Those who had undergone resection before 1997 had their disease reclassified according to the 1997 TNM system.

2.3. Statistical analysis

The chi-square method was used to compare differences between two groups. The Mann–Whitney *U*-test was used to analyze continuous variables. Survival was defined as the time between the date of operation and death. Surgical mortality was 0.2% (1/483) in adenocarcinoma patients and 0.4% (1/225) in squamous cell carcinoma patients. The mean follow-up period was 57.6 months. The survival rates were calculated using the Kaplan–Meier method and compared by log-rank test. The relative importance of various prognostic factors for postoperative survival as identified by multivariate analysis was performed with Cox's proportional hazards model. A p-value <0.05 was considered statistically significant.

Table 1
Patient characteristics.

	Ad (n = 483) (%)	Sq (n = 225) (%)	p-Value
Age			
Median ± SD (year)	62.4 ± 10.1	65.4 ± 9.3	p = 0.0001
Range (year)	19–83	15–85	
Gender			
Male	255 (52.8)	202 (89.8)	p < 0.0001
Female	228 (47.2)	23 (10.2)	
Tumor size (cm)	2.8 ± 1.8	3.8 ± 1.8	p < 0.0001
Smoking status (pack-yr)	21.1 ± 29.3	51.6 ± 40.8	p < 0.0001
Clinical stage			
I	398 (82.4)	129 (57.3)	p < 0.0001
II	32 (6.6)	48 (21.3)	
III	45 (9.3)	48 (21.3)	
IV	8 (1.7)	0 (0)	
Surgical procedure			
Lobectomy	469 (97.1)	189 (84.0)	p < 0.0001
Pneumonectomy	14 (2.9)	36 (16.0)	
Pathologic stage			
I	334 (69.2)	127 (56.4)	p < 0.0001
II	38 (7.9)	45 (20)	
III	96 (19.9)	48 (21.3)	
IV	15 (3.1)	5 (2.2)	

Ad, adenocarcinoma; Sq, squamous cell carcinoma.

3. Results

3.1. Patient characteristics

The clinical characteristics of patients enrolled in the study are presented in Table 1. Among a total of 708 patients, 483 had adenocarcinoma and 225 had squamous cell carcinoma. The mean ages of these two groups were 62.4 ± 10.1 years and 65.4 ± 9.3 years, respectively (p = 0.0001). The difference in the proportional incidence of gender between these two histological groups was significantly different (p < 0.0001); about 90% of patients with squamous cell carcinoma were male. The mean tumor size of squamous cell carcinoma was significantly grater than that of adenocarcinoma (3.8 ± 1.8 cm vs. 2.8 ± 1.8 cm; p < 0.0001). The smoking status was significantly different between these two groups (p < 0.0001). The distribution of surgical procedures was also significantly different (p < 0.0001). Squamous cell carcinoma was more likely to undergo pneumonectomy. Of all, 94% of adenocarcinoma was located in the peripheral, while 70% of squamous cell carcinoma was located in the peripheral.

3.2. Comparison of clinical and pathologic N-status according to tumor histology

The distributions of clinical and pathologic N-status are shown in Table 2. Among 483 adenocarcinoma patients, 413 (85.5%) had clinical N0 disease and 45 (9.3%) had clinical N2 disease, while 358 (74.1%) had pathologic N0 disease and 86 (17.8%) had patho-

Table 2
Clinical and pathologic N-status.

	Clinical N-status	Pathologic N-status	p-Value
Adenocarcinoma (n = 483) (%)			
N0	413 (85.5)	358 (74.1)	p < 0.0001
N1	25 (5.2)	39 (8.1)	
N2	45 (9.3)	86 (17.8)	
Squamous cell carcinoma (n = 225) (%)			
N0	148 (65.8)	151 (67.1)	p = 0.63
N1	38 (16.9)	42 (18.7)	
N2	39 (17.3)	32 (14.2)	