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ORIGINAL PAPER

Accuracy of positron emission tomography in mediastinal node assessment in coal workers with lung cancer

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Abstract The purpose of this study was to explore the accuracy of ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) in the assessment of mediastinal lymph node in coal workers who had non-small cell lung cancer. We retrospectively reviewed 42 retired coal workers who had lung cancer without distant metastasis, between May 2007 and May 2010. Regarding the mediastinal lymph nodes, when the standard uptake value was greater than 2.5, it was considered "malignancy positive." After histological examination of the mediastinal lymph nodes, anthracotic and metastatic ones were detected. The results of PET/CT were analyzed to determine its accuracy. Of these 42 patients, PET/CT detected 47 positive mediastinal lymph nodes in 24 patients with a mean SUV maximum of 6.2 (2.6–13.8). One hundred and thirty-one mediastinal lymph node foci were dissected. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDG-PET/CT in detecting nodal metastases were 84% (16/19), 65% (15/23), 66% (16/24), 83% (15/18), and 74% (31/42) on a per-patient basis, respectively. Mediastinal node staging with FDG-PET/CT in coal workers is insufficient due to the high false-positive rates due to the presence of pneumoconiosis. In these patients, an invasive technique such as mediastinoscopy seems mandatory for confirmation of ipsilateral or contralateral mediastinal lymph node metastasis.

Keywords Anthracosis · Coal workers' pneumoconiosis · Lymph nodes · Positron emission tomography

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Introduction

In non-small cell lung cancer (NSCLC), when there is no distant metastasis, the status of the mediastinal lymph nodes is crucial in determining the therapy and survival [1, 2]. Noninvasive mediastinal lymph node assessment is made by computed tomography (CT) scanning of the chest and ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET). FDG-PET is a functional imaging modality that is based on the increased glucose metabolism of malignant cells [3]. FDG-PET is superior to CT scanning in accuracy, especially after integration of the CT scan.

FDG-PET/CT has a lower sensitivity in assessing the mediastinal lymph nodes in patients with lung cancer who also have granulomatous or inflammatory diseases [4, 5]. However, there is not a great deal of data about the false-positive rates of pulmonary nodules in coal workers' pneumoconiosis (CWP) [6, 7], and there are no data on mediastinal lymph node evaluation with FDG-PET/CT in coal workers who have NSCLC.

CWP is caused by the inhalation and prolonged retention of respirable coal dust particles. Occupational exposure to coal dust causes CWP, which is a chronic inflammatory and fibrotic lung disease. Recently, chronic inflammation has been accepted as a crucial factor in the pathogenesis of neoplasia [8, 9]. In Turkey, which is a

developing country according to statistics of Ministry of Labor in the past 20 years, the number of definitive occupational diseases has not gone above 1,500 cases/year and during the recent years, it is in between 300 and 500 cases/year [10]. About 30% of patients with CWP have calcifications with nodules on CT. Hilar or mediastinal lymph node enlargement has also been reported in 30% of patients with CWP. The role of PET in the diagnosis of malignancy in the setting of pneumoconiosis remains unclear, as both lung cancer and the fibrotic mass of complicated CWP may demonstrate increased uptake of FDG [11].

The purpose of this study was to explore the accuracy of FDG-PET/CT in mediastinal lymph node assessment in coal workers who had NSCLC.

Materials and methods

Location

Approximately 50,000 retired coal workers live in Zonguldak, northern Turkey. In pneumoconiosis, surveillance programs and dust control measures are in effect, but published pneumoconiosis incidence from this area is lacking. Mean respirable coal dust concentrations in workplaces underground and on the ground were 1.66 and 0.73 mg/m^3, respectively. Incidence of pneumoconiosis ranged between 0.17 and 2.8%, and prevalence ranged between 1.23 and 6.23% between 1985 and 2004 in Zonguldak [10].

Patients

This study was performed in between June 2007 and June 2010, in which we retrospectively reviewed 42 (42 men) retired coal workers who had NSCLC with no distant metastasis. In anamnestic information, there were no comorbidities causative of increased FDG uptake in mediastinal lymph nodes, such as tuberculosis, sarcoidosis, and nonspecific infection.

Diagnostic process and surgical approach of lung cancer

After having established a mass in the pulmonary parenchyme on chest X-ray, all patients underwent a contrast-enhanced CT scanning of the thorax. NSCLC was diagnosed with bronchoscopic biopsy or transthoracic needle aspiration biopsy. Having made the diagnosis, the patients were referred to whole-body FDG-PET/CT imaging and cranial magnetic resonance imaging for preoperative staging of the lung cancer. In the assessment of the mediastinal lymph nodes greater than 1 cm, when the standard uptake value (SUV) was greater than 2.5, it was considered "malignancy positive."

Lymph node sampling

All the patients then underwent cervical mediastinoscopy; subcarinal, upper, and lower paratracheal lymph nodes were sampled. Four patients who had left upper lobe tumor underwent extended mediastinoscopy for sampling of the subaortic and para-aortic nodes. When no metastatic lymph nodes were detected on mediastinoscopy, thoracotomy was performed, and mediastinal node sampling was performed before the planned pulmonary resection. After the histological examination of mediastinal lymph nodes, the anthracotic and metastatic ones were detected.

Imaging with PET/CT

Patients were instructed to fast, except for glucose-free oral hydration, for 4–6 h before the injection of 370–555 MBq (10–15 mCi) ^{18}F-FDG. Blood glucose was measured before this injection of the tracer to ensure glucose blood levels of <200 mg/dl. After injection of the ^{18}F-FDG, patients were kept lying comfortably. No oral muscle relaxant drugs were administered. Whole-body PET and non-contrast-enhanced CT were acquired consecutively 1 h after the ^{18}F-FDG using a PET/CT system, combining a spiral CT scanner. PET, CT, and fused PET/CT images were available for review, displayed in axial, coronal, and sagittal planes.

Pathological examination

Resection materials as primary tumor and resected mediastinal lymph nodes were fixed in 10% formalin. Samples were sliced using cryostat and treated in the standard manner. Samples were stained with hematoxylin-eosin and then examined. The presence of mediastinal metastatic disease was confirmed histopathologically. Besides conventional morphopathological examination, differential diagnosis was performed by immunohistochemical examination for NSCLC. Immunohistochemistry was used to detect the presence of some biomarkers including synaptophysin, chromogranin, TTF-1, CEA, cytokeratin (CK)-7, and CK-21. Malignant cell-free lymph nodes seen in fine anthracotic pigments, also nodal hyaline scars, pigment-laden macrophages (staining with CD38), and polarizable material suggest the diagnosis of CWP.

Follow-up

All patients discovered to have single- or multiple-station N2 or N3 disease postoperatively were referred to adjuvant

chemotherapy and radiotherapy. Patients had been followed by different centers and oncology experts. Follow-ups and treatment data were not homogenous in this retrospective study.

Ethics

All patients were informed before the operation and invasive staging methods by "patient consent form." Informed patient consent forms could not be obtained from the patients since the study was conducted retrospectively.

Statistical evaluation

All data were expressed as mean ± SD or median range as appropriate. The distribution of variables was analyzed with the Kolmogorov–Smirnov test. Nonparametric variables were analyzed with the Mann–Whitney U test, and chi-square test was used for parametric ones. The results of the FDG-PET/CT were analyzed to determine its accuracy. The relationship between true-positive and false-positive groups with histologic type, smoking, lymph node station, hypermetabolic node numbers, pneumoconiotic nodule numbers, and SUV values determined by PET/CT was made by using Spearman correlation coefficient and logistic regression analysis. The changes in SUV values before and after neoadjuvant treatment were compared using paired *t*-test. Initially, a univariate analysis was performed, and the factors identified as significant were included in a multivariate analysis. Univariate analysis for the efficient variables (age, smoking, surgical-pathologic N status, histological type of tumor, presence of pulmonary nodule, SUV values for mediastinal lymph nodes, neoadjuvant therapy, and node station) was performed using a Cox proportional hazard regression model. Results were evaluated in 95% confidence interval (CI), at $P < 0.05$ significance level. All analyses were performed using the Statistical Program for Social Sciences (SPSS) version 11.

Results

The study group comprised 42 men with a mean age of 67 (range: 56–78) years. Twenty-seven cases (64%) had squamous cell carcinoma, 14 (34%) had adenocarcinoma, and 1 (2%) had large-cell carcinoma. Of these 42 patients, FDG-PET/CT detected 47 positive mediastinal lymph nodes in 24 patients with a mean SUV of 6.2 (range: 2.6–13.8). One hundred and thirty-one mediastinal lymph node foci were dissected.

Mediastinoscopy detected no metastasis in 9 patients with FDG-PET/CT-positive lymph nodes, but one of them was found to have single lymph node metastasis on thoracotomy. This patient and 8 patients who had one node metastasis on mediastinoscopy were referred to neoadjuvant therapy. After neoadjuvant therapy, they were restaged by FDG-PET/CT or remediastinoscopy; 3 of them were referred to oncology for chemoradiotherapy, and 6 of them underwent pulmonary resection. We performed appropriate pulmonary resections in 23 patients who had no lymph node metastasis. Ten cases that had ipsilateral multiple lymph node metastasis or contralateral lymph node metastasis were referred to oncology for chemoradiotherapy (Table 1).

Table 1 Therapies according to mediastinal node metastasis

	Chemoradiotherapy	Neoadjuvant	Therapy surgery
Multiple N2/N3	10 + 3*	–	–
Single N2	–	9	–
N0/N1	–	–	23 + 6*

N0 No lymph node metastasis, *N1* intrapleural node metastasis, *N2* ipsilateral lymph node metastasis, *N3* contralateral lymph node metastasis

* Patients after neoadjuvant therapy

We detected pneumoconiotic nodules in the pulmonary parenchyme of 12 patients histologically. The mean SUV of these nodules was 8.3 (range: 4.1–10.2). In seven of these cases, the nodules were in the contralateral hemithorax, and they were diagnosed by transthoracic needle biopsy or thoracoscopic biopsy, and in the remaining 5 cases, the nodules were in the ipsilateral hemithorax and diagnosed on thoracotomy by frozen-section examination.

On histopathological examination, anthracosis due to CWP was found in 18 mediastinal nodes of 8 patients who had positive FDG-PET/CT (Fig. 1). Six of these cases also had pneumoconiotic nodules in the pulmonary parenchyme.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG-PET/CT in detecting lymph node metastases have been presented in Table 2.

True-positive and false-positive groups compared for histologic type, smoking, neoadjuvant therapy, and presence of pneumoconiotic nodule. For all of these, features between the two groups were not significantly different ($P = 0.091$, $P = 0.547$, $P = 0.342$, and $P = 0.539$, respectively). The mean SUV in true-positive and false-positive groups was similar; 6.1 (range: 2.8–13.8) and 5.9 (range: 2.6–12.7) ($r = 0.187$, $P = 0.232$, respectively). There were significant differences between patients with true-positive group and false-positive group with nodal status and hypermetabolic node station detected by PET/CT ($P = 0.034$ and $P = 0.038$, respectively) (Table 3). The Spearman's correlation test revealed a highly negative

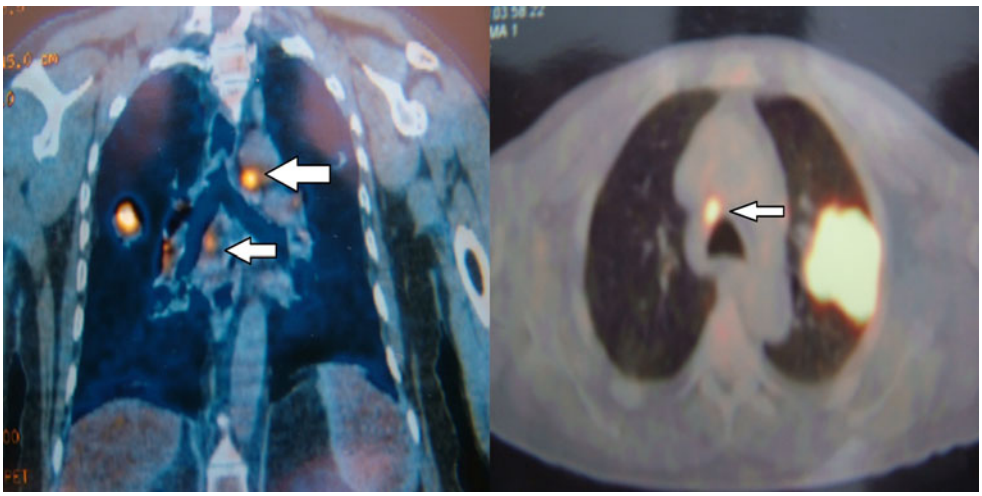

Fig. 1 Two samples of false-positive mediastinal lymph nodes in FDG-PET/CT

Table 2 Sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET/CT in mediastinal nodes in coal workers with NSCLC

Parameter	Per-patient	Per-nodule
Sensitivity	0.84	0.87
Specificity	0.65	0.81
PPV	0.66	0.61
NPV	0.83	0.95
Accuracy	0.74	0.83

PPV Positive predictive value, *NPV* negative predictive value, *FDG-PET/CT* ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography, *NSCLC* non-small cell lung cancer

correlation in true-positive groups between nodal status and hypermetabolic lymph node station ($r = -0{,}613$, $P = 0.04$ and $r = -0.546$, $P = 0.032$, respectively).

Initially, univariate analysis was performed to enable identification of the factors that were significant for both groups (true-positive group vs. false-positive group) for PET/CT's accuracy. The variable that showed significance in the analysis was surgical-pathologic nodal status ($P = 0.002$). The following factors were found to be nonsignificant: age ($P = 0.497$), smoking ($P = 0.235$), histology type ($P = 0.128$), neoadjuvant therapy ($P = 0.064$), presence of pneumoconiotic nodule ($P = 0.214$), SUV value ($P = 0.264$), and hypermetabolic lymph node station ($P = 0.458$) (Table 4).

After grouping the variables in steps, multivariate analysis was performed. Nodal status (N0/single–station N2 vs. multiple-station N2/N3) was found to be an independent efficient factor ($P = 0.013$, Hazard ratio 18.71 95% CI 1.98–11.42). This result, even if multiple hypermetabolic malignant nodes, could be explained by only one station.

Table 3 Clinicopathologic characteristics of patients with true-positive group and false-positive group

Variables	True-positive group	False-positive group	*P*
Patients (*n*)	16 (62%)	9 (38%)	
Histology			
ACA	3	5	0.091
SCC	12	14	
Nodal status			
N0	2	6	0.04
Single-station N2	6	3	
Multiple-station N2/N3	7	0	
SUV values	6.1	5.9	0.032
Pneumoconiotic nodules			0.539
Present	4	3	
Absent	11	6	
After neoadjuvant therapy			0.547
Present	6	3	
Absent	9	6	
Hypermetabolic node station			
2R	1	2	0.33
4L	10	7	0.18
4R	6	3	0.03*
5L	1	1	0.50
6L	1	1	0.50
7	10	5	0.006*

ACA Adenocarcinoma, *SCC* squamous cell carcinoma

* Spearman correlation analysis value; $r = -0.772$ and $r = -0.577$ for station 4R and station 7

Multivariate analysis resulted that histology type, smoking, lymph node station, neoadjuvant therapy, SUV value, and presence of pneumoconiotic nodule had no effects on accuracy of PET/CT (Table 4).

Table 4 Univariate and multivariate analysis of the factors accuracy for PET/CT in true-positive and false-positive groups in our study

	Hazard ratio (95% CI)	*P* value
Univariate factors		
Smoke	1.64 (0.34–6.34)	0.235
Histology	0.36 (0.18–0.67)	0.128
Neoadjuvant therapy	2.43 (2.14–11.48)	0.064
N status	24.06 (4.72–76.15)	0.002*
SUV value	1.44 (0.63–9.48)	0.264
Node station	1.74 (0.42–5.78)	0.458
Presence of pneumoconiotic nodule	1.62 (0.29–5.87)	0.214
Multivariate factors		
N status	18.82 (1.98–11.42)	0.013*

* The variables that showed significance in the analysis were nodal status (N0/single-station N2 vs. multiple-station N2/N3) that was found to be independent prognostic factor ($P = 0.013$) (95% confidence interval, at $P < 0.05$ significance level)

Conclusion

In our study, we found that at mediastinal initial staging, the sensitivity and specificity rates for FDG-PET at coal workers with NSCLC were 75 and 90%, respectively.

Accurate staging of mediastinal lymph nodes in patients with NSCLC is important, not only for determining the presence of contralateral metastatic mediastinal lymph nodes (N3 disease) and unresectability, but also to assist in the selection of those patients with ipsilateral metastatic mediastinal lymph nodes (N2 disease) who may be candidates for adjuvant or neoadjuvant treatment protocols [12].

Despite mediastinoscopy being the gold standard in the staging of the mediastinal lymph nodes, CT scanning and FDG-PET are useful noninvasive methods. CT scanning is neither sufficiently sensitive nor specific in the diagnosis of lymph node metastasis, because the size is the only criterion used to differentiate benign from malignant lymph nodes, and lymph nodes of >1 cm are considered abnormal [13].

With its ability to show increased tumor metabolism in normal-sized lymph nodes, FDG-PET is more sensitive than CT scanning in detecting early metastatic disease in lymph nodes [14]. With the integration of FDG-PET and CT, it is possible to reduce the false-positive and false-negative results in detecting metastatic lymph nodes. Albes et al. [15] reported an accuracy of 85% with FDG-PET/CT.

One of the problems in the staging of mediastinal lymph nodes with FDG-PET/CT is the high false-positive rates, especially in some concomitant benign conditions such as granulomatous inflammation, aspergillosis, tuberculosis, histoplasmosis, sarcoidosis, and silicosis and other pneumoconiosis. CWP is caused by long exposure to coal dust. Coal dusts that enter the lungs can neither be destroyed nor be removed by the body. The particles are engulfed by the resident's alveolar or interstitial macrophages and remain in the lungs, residing in the connective tissue or pulmonary lymph nodes [16]. Katabami et al. [17] determined that a "positive causal relationship between diffuse interstitial fibrosis-type pneumoconiosis and peripheral-type SCCs of the lung" exists. In our study, the most common histological type of lung cancer in coal workers was found to be SCC (64% of all cases).

In CWP patients, it is very difficult to distinguish lesions from lung cancer with FDG-PET/CT. This is because CWP often shows a significant increase in the FDG uptake related to the presence of inflammatory cells such as macrophages, as well as fibroblasts [18]. Anthracosis is a form of pneumoconiosis that often causes intrapulmonary node, but sometimes causes mediastinal lymphadenopathy [19].

Having detected the high number of false-positive results of FDG-PET/CT in coal workers with NSCLC, we decided to explore the mediastinal lymph nodes in these cases. In the literature, the specificity of FDG-PET/CT ranges between 74 and 84% in the general population in large series [20, 21], but in our study, it was only 66%, and PPV was 65%. NPV is reasonable, but false-positive results can be encountered in cases with CWP as in anthracosilicosis, infection or granulomatous disorders [22].

Tobacco use appears to lower maximum SUV, and both smoking status and maximum pack years are independently associated with a decreased accuracy of 18F-FDG-PET for mediastinal staging [23]. A retrospective study of 18F-FDG false-negative results found that occult metastases were more likely to occur with increasing T-stage, central tumors, adenocarcinoma histology, and higher primary tumor SUV (>6), although the actual number of false-negative lymph nodes in this study was small ($n = 16$) [24]. There was no correlation found between smoking ($P = 0.235$) and histology type ($P = 0.128$) with PET/CT accuracy for mediastinal lymph node in coal workers with NSCLC, in our present study.

In conclusion, our data suggest that mediastinal nodal staging by FDG-PET/CT in coal workers is insufficient due to the high false-positive rates due to the presence of pneumoconiosis. In these patients, an invasive technique such as mediastinoscopy seems mandatory for confirmation of N2 or N3 disease.

According to our study, multiple N2/N3 disease is an independent factor affecting the accuracy of PET/CT in coal workers with NSCLC. This result can be explained by the insufficient number of patients. Therefore, this study should be supported by multicenter studies, in which more

patients are included, and different clinical and histopathologic features are compared.

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