The Role of Computed Tomography in Mediastinal Lymph Node Staging in Non-Small Cell Lung Cancer

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Abstract

This study was designed to make a retrospective analysis of imaging factors which improve the positive predictive values (PPVs) in NSCLC and to discuss the role of CT in mediastinal (N2) disease staging.

Between 1982 and 1997, 90 patients with enlarged mediastinal lymph nodes (MLNs) on CT underwent surgical staging.

The overall PPV was 44% and the PPVs on a station-by-station basis were 28 to 40%. A logistic regression model showed that tumors larger than 3 cm ($p=0.01$) and enlarged hilar lymph nodes ($p<0.01$) were significant predictors of N2-disease. When the two factors were combined, the overall PPV and the PPVs on a station-by-station basis improved to 74% and 54 to 60%, respectively.

These results are not sufficiently reliable for clinical use and histologic confirmation is mandatory. CT defines mediastinal anatomy and can help the surgeon in the selection of the most appropriate procedures to evaluate N2-disease. CT and invasive procedures are complementary in the staging of NSCLC.

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Key words: *lung cancer, mediastinal lymph node, N2-disease, computed tomography*

Introduction

Although computed tomography (CT) of the chest is the most commonly used noninvasive method of staging mediastinal (N2) lesions, its role in non-small cell lung cancer (NSCLC) remains controversial. Most studies report CT to have a negative predictive value (NPV) in the range of 81 to 92.9% (1-5). This value has remained relatively constant despite the different criteria used in the assessment of mediastinal lymph nodes (MLNs) and differences in populations studied. On the other hand, the positive predictive value (PPV) has been reported to be 32 to 68.7%, warranting invasive methods for accurate staging of N2-disease (1-5). We reviewed the records of 90 patients with enlarged MLNs on CT to assess the reliability of CT in detecting N2-disease.

Patients and Methods

a) Patients: From September 1982 to March 1997, 94 patients with clinical N2 (cN2) NSCLC on CT underwent anatomic resection and systemic mediastinal dissection at Hokkaido University Hospital. Regardless of size, all the ipsilateral hilar

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Table 1. Predictive accuracy of computed tomography in 90 patients with non-small cell lung cancer

MLN station	computed tomography findings				PPV (%)	NPV (%)	Accuracy (%)
	TP	FP	FN	TN			
overall	40	50	-	-	44	-	-
1	1	2	2	85	(33) **	98	96
2	3	5	7	75	38	91	87
3	17	27	5	41	39	89	64
4	9	23	6	52	28	90	68
5*	8	15	0	14	35	100	59
6*	2	3	0	32	40	100	92
7	13	20	4	53	39	93	73
8	0	2	1	87	(0) **	99	97
9	1	0	1	88	(100) **	99	99

MLN, mediastinal lymph node; TP, true positive; FP, false positive; FN, false negative; TN, true negative; PPV, positive predictive value; NPV, negative predictive value.
*In stations 5 and 6, the sum of two subgroups equals 37 because surgical exploration was performed only in patients with a left-sided tumor.
**Values in parentheses indicate that data from fewer than six patients were used in calculations.
No significant differences in the PPVs, NPVs and the accuracy were noted between MLN stations in the χ^2 test.

and mediastinal nodes were dissected and examined. Prior to March 1997, thoracotomy was recommended in patients with cN2-disease, except for bulky cN2. Four patients were excluded because their preoperative lymph node status was not known in detail. The remaining 90 patients comprised this study group and included 72 men and 18 women with a mean age of 63 years (range, 33 to 81 years).

b) Diagnostic evaluation: Each patient underwent assessment by plain chest roentgenography, bronchoscopy, CT of the chest and abdomen with contrast medium, magnetic resonance imaging (MRI) or CT of the brain, and bone scan. Sputum cytology and/or bronchoscopic biopsy/cytology was done to establish the diagnosis and the histologic type of the cancer. Mediastinoscopy was not performed except when contralateral nodal involvement was suspected. CT was performed on two different machines. From September 1982 to May 1994, all studies were performed on an SCT-7000 TX/TH (Shimadzu, Kyoto, Japan), which was replaced in 1994 by a SOMATOM Plus4 (Siemens, Forchheim, German). Continuous 10-mm thick sections were used to evaluate the mediastinal and hilar lymph nodes. Staff radiologists reviewed all scans. Mediastinal and hilar lymph nodes larger than 1 cm in short-axis diameter without calcification were defined as positive (4). Subcarinal nodes (station 7) larger than 1.5 cm in the short-axis without calcification were considered metastatic lesions (4). Staging was based on the TNM classification of the International Union Against Cancer (UICC) (6). MLN classification was performed according to the method of Naruke et al (7).

c) Comparison of subgroups: CT records were classified based on the following criteria: (a) characteristics of the primary tumor (side, centrality, lobar distribution, and size), (b) characteristics of the lymph nodes (location of enlarged MLN stations, the number of enlarged MLN stations, and enlargement of hilar lymph nodes). Tumors located in the inner third of the lung lesions were described as central and other lesions as peripheral.

d) Statistical analysis: Univariate and multivariate analyses were carried out with a logistic regression procedure to determine the relationship between different imaging factors and their predictive value in N2-disease (8). The χ^2 test was used to determine the region-differential accuracy and the accuracy between subgroups with and without positive imaging factors for N2-disease. Data were considered significant when the p-value did not exceed 0.05.

Results

Accuracy of CT in mediastinal staging: Among the 90 patients with enlarged MLNs on CT, 39 patients (43%) actually had N2-disease, 42 patients (47%) had N0-disease, 8 patients (9%) had N1-disease, and 1 patient (1%) had N3-disease. The overall PPV was 44% (40/90) on a patient-by-patient basis (Table 1). Subsequently, we investigated the region-differential accuracy on a station-by-station basis. The PPVs were 28 to 40%, excluding stations 1, 8, and 9 where the numbers of patients were insufficient for statistical analysis, and the NPVs were 89 to 100% (Table 1). The PPVs, the NPVs, and the accuracy for different MLN stations were similar.

Imaging factors of N2-disease on CT: To determine whether N2-disease correlated with imaging factors, we used logistic regression analysis to test for relationships between CT findings and metastasis to MLNs (Table 2). Thirty-four (57%) of 64 patients with tumors larger than 3 cm on CT

Table 2. Computed tomography reliability in the detection of N2-disease based on tumor and lymph node status

Descriptors	Number of patients		p-value*
	Enlarged MLNs on CT	Metastatic MLNs	
Overall	90	40 (44%)	-
Tumor side			
Right	53	25 (47%)	0.53
Left	37	15 (41%)	
Tumor centrality			
central	34	18 (53%)	0.21
peripheral	56	22 (39%)	
Lobar distribution			
Upper or middle lobe	57	25 (44%)	0.82
Lower lobe	27	13 (48%)	0.64
Main bronchus	6	2 (33%)	
Tumor size on CT**			
≤ 3 cm	26	6 (23%)	0.01
> 3 cm	60	34 (57%)	
Obstructive pneumonitis or atelectasis			
Absent	82	38 (46%)	0.26
Present	8	2 (25%)	
Number of enlarged MLN stations			
One or two	76	31 (41%)	0.12
More than two	14	9 (64%)	
Enlarged hilar lymph nodes			
Absent	46	12 (26%)	< 0.01
Present	44	28 (64%)	

CT, computed tomography; MLN, mediastinal lymph node.
*p-value in univariate analysis in the logistic regression model.
**The sum of the subgroups does not equal 90 since the tumor size on CT was unknown in 4 cases because of obstructive pneumonitis or atelectasis.

Table 3. Covariates related to detection of N2-disease in the logistic regression model in 86 patients with enlarged MLN

Variables	Odds ratio	95% CI	p-value*
Tumor size on CT			
> 3 cm vs ≤ 3 cm	3.53	1.15 –10.79	0.03
Enlarged hilar lymph nodes			
Present vs absent	5.19	1.98 –13.57	< 0.01

CI, confidence interval; CT, computed tomography; MLN, mediastinal lymph node.
*p-value in the multivariate analysis in the logistic regression model.

had N2-disease, whereas only 6 (23%) of 22 patients with tumors 3 cm or less had N2-disease (p=0.01). Tumor side, tumor centrality, lobar distribution, and presence of obstructive pneumonitis or atelectasis did not predict N2-disease. Hilar lymph node status was a significant predictor of N2-disease (present *vs* absent, 64% *vs* 26%; p<0.01). More than two enlarged MLN stations tended to predict N2-disease (p=0.12).

In the multivariate analysis, forward and backward stepwise procedures showed that tumors larger than 3 cm and the presence of enlarged hilar lymph nodes were predictors of N2-disease (p=0.03 and <0.01, respectively; Table 3). The overall PPV in patients with both factors was 74%, and that in patients with one or no factor was 29% (p<0.01, Table 4). On a station-by-station basis, the PPVs in patients with both factors improved to 54 to 60% compared with the others' PPVs of 11 to 30%, excluding stations 1, 2, 6, 8, and 9 where the numbers of patients were insufficient for analysis.

Discussion

Prior to March 1997, patients with cN2-disease, except for bulky cN2, who had otherwise operable NSCLC were considered to be candidates for resection in our hospital. Subsequently, we have taken the position that patients with N2-disease should undergo neoadjuvant chemotherapy followed by surgery, unless they have some favorable prognostic factors. To date, we have used thoracoscopy with sampling of suspicious N2-disease based on CT for mediastinal staging. For this reason, we believe that CT, which identifies sus-

Table 4. Predictive accuracy of computed tomography based on tumor larger than 3 cm and enlarged hilar lymph nodes

	PPV (%)				NPV (%)		
MLN station	With both factors (n=34)	With one or no factors (n=52)	p-value (χ^2 test)	MLN station	With both factors (n=34)	With one or no factors (n=52)	p-value (χ^2 test)
overall	74	29	< 0.01	overall	-	-	-
1	(100) *	(0) *	-	1	94	100	0.03
2	(100) *	(0) *	-	2	87	94	0.32
3	60	30	0.05	3	89	88	0.88
4	54	11	0.01	4	76	97	0.02
5	55	20	0.1	5	100	100	-
6	(25) *	(0) *	-	6	100	100	-
7	57	28	0.09	7	80	100	0.01
8	-	(0) *	-	8	100	98	0.41
9	(100) *	-	-	9	97	100	0.21

MLN, mediastinal lymph node; PPV, positive predictive value; NPV, negative predictive value.
*Values in parenthesis indicate that data from fewer than six patients were used in calculations.

pected N2-disease as well as providing precise information about the anatomic location of MLNs, plays an important role in the evaluation of N2-disease.

Looking at the predictive value of CT, our low PPV of 44% on a patient-by-patient basis and the PPVs of 28 to 40% on a station-by-station basis are similar to the findings of others, who reported overall PPVs of 32 to 68.7% (1-5). These data support the principle that patients with enlarged MLNs on CT require definitive histologic staging. In contrast, our NPV of 89 to 100% on a station-by-station basis, and previous studies reporting an overall NPV of 81 to 92.9% appear to be acceptable for clinical use (1-5).

We tried to determine what imaging factors predict N2-disease on CT and whether a subgroup of patients exist who can avoid an invasive procedure based on improved PPVs. According to the multivariate analysis, presence of tumors larger than 3 cm and enlarged hilar lymph nodes on CT were reliable findings as predictors of N2-disease. While the overall PPV improved to 74% in patients who had both positive factors and the PPVs on a station-by-station basis were 54 to 60%, these results are not satisfactory. At present, CT clearly is limited in its ability to detect metastatic disease. This is because the criteria for the two positive factors as well as the criteria for positive MLNs on CT (enlarged MLNs) are based only on their sizes. Meaningful advances, such as positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET), which reflect the biological features of the tumor, need to be developed for the noninvasive detection of N2-disease (5). At present, invasive histological staging remains mandatory for all patients with enlarged MLNs on CT.
Mediastinoscopy is a standard invasive procedure for staging of N2-disease, and several studies have documented its accuracy (9,10). Nonetheless, even the combination of cervical and anterior mediastinoscopy cannot reach station 3p, the posterior part of station 7, station 8, or station 9. It was reported that 32 (33%) of 95 patients with N2-disease had false negative results on mediastinoscopy (11). Of the 32 patients with false-negative results, 17 (53%) had MLN lesions in stations 7, 8, and/or 9. When it is necessary to obtain biopsy specimens from the MLN stations inaccessible to cervical and anterior mediastinoscopy, mediastinal exploration must be performed by thoracotomy or thoracoscopy (12-14). Thus invasive procedures must be individualized based on the clinical situation. CT and invasive procedures are complementary, which is consistent with recommendations made by others (15). CT, which can be equally reliable for all MLN stations is useful in this setting to help the surgeon choose the most appropriate procedure for N2-staging.

Thus it can be concluded that although tumors larger than 3 cm on CT and the presence of enlarged hilar lymph nodes predict N2-disease, histological confirmation is still mandatory. However, when invasive measures are required, CT can help in the selection of the most appropriate procedure.

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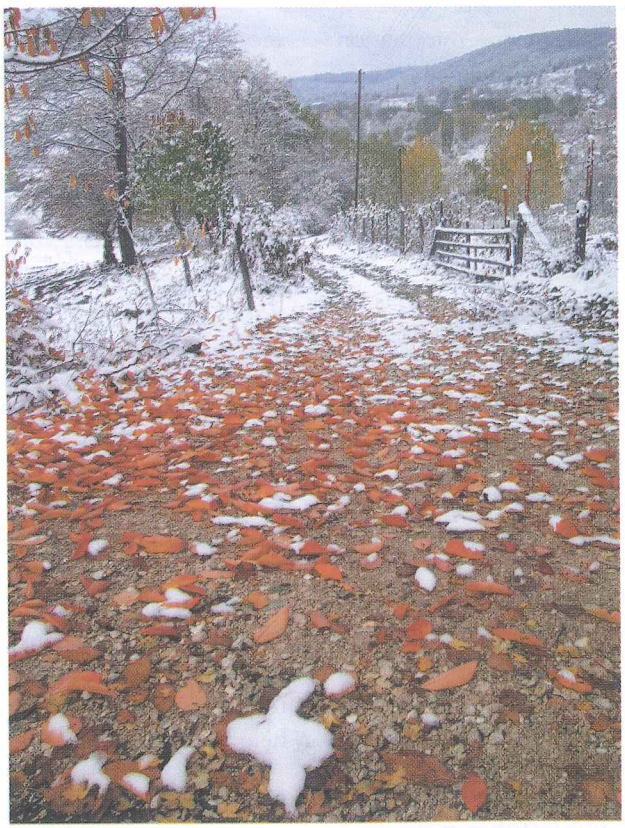

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