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Impact of Parenchymal Tuberculosis Sequelae on Mediastinal Lymph Node Staging in Patients with Lung Cancer

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Because tuberculous (TB) involvement of mediastinal lymph nodes (LN) could cause false positive results in nodal staging of lung cancer, we examined the accuracy of nodal staging in lung cancer patients with radiographic sequelae of healed TB. A total of 54 lung cancer patients with radiographic TB sequelae in the lung parenchyma ipsilateral to the resected lung, who had undergone at least ipsilateral 4- and 7-lymph node dissection after both chest computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT were included for the analysis. The median age of 54 subjects was 66 yr and 48 were males. Calcified nodules and fibrotic changes were the most common forms of healed parenchymal pulmonary TB. Enlarged mediastinal lymph nodes (short diameter > 1 cm) were identified in 21 patients and positive mediastinal lymph nodes were identified using FDG-PET/CT in 19 patients. The overall sensitivity and specificity for mediastinal node metastasis were 60.0% and 69.2% with CT and 46.7% and 69.2% with FDG-PET/CT, respectively. In conclusion, the accuracy of nodal staging using CT or FDG-PET/CT might be low in lung cancer patients with parenchymal TB sequelae, because of inactive TB lymph nodes without viable TB bacilli.

Key Words: Latent Tuberculosis; Lung Neoplasms; Mediastinum; Tuberculosis; Lymph Node

INTRODUCTION

Accurate nodal staging of lung cancer is crucial for deciding the optimal treatment, because patients with mediastinal lymph node metastases are generally offered chemotherapy rather than surgery (1). If enlarged lymph nodes or hot uptake on fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) are observed in patients diagnosed with lung cancer, metastases to the lymph nodes should be suspected.

However, mediastinal lymph nodes are one of the main sites of *Mycobacterium tuberculosis* in latent tuberculosis (TB) infection (2). The involvement of lymph nodes in TB also causes increased lymph node size (3) because of the accumulation of stimulated phagocytes caused by surviving mycobacteria and the fusion of phagosomal compartments, with possible fibrotic changes (4). TB also causes hot uptake on FDG-PET because glucose metabolism is increased with the accumulation of FDG in the inflammatory phagocytes and macrophages in the granulation tissue (5). Thus, TB involvement of mediastinal lymph nodes could cause false-positive nodal staging, especially in patients with evidence of previous TB. In this study, we examined the accuracy of nodal staging in lung cancer patients with radiographic sequelae of healed TB.

MATERIALS AND METHODS

The subjects screened for this study were patients who had undergone surgical lung resection with lymph node dissection for the treatment of primary or metastatic lung cancer between January 2004 and December 2006 at the Seoul National University Hospital, a university-affiliated tertiary referral hospital. Among them, patients with radiographic TB sequelae ipsilateral to the resected lung were screened for the analysis. If fibrotic bands, small calcified nodules, or bronchiectasis in the upper lobes were observed on chest CT preoperatively, the patients were regarded as having healed TB (6, 7). Patients who underwent both chest CT and FDG-PET/CT before surgical resection and who underwent at least ipsilateral 4- and 7-lymph node dissection during the operation were finally included in the study.

Medical records were reviewed, including the pathology results and radiographic examinations. On CT, mediastinal lymph node enlargement was defined as the presence of lymph nodes larger than 1 cm in their smallest diameter (7, 8). On FDG-PET/CT, mediastinal nodes with increased glucose uptake satisfying both qualitative (greater than that of the surrounding tissue) and quantitative (a maximum standardized uptake value [SUV] adjusted for patient body weight of ≥ 3.0 with a distinct margin)

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criteria were considered positive (9, 10).

Diagnosis of mediastinal tuberculous lymphadenitis

The histology of the dissected lymph nodes stained with hematoxylin and eosin was reviewed. The presence of granulomas, with or without caseating necrosis, was confirmed. Additionally, the results of acid-fast staining or the polymerase chain reaction (PCR) for *M. tuberculosis* DNA were also screened when available. If acid-fast bacilli were seen in the specimen or PCR for *M. tuberculosis* DNA was positive, a definite diagnosis of TB lymphadenitis was made. If only a caseating granuloma was identified, we classified the specimen as probable TB lymphadenitis. We also classified patients who had granulomas with nonspecific necrosis as suspicious cases of TB lymphadenitis.

Diagnosis of mediastinal lymph node metastasis

During surgical resection, encountered lymph nodes were removed from American Thoracic Society (ATS) lymph-node stations 10R, 9, 8, 7, 4R, 3, and 2R in tumors of the right lung and from stations 10L, 9, 8, 7, 6, 5, and 4L of the left lung (11). When necessary, station 1 (the highest mediastinal) or 2L (when tumors were located in the left lung) nodes were also evaluated during the procedure. An experienced lung pathologist described the location and number of lymph nodes according to the surgeons' labeling of the dissected lymph nodes. Then, the pathologist evaluated the nodes for the presence or absence of tumor as numbered in the surgical field and reported the presence or absence of tumor in the nodes. Specimens were stained with hematoxylin and eosin, and then examined by light microscopy.

Ethics statement

The study protocol was approved by the institutional review board of the Seoul National University Hospital (H-0710-003-221). Informed consent was waived in this study by the board.

RESULTS

During the study period, 796 patients with lung cancer underwent surgical resection. Of these, 84 patients had radiographic TB sequelae ipsilateral to the resected lung. Among this latter group, the analysis included 54 patients for whom chest CT and FDG-PET/CT were available and the lymph node dissection included at least 4- and 7-lymph node sites.

Of the 54 patients, 48 (88.9%) were males. Their median age was 66 (range 45-83) yr. Their mean body mass index was 22.1 ± 2.7 kg/m^2. No patient was anti-HIV antibody seropositive. Fourteen patients (25.9%) had a history of pulmonary TB and 42 patients (77.8%) were current or ex-smokers (Table 1). The most common pathological stage of the lung cancer was IB (18 patients, 33.3%). Mediastinal lymph node enlargement, larger than 1 cm in the smallest diameter on CT, was observed in 21 patients (32.3%) and metastatic mediastinal lymph nodes were suggested by FDG PET/CT in 19 patients (29.2%).

As seen in Table 1, calcified nodules (75.9%) and fibrotic changes (35.2%) were the most common forms of parenchymal

Table 1. Demographic and clinical characteristics of lung cancer patients with TB sequelae in the ipsilateral lung who underwent surgery with lymph node dissection

Characteristics	Findings
No. of patients	54
Median age (range), yr	66 (45-83)
Sex (M:F)	48 (88.9%):6 (11.1%)
Body mass index (kg/m^2), mean ± SD	22.1 ± 2.7
Past history of tuberculosis	14 (25.9%)
Current or ex-smoker	42 (77.8%)
Positive HIV antibody	0 (0%)
Underlying disease	
Diabetes	7 (13.0%)
Hypertension	15 (27.8%)
Chronic renal failure	1 (1.9%)
Gastric ulcer or early gastric cancer	4 (7.4%)
Chronic obstructive pulmonary disease	2 (3.7%)
Pathologic stage of lung cancer	
IA	11 (20.4%)
IB	18 (33.3%)
IIA	1 (1.9%)
IIB	6 (11.1%)
IIIA	10 (18.5%)
IIIB	4 (7.4%)
IV	0 (0%)
Other cancer metastasis to the lung	4 (7.4%)
Operation site	
Right	39 (72.2%)
Left	15 (27.8%)
Radiographic characteristics of lesions suggesting old healed TB	
Fibrotic change	19 (35.2%)
Calcified nodule	41 (75.9%)
Bronchiectasis	10 (18.5%)
Calcified lymph nodes	7 (13.0%)

Table 2. Pathological diagnosis of the dissected lymph nodes with positive findings on CT and FDG-PET/CT among patients who had undergone both CT and FDG-PET/CT

Variables	Lymph node in CT and FDG-PET/CT			
	CT findings		FDG-PET findings	
	Positive*	Negative	Positive†	Negative
Patients number	21	33	19	35
Excised LN No., total	219	1,024	158	1,129
Excised LN No., per patient	1-31	11-49	1-25	11-76
Patients with metastatic mediastinal lymph node	9	6	7	8
Patients with definite TB mediastinal lymph node‡	0	1	0	1
Patients with suspicious TB mediastinal lymph node§	0	2	1	1

*The presence of lymph nodes ≥ 1 cm in their smallest diameter was considered to be positive on CT; †The presence of lymph nodes with a maximum SUV ≥ 3.0 was considered to be positive on FDG-PET/CT; ‡Granulomas and acid-fast bacilli were observed on microscopic evaluation in one patient only; §Only granulomas were observed on microscopic evaluation in two patients. CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; LN, lymph node; SUV, standardized uptake value; TB, tuberculosis.

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lesions, and bronchiectatic changes in the upper lobes were found in ten patients (18.5%). Using the above-mentioned criteria, lymph node enlargement was found in 21 patients and calcified lymph nodes were seen in seven.

The median number of dissected lymph nodes per patient was 32 (range, 1-76). Of the 21 patients with enlarged mediastinal lymph nodes on CT, nine were confirmed to have mediastinal lymph node metastasis. In contrast, six of the 33 patients with negative CT findings were confirmed to have mediastinal lymph node metastasis; one of these patients was confirmed to have TB lymphadenitis, based on the presence of acid-fast bacilli. Of the 19 patients with positive mediastinal lymph nodes by FDG PET/CT, seven were confirmed to have mediastinal lymph node metastasis. Eight of the 35 patients with a negative FDG-PET/CT were confirmed to have mediastinal lymph node metastasis; one of these patients was confirmed to have TB lymphadenitis by the presence of acid-fast bacilli.

On a per-person basis, the overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for mediastinal nodal metastasis were 60.0%, 69.2%, 66.7%, 42.9%, and 81.8% for CT and 46.7%, 69.2%, 63.0%, 36.8%, and 77.1% for FDG-PET/CT, respectively (Table 2).

DISCUSSION

Our study involving lung cancer patients with TB sequelae showed that the accuracy of mediastinal staging using CT and FDG-PET/CT was low (66.7% and 63.0%), compared with previous reports from Korea (83.0% and 90.0%) (12). Especially, the specificity of mediastinal nodal staging using CT and FDG-PET/CT for nodal metastasis was considerably lower in our study (69.2% for both tests), compared to 89% and 100% in a previous report for Korea (12), and 93% and 98% in a report for low TB burden country (13).

Although definite TB involvement was identified only in one patient and suspicious TB in two patients, the lower specificity for nodal metastasis in our study could be explained by TB involvement. In patients with previous TB, mediastinal lymph node enlargement might represent inflammation of previously normal nodes draining areas of active TB in the lungs to other sites. These lymph nodes were defined as inactive TB lymphadenopathy (7). In previous reports, live TB bacilli could not be cultivated from the majority of inactive TB lesions (15). In fact, according to a previous report, as many as 77% of 78 lung cancer patients with calcified mediastinal lymph nodes were confirmed not to have cancer metastasis or definite TB lymphadenitis (14). Therefore, we can consider preoperative surgical staging to mediastinal lymph nodes in lung cancer patients with parenchymal TB sequelae, even though they have positive mediastinal lymph nodes in the chest CT and/or FDG-PET/CT.

Because only one of the 54 patients with radiographic TB sequelae was diagnosed as having definite mediastinal TB lymphadenitis, it is possible that mediastinal lymph nodes are rarely a focus of latent TB infection, contrary to the general assumption. That is, this observation indicates that mediastinal lymph nodes are not likely a focus of TB reactivation in patients with healed TB who belong to the supposed high-risk group for reactivation of TB (16).

Our data differ from a report from Turkey, which showed a 5.1% prevalence of mediastinal TB among lung cancer patients regardless of previous TB sequelae shown on chest radiographs (17). Although the reason for the difference between the two studies is unclear, the fact that a considerable portion of our patients (26%) had been treated for pulmonary TB could result in the lower prevalence of the presence of TB bacilli in our study.

To appreciate our results correctly, we should consider several limitations of the study that might have underestimated the actual prevalence of mediastinal TB. First, not all mediastinal lymph nodes were resected and reviewed because this study was performed retrospectively. Additionally, acid-fast staining and PCR for *M. tuberculosis* DNA without mycobacterial culture for the diagnosis of TB might be insufficient for detecting the presence of mediastinal TB. Thus, the prevalence of mediastinal TB could have been underestimated. A well-designed prospective study is needed to determine the actual prevalence of mediastinal TB in patients with radiographic sequelae of healed TB.

In conclusion, the accuracy of nodal staging using CT or FDG-PET/CT is low in lung cancer patients with parenchymal TB sequelae, because of inactive TB lymph nodes without viable TB bacilli.

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AUTHOR SUMMARY

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