THE ROLE OF COMPUTED TOMOGRAPHIC SCANNING IN DIAGNOSING MEDIASTINAL NODE INVOLVEMENT IN NON-SMALL CELL LUNG CANCER

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Objectives: The reliability of computed tomographic scanning in evaluating mediastinal node involvement is controversial because of the high false result rate. We attempted to identify significant factors responsible for false-positive and false-negative scans.

Methods: From August 1992 through April 1997, 401 patients with lung cancer who underwent major lung resection and systematic lymph node dissection were enrolled in this study. We retrospectively examined mediastinal node size, tumor location, maximum tumor dimension, the presence or absence of obstructive pneumonia, atelectasis, pulmonary fibrosis, and lymph node calcification on contrast-enhanced computed tomographic scans. We identified clinical and radiologic factors responsible for the false results by using univariate and multivariable analysis.

Results: Central tumor location proved to be a significant factor of false-positive scans. Elevated carcinoembryonic antigen level and larger tumor dimension were significant factors of false-negative scans. In patients with a peripheral tumor smaller than 40 mm and normal levels of serum carcinoembryonic antigen, sensitivity, specificity, positive predictive value, and negative predictive value were 6%, 93%, 8%, and 90%, respectively. The reliability of computed tomographic scanning in this low-risk subgroup was high in detecting N0-1 disease but low in diagnosing N2 disease.

Conclusion: It is not possible to accurately diagnose N2 disease by using lymph node size on computed tomographic scanning alone, especially in patients with a central tumor, an elevated serum carcinoembryonic antigen level, or a tumor of 40 mm or larger. A preoperative invasive staging procedure is indicated in these populations and may not be indicated in the population with normal computed tomographic scan results without any of these risk factors. (*J Thorac Cardiovasc Surg* 2000;119:1135-40)

Computed tomographic (CT) scanning is a widely used noninvasive imaging procedure for diagnos-

ing mediastinal node involvement (N2) in patients with non-small cell lung cancer (NSCLC). However, the reliability of CT scanning in predicting N2 disease is controversial. Various results have been reported concerning the accuracy of CT scans in diagnosing N2 disease.¹⁻⁹

Dales and associates¹⁰ performed a meta-analysis of CT accuracy in diagnosing N2 disease in patients with NSCLC by using data from 42 studies published between 1980 and 1988. They concluded that the overall accuracy of mediastinal CT scanning was only 80%, with approximately 20% false-positive and 20% false-negative results. A high false-positive rate reduces specificity and the positive predictive value, whereas a high false-negative rate impairs sensitivity and the negative predictive value of an examination. The high frequency of false-positive and false-negative results sub-

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Table I. Clinical characteristics of patients

	Overall	FP	FN
No. of patients	401	57	56
Age, y (mean $\pm$ SD)	63 $\pm$ 10	66 $\pm$ 9	63 $\pm$ 10
Sex (M/F)	245/156	46/11	32/24
Smoking, pack-years (median)	29	41	34
25th-75th percentile	(0-50)	(14-55)	(0-52)
Pack-years >40	134	29	22
Pack-years $\leq$ 40	267	28	34
CEA, ng/mL (median)	11.7	10.8	22.1
25th-75th percentile	2.5-7.3	3.1-10.0	3.4-11.2
Histologic typing			
Adenocarcinoma	290	29	44
Squamous cell carcinoma	85	19	11
Large cell carcinoma	15	3	0
Adenosquamous cell carcinoma	11	6	1

FP, False-positive scans; FN, false-negative scans; CEA, carcinoembryonic antigen.

stantiated the poor reliability of CT scanning in mediastinal lymph node evaluation.

Therefore, we attempted to identify clinical and radiologic factors responsible for false-positive and false-negative results of CT scanning. We also re-evaluated the efficiency of CT scans in predicting N2 disease on the basis of lymph node size, taking these factors into account.

Methods

From August 1992 through April 1997, 634 patients with lung cancer underwent surgical intervention at our institute. Among them, 401 patients who underwent major lung resection and systematic lymph node dissection were enrolled in this study. Seven of them underwent preoperative mediastinoscopy, which revealed no mediastinal node involvement. The following patients were excluded: (1) patients who received induction therapy, (2) patients with multiple primary lung cancers, and (3) patients with a primary tumor directly invading the mediastinum. The time interval between CT scanning and surgical dissection was less than 1 month in all the patients. CT scans were done on an X-Vision/SP system (Toshiba, Tokyo, Japan), and contiguous 10-mm thick sections were obtained from the pulmonary apices to the bases in a supine position at full inspiration. Dynamic incremental scanning was always performed, and scans were nearly always obtained after bolus injection of 100 mL of iopamidol by using an automatic injector.

All CT scans were reviewed by 3 authors (K.T., Y.O., and K.S.), who were not informed of the surgical outcome, to obtain the following information: the maximum dimension and location of the primary lesion, the sizes of mediastinal lymph nodes, and the presence of obstructive pneumonia, atelectasis, pulmonary fibrosis, or lymph node calcification. If multiple nodes within a single station were enlarged, the

size of the largest node was recorded. The location of a tumor was considered to be central when it was located in the inner one third of the lung field on CT scanning and peripheral when in the outer two thirds. Histologic typing was determined according to the World Health Organization classification.¹¹ The stage of the disease was based on the TNM classification of the International Union Against Cancer (UICC).¹² The mediastinal lymph node evaluation on CT scanning and node mapping on thoracotomy were based on Naruke's lymph node mapping.¹³ All resected lymph nodes were fixed in formalin and examined microscopically by means of standard hematoxylin and eosin stain. Clinical N2 disease was defined when any mediastinal lymph node was 1.0 cm or larger in the shortest dimension. Pathologic N2 disease was defined when any mediastinal node was histologically involved. A true-positive result was documented when a patient had both clinical N2 and pathologic N2 findings.

The clinical record of each patient was reviewed for age, sex, histologic typing, smoking status, and serum carcinoembryonic antigen (CEA) level. Serum CEA was measured by means of the two-site immunoenzymometric assay (Tosoh Inc, Yamaguchi, Japan), and the upper normal limit for this assay was 5 ng/mL.

Univariate and multivariable analyses were performed by the logistic regression procedure on StatView 5.0 software (SAS Institute, Inc, Cary, NC) with a Macintosh Performa 6420 computer (Apple Computer, Cupertino, Calif) to determine the relationship between false-positive and false-negative scans and the following clinical or radiologic findings: age, sex, smoking status (pack-years >40 vs $\leq$ 40), histologic typing (squamous cell carcinoma vs others), serum CEA level, tumor location, maximum tumor dimension, the presence or absence of obstructive pneumonia, atelectasis, pulmonary fibrosis, and lymph node calcification on CT scan. The variables, such as age, node, and tumor dimension, were not skewed. The serum CEA level and smoking (pack-years) were severely skewed. Thus, we used the continuous variables for age, node, tumor dimension, and the log-transformed serum CEA level. For smoking status, we used the categories of pack-years of greater than 40 versus pack-years of 40 or less because the pack-years showed a two-peak distribution. The potential factors of false results in univariate analyses were also evaluated by using multivariable analyses. Differences were considered statistically significant when the *P* value was less than .05.

Results

The clinical characteristics of the patients are presented in Table I, and the radiologic characteristics of the tumors are presented in Table II. There were 57 (14%) cases of false-positive scans and 56 (14%) cases of false-negative scans.

Univariate analysis revealed 9 potential factors for false-positive scans (Table III): age, sex, smoking status, serum CEA level, histology, tumor location, obstructive pneumonia, atelectasis, and lymph node calcification. In

Table II. Radiologic characteristics of tumors

	Overall	FP	FN
No. of patients	401	57	56
Shortest dimension of lymph node, mm (mean $\pm$ SD)	7 $\pm$ 4	11 $\pm$ 2	6 $\pm$ 3
Longest dimension of lymph node, mm (mean $\pm$ SD)	11 $\pm$ 6	17 $\pm$ 4	11 $\pm$ 6
Maximum tumor dimension, mm (mean $\pm$ SD)	32 $\pm$ 16	35 $\pm$ 16	37 $\pm$ 17
Tumor location (central/peripheral)	44/357	14/43	6/50
Obstructive pneumonia, n (%)	33 (8)	10 (18)	3 (5)
Pulmonary fibrosis, n (%)	14 (3)	4 (7)	0 (0)
Atelectasis, n (%)	14 (3)	5 (9)	1 (2)
Lymph node calcification, n (%)	34 (8)	10 (18)	5 (9)

FP, False-positive scans; FN, false-negative scans.

Table III. Relationship between clinicoradiologic factors and false-positive scans: Univariate analysis

Variable	OR	95% CI	P value
Age	1.03	1.00-1.07	.05
Sex (male vs female)	3.05	1.53-6.09	.002
Smoking (pack-years >40 vs ≤ 40)	2.36	1.34-4.16	.003
CEA*	1.82	1.00-3.29	.05
Histology (SCC vs others)	2.11	1.14-3.89	.02
Maximum tumor dimension (mm)	1.01	0.99-1.03	.2
Tumor location (central vs peripheral)	3.41	1.68-6.93	$<.001$
Obstructive pneumonia	2.97	1.33-6.63	.008
Pulmonary fibrosis	2.52	0.76-8.33	.1
Atelectasis	3.58	1.15-11.10	.03
Lymph node calcification	2.84	1.28-6.31	.01

OR, Odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma.

*Log-transformed serum CEA levels were used.

multivariable analysis only tumor location proved to be a significant factor of false-positive scans. Lymph node calcification was a marginally significant factor ($P = .06$, Table IV). Patients with central-type lung cancer were prone to be overestimated as having N2 disease.

Univariate analysis revealed two potential factors of false-negative scans: serum CEA level and maximum tumor dimension on CT scan (Table V). These potential factors were also significant in multivariable analysis (Table VI).

In patients with a central tumor, the false-positive rate was 32%. In patients with an elevated CEA level, the false-negative rate was 18%, and in patients with a tumor 40 mm or larger in the maximum dimension, it was 20%. The reliability of CT scanning was poor in these populations (Tables VII and VIII).

In patients with a peripheral tumor smaller than 40 mm and a normal serum CEA level, both the false-positive and false-negative rates were lower than those found in overall patients. Specificity and negative predictive value were extremely high (93% and 90%,

respectively). Thus, the reliability of CT scanning in this low-risk subgroup was high in detecting the population without mediastinal node involvement. However, CT scanning was not reliable in diagnosing mediastinal node involvement because sensitivity and positive predictive value were extremely low (6% and 8%, respectively; Table IX).

Discussion

Mediastinal node involvement is a very important prognostic factor in patients with potentially resectable NSCLC.^{14,15} Several studies have suggested that induction chemotherapy or chemoradiation followed by surgical resection results in pathologic down-staging and better long-term survival in patients with N2 disease.¹⁶⁻¹⁸ Therefore, accurate preoperative evaluation of the mediastinal nodes is important in deciding NSCLC treatment strategy.

The CT scan is a routine examination for the diagnosis and locoregional staging of lung cancer at most institutes. CT scans have revealed evident reliability in

Table IV. Relationship between clinicoradiologic factors and false-positive scans: Multivariable analysis

Variable	OR	95% CI	P value
Age	1.03	1.00-1.07	.08
Sex (male vs female)	2.15	0.94-4.94	.07
Smoking (pack-years >40 vs ≤40)	1.08	0.54-2.19	.8
CEA*	1.24	0.63-2.44	.5
Histology (SCC vs others)	1.14	0.56-2.32	.7
Tumor location (central vs peripheral)	2.64	1.16-6.01	.02
Obstructive pneumonia	1.54	0.58-4.09	.4
Atelectasis	1.84	0.44-7.62	.4
Lymph node calcification	2.29	0.97-5.45	.06

OR, Odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma.

*Log-transformed serum CEA levels were used.

Table V. Relationship between clinicoradiologic factors and false-negative scans: Univariate analysis

Variable	OR	95% CI	P value
Age	1.00	0.97-1.03	.9
Sex (male vs female)	0.83	0.47-1.46	.5
Smoking (pack-years >40 vs ≤40)	1.35	0.75-2.41	.3
CEA*	2.02	1.12-3.64	.02
Histology (SCC vs others)	0.90	0.44-1.82	.8
Maximum tumor dimension (mm)	1.02	1.00-1.04	.03
Tumor location (peripheral vs central)	0.97	0.39-2.41	.9
Obstructive pneumonia	0.59	0.18-2.02	.4
Atelectasis	0.46	0.06-3.62	.5
Lymph node calcification	1.07	0.40-2.89	.9

OR, Odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma.

*Log-transformed serum CEA levels were used.

Table VI. Relationship between clinicoradiologic factors and false-negative scans: Multivariable analysis

Variable	OR	95% CI	P value
CEA*	1.92	1.05-3.51	.03
Maximum tumor dimension (mm)	1.02	1.00-1.04	.04

OR, Odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen.

*Log-transformed serum CEA levels were used.

Table VII. CT scan reliability in diagnosing mediastinal node involvement: Relationship between a significant factor of FP and FPR

	No. of cases	No. of FP scans	FPR (%)
Tumor location			
Central	44	14	32
Peripheral	357	43	12

FP, False positive; FPR, false-positive rate.

examining the primary tumor in terms of size, location, and extrapulmonary extension.⁴ However, they are far from satisfactory and less accurate than mediastinoscopy in node involvement evaluation.^{19,20} Detection of lymph node metastasis on CT scan is based on the demonstration of lymph node enlargement. However, several investigators reported that benign nodes might be enlarged as a result of reactive hyperplasia, obstructive pneumonia, or atelectasis attributable to primary tumor or prior granulomatous disease, whereas metastatic nodes may appear normal in size if the metastasis is microscopic.^{5,21,22} These fac-

tors can lead to false-positive or false-negative scans, which impair the reliability of CT scans in detecting node involvement. Therefore, we attempted to clarify which clinical and radiologic factors were significantly related to false results on CT scans.

Multivariable analysis revealed only one significant factor of false-positive scans: central tumor location. Mediastinal lymph nodes may be swollen reactively by obstructive pneumonia or atelectasis associated with the tumor.^{5,21} In our study, patients with obstructive pneumonia or atelectasis were more likely to have false-positive scans. However, once tumor location was

Table VIII. CT scan reliability in diagnosing mediastinal node involvement: Relationship between significant factors of FN and FNR

	No. of cases	No. of FN scans	FNR (%)
Serum CEA level			
≥5 ng/mL	173	31	18
<5 ng/mL	228	25	11
Maximum tumor dimension			
≥10 mm	397	56	14
≥20 mm	329	51	16
≥30 mm	195	32	16
≥40 mm	104	21	20
≥50 mm	50	12	24
≥60 mm	31	8	26
≥70 mm	16	4	25

FN, False negative; FNR, false-negative rate; CEA, carcinoembryonic antigen.

accounted for, obstructive pneumonia or atelectasis per se did not provide additional information concerning false-positive results. Several reports compared the reliability of CT mediastinal evaluation between central and peripheral tumors. Daly and associates³ reported that CT detection of positive mediastinal lymph nodes had an accuracy of 79% for central tumors and 90% for peripheral ones. Moreover, the false-positive rate was higher in central tumors (14%) than in peripheral ones (5%). Our results were generally consistent with theirs. However, our series revealed a higher false-positive rate (32%) in the central tumor population than that found in their series. Because these false-positive populations can benefit from primary surgery alone, an invasive staging procedure, such as mediastinoscopy, may be indicated.

Elevated serum CEA level and larger tumor dimension were significant factors of false-negative scans in both univariate and multivariable analyses. The larger a tumor has grown, the more normal-sized lymph nodes may have microscopic metastases. Some investigators reported a relationship between elevated serum CEA levels and advanced disease or poor prognosis. The patients with marked elevation of preoperative serum CEA levels are highly likely to have occult metastases.²³⁻²⁵ In patients with an elevated CEA level, metastatic nodes may appear normal in size. The prognosis of patients with false-negative scans for mediastinal node involvement has been reported to be poor, even though it was better than that of patients with true-positive scans.^{26,27} The false-negative subgroup may benefit from induction therapy, which might indicate an invasive staging procedure.

Table IX. Comparison of reliability of CT scans in diagnosing mediastinal node involvement between overall patients and patients without risk factors of false results

	Overall	Patients without risk factors*
No. of patients	401	165
No. of patients with pN2 (%)	80 (20)	17 (10)
Sensitivity (%)	30	6
Specificity (%)	82	93
Accuracy (%)	72	79
PPV (%)	30	8
NPV (%)	83	90
FPR (%)	14	6
FNR (%)	14	10

pN2, Pathologic N2 disease; PPV, positive predictive value; NPV, negative predictive value; FPR, false-positive rate; FNR, false-negative rate.

*Patients with a peripheral tumor smaller than 40 mm and a normal serum CEA level.

In patients without risk factors of false results (ie, patients with a peripheral tumor smaller than 40 mm and an elevated serum CEA level), CT scanning was extremely reliable in detecting the population without mediastinal node involvement. One hundred thirty-seven (90%) of 153 patients with clinical N0-1 disease on CT scanning had pathologic N0-1 disease. Thus, patients with normal CT results in this low-risk population can proceed directly to thoracotomy. A preoperative invasive staging procedure may not be indicated. Phillips and colleagues²⁸ reported that as prevalence of disease decreases, the reliability of a positive result will drop, and the reliability of a negative result will increase. The prevalence of N2 disease in our proposed low-risk subgroup of false results was extremely low, which results in low reliability of CT scanning in diagnosing mediastinal node involvement.

In conclusion, it is not possible to accurately diagnose N2 disease by using lymph node size on CT scan alone, especially in patients with a central tumor, an abnormal serum CEA level, or a tumor 40 mm or larger. A preoperative invasive staging procedure, such as mediastinoscopy, is indicated in these populations to decide the appropriate treatment strategy and may not be indicated in the population of normal CT results without any of these risk factors.

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