

*Full Length Research Paper*

# **Analysis of false positive positron emission tomography with 2-fluoro (18-F)-2-deoxy-D glucose as a tracer in patients with suspected lung cancer**

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**Accurate diagnosis of lung cancer is a critical factor determining operability in patients with non-small cell lung cancer (NSCLC). Positron emission tomography with 2-fluoro (18F)- 2-deoxy-D glucose as a tracer (FDG-PET) has been reported to be effective in detecting tumor and involvement in mediastinal and hilar lymph nodes. In this study, we analyzed the accuracy of FDG-PET in pulmonary lesions which were suspected as lung cancer and mediastinal lymph node involvements. Forty patients with pulmonary lesions which were suspected as lung cancer underwent preoperative analysis including thoracic computerized tomography (CT), and wholebody FDG-PET were evaluated retrospectively. All patients underwent surgical resection of primary tumors and hilar and/or mediastinal lymph nodes between 2009 and 2010. A total of 40 resected and histologically examined pulmonary specimens were used for analysis which were all reported as FDG-PET positive and suspected lung cancer preoperatively. Thoracotomy was performed for treatment or diagnosis. Thirtyfour of them were NSCLC, one of them was schwannoma, three of the patients were tuberculosis, one had chronic and active nonspecific infection, and the last one had severe dysplasia and granulomatous reaction. In this study, the sensitivity and the specificity of FDG-PET was calculated as 86 and 68%, respectively. FDG-PET illuminates the physicians in diagnosis of lung cancer and staging of mediastinal or hilar lymph nodes. However, as a differential diagnosis, active pulmonary tuberculosis and other granulomatous or inflammatory diseases should be thought in FDG-PET positive patients before decision to thoracotomy.**

**Key words:** Positron emission tomography, lung cancer, false positive.

## **INTRODUCTION**

Lung cancer is the most common form of malignancy, and its incidence is increasing throughout the world. Accurate staging as well as early detection in patients with lung cancer would increase the chances of prolonged survival. Lung cancer is generally classified into small cell lung cancer and non-small cell lung cancer (NSCLC), and patients with early-stage NSCLC may benefit from surgical resection. Therefore, correct evaluation of the presence or absence of metastases in mediastinal and hilar lymph nodes is a critical factor which may determine operability and long-term survival in patients with NSCLC. Positron emission tomography

(PET) is integrated with computerized tomography (CT) in PET-CT method, owing to this method lesions can be assessed in an accurate staging of malignancies by means of combined anatomical and metabolic images (Jeong et al., 2007). Positron emission tomography using 2-fluoro (18F)-2-deoxy-D-glucose as a tracer (FDG-PET) is being used more widely as a means to physiologically assess tumor spread (Vansteenkiste et al., 1999; Pieterman et al., 2000). FDG-PET is based on the fact that malignant cells have higher rates of glycolysis than most surrounding normal structures (Dahlbom et al., 1992; Nolop et al., 1987). FDG competes with glucose for uptake into cells and, as it accumulates in tumor-involved areas, a higher activity is seen (Wahl et al., 1991). FDG-PET has been reported to detect metastasis in lymph nodes and is more effective for lymph node staging in

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patients with NSCLC than CT (Vansteenkiste et al., 1997; Steinert et al., 1997). In this retrospective study, we analyzed the rate and the reasons of false positive FDG-PET findings in patients who had undergone thoracotomy for any reason.

## PATIENTS AND METHODS

### Patients

Between January 2009 and December 2010, patients with suspected lung cancer, who underwent pre-operative examinations by whole-body FDG-PET as well as CT and surgical resection of primary tumor and hilar and mediastinal lymph nodes in Chest Diseases and Thoracic Surgery Hospital (Samsun, Turkey), were retrospectively identified as potential candidates for inclusion in this study. The patient group consisted of 40 patients. We reviewed clinical, radiological and pathological findings of all the patients. The study cohort comprised 38 men and 2 women aged 32 to 78 years (average age at diagnosis 57, 10 years). Collection and analysis of data belonging to patients who were enrolled to study was sanctioned by committee of the tertiary education and research hospital as ethical.

### FDG-PET

FDG-PET was performed using a whole-body scanner (Philips Medical System Gemini TF with TOF). Patients fasted for at least 6 h. Whole-body emission images were obtained 60 min after injection of 185 MBq FDG using the three-dimensional acquisition method. All patients were asked to remain resting and quiet, and to void just before scanning. These images were reconstructed by filtered back projection using a ramp filter without attenuation correction. Attenuation correction was performed using a transmission scan. Features of both attenuation-corrected and non-corrected images were identified based on consensus of at least two experienced nuclear physicians, and discrepancies were resolved after consultation. The maximum standard uptake value (SUVmax) was calculated (Shiga et al., 2001; Kato et al., 2002). SUVmax is used as a parameter in semiquantitative assessment. SUVmax value indicates the amount of activity in the appropriate field (mCi/ml) / injected dose (mCi) / body weight. Lesions were considered positive if area of higher uptake is definite and localized.

### Surgical resection

All of forty patients were operated on within 4 weeks of their PET CT and resection was accomplished via open thoracotomy, and 23 patients had lobectomy, 3 patients had bilobectomy, 13 patients had pneumonectomy and 1 patient had wedge resection operatively. Mediastinal and/or hilar lymph node stations were resected and histologically examined for the presence of tumor cells. Preoperative mediastinoscopic intervention was performed on two patients who had PET positive N2, after confirmation of N2 negativity surgical resection was done. Histopathological frozen analysis of the lesions were performed during the surgical interventions, in the absence of definite diagnosis preoperatively

### Patient outcomes and follow up

As a result 34 of the patients were NSCLC without any distant metastasis and underwent surgical complete therapy. One of them

was schwannoma and resection of benign tumor was satisfactory for therapy. Three of the patients were diagnosed as tuberculosis and antituberculous treatment was started after histologic report of the surgical specimens as caseification necrosis and granulomatous reaction. Three of the patients were tuberculosis, and antituberculous treatment was started. These three patients were followed by direct observational therapy. One patient had diagnosis of chronic and active nonspecific infection, and recovered by antibiotics. One patient had severe dysplasia and granulomatous reaction, and was followed by medical treatment without occurrence of malignancy after six months; it was thought that he had a precancerous dysplastic changes and previous pulmonary tuberculosis.

### Analysis of data

CT and FDG-PET findings were compared with histological findings in the tumor and resected lymph node stations in order to determine their diagnostic sensitivity  $[TP/(TP+FN)]$ , specificity  $[TN/(TN+FP)]$ , positive predictive value  $[TP/(TP+FP)]$ , and negative predictive value  $[TN/(TN+FN)]$ , (TP = true positive, TN = true negative, FP = false positive and FN = false negative)..

## RESULTS AND DISCUSSION

Forty patients with pulmonary lesions who were suspected as lung cancer, underwent preoperative analysis including chest CT, and wholebody FDG-PET were evaluated retrospectively. All patients underwent surgical resection of primary tumors, and hilar and/or mediastinal lymph nodes between January 2009 and December 2010 in our hospital. A total of 40 resected and histologically examined pulmonary specimens were used for analysis which were all reported as PET positive and suspected lung cancer, preoperatively. Thirty-four of the patients were diagnosed as NSCLC histopathologically; one of them was a benign tumor originating from sheath of myelinated nerve fibers named as schwannoma, 3 of the patients were diagnosed as tuberculosis, 1 had chronic and active nonspecific infection and one patient had severe dysplasia and granulomatous reaction. Our study findings showed that the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET in determining cancer of lungs or mediastinal lymph nodes were 86, 68, 78 and 80%, respectively. FDG-PET predicted the metastasis in hilar and/or mediastinal lymph nodes with a 45% sensitivity, 82% specificity, 50% positive predictive value and 80% negative predictive value.

Patient outcomes were represented in the table with the findings of age, gender, SUVmax values of FDG-PET in pulmonary masses and intrathoracic lymph nodes and also their final pathological reports (Table 1).

Malignant tumors, due to increased glucose metabolism, can be viewed easily and noninvasively by FDG-PET method. Tomography integrated PET scanners are used in lung cancer field with many aims: evaluation of the potential malignancy in solitary pulmonary nodules,

Table 1. Patients outcome.

Name	Age	Sex	Tumor (cm)	Suv <sub>max</sub> values		Operation	Pathology results	
			Dimensions	TM	LN		TM	LN
AK	55	M	1.8 × 1.6	6.9	-	Wedge resection	Squamous cell ca	Reactive
DHÜ	58	M	2.3 × 1.8	4.7	-	Lobectomy	Squamous cell ca	Reactiv.
MK	52	M	4.0 × 3.0	8.1	-	Pneumonectomy	Squamous cell ca	Reactive
HAB	61	M	2.2 × 1.1	9.2	-	Bilobectomy	Squamous cell ca	Metastasis
RS	63	M	3.6 × 3.3	17.2	-	Lobectomy	Squamous cell ca	Reactive
RE	60	M	5.0 × 4.0	14.2	-	Bilobectomy	Squamous cell ca	Reactive
AA	64	M	6.2 × 4.4	23.4	-	Pneumonectomy	Squamous cell ca	Metastasis
İT	56	M	2.0 × 1.9	16.1	14.9	Pneumonectomy	Squamous cell ca	Metastasis
İİ	55	M	6.9 × 4.5	11.1	-	Lobectomy	Squamous cell ca	Reactive
FK	60	M	5.0 × 4.0	14.8	-	Lobectomy	Squamous cell ca	Reactive
KA	57	M	8.5 × 6.8	15.9	3.2	Pneumonectomy	Squamous cell ca	Metastasis
NA	55	M	3.3 × 3.0	5.2	2.1	Bilobectomy	Squamous cell ca	Reactive
AD	63	M	5.0 × 1.4	7.5	-	Lobectomy	Squamous cell ca	Reactive
ME	64	M	3.3 × 3.2	9.9	4.3	Lobectomy	Squamous cell ca	Reactive
HA	58	M	8.0 × 7.0	11.4	-	Pneumonectomy	Squamous cell ca	Reactive
TA	47	M	6.2 × 4.1	9.7	-	Pneumonectomy	Squamous cell ca	Metastasis
MP	72	M	5.0 × 3.0	25.8	-	Lobectomy	Nonsmall cell ca	Reactive
SK	53	M	3.0 × 3.0	3.2	2.1	Pneumonectomy	Mucoepidermoid cell ca	Reactive
TÇ	54	M	5.7 × 5.3	9.8	2.0	Lobectomy	Adeno ca	Reactive
HS	72	M	3.8 × 3.2	8.0	-	Lobectomy	Adeno ca	Reactive
HY	66	M	5.5 × 4.3	6.7	-	Pneumonectomy	Adeno ca	Reactive
MU	32	M	2.4 × 1.5	6.6	-	Lobectomy	Adeno ca	Metastasis
ME	47	F	2.0 × 2.0	6.2	-	Lobectomy	Adeno ca	Reactive
FM	55	M	2.2 × 1.7	6.2	3.5	Lobectomy	Adeno ca	Metastasis
DD	56	M	6.3 × 5.3	12.4	-	Lobectomy	Adeno ca	Reactive
NC	46	M	4.3 × 3.6	7.2	-	Lobectomy	Adeno ca	Reactive
CY	60	M	4.2 × 3.8	9.5	-	Lobectomy	Large cell ca	Reactive
HÇ	54	F	2.5 × 2.4	12.2	-	Lobectomy	Large cell ca	Reactive
AE	76	M	1.3 × 7.5	5.3	3.1	Lobectomy	Bronchoalveolar ca	Metastasis
SU	51	M	3.6 × 2.7	10.8	-	Lobectomy	Bronchoalveolar ca	-
HC	52	M	4.0 × 4.0	-	-	Lobectomy	Bronchoalveolar ca	Reactive
DY	70	M	5.5 × 4.1	11.2	-	Pneumonectomy	Urinary bladder ca metastasis	-
VE	44	M	3.0 × 2.6	10.5	5.9	Pneumonectomy	Renal cell ca metastasis	Reactive
NG	62	M	3.4 × 3.4	4.2	-	Lobectomy	Schwannoma	-
İE	78	M	1.2 × 1.3	3.4	-	Pneumonectomy	Severe displasia	Granulomatous N.

AV	37	M	3.2 × 1.8	4.6	-	Lobectomy	Inflamation	-
AA	61	M	3.0 × 2.2	8.3	-	Lobectomy	Tuberculosis	Reactive lymph N.
EY	47	M	1.0 × 1.0	4.4	-	Lobectomy	Tuberculosis	Tuberculosis
AR	57	M	1.5 × 1.5	5.1	7.0	Pneumonectomy	Tuberculosis	Tuberculosis
EÖ	54	M	5.0 × 7.0	8.6	-	Pneumonectomy	Squamous cell ca	Reactive

\*\* TM: tumor, LN: lymph node, M: male, F: female.

staging of lung cancers and determination of response to treatment, investigation of relapse and re-staging, the diagnosis, staging and following up of pleural malignancies. Several studies have found highly accurate results by FDG-PET for differentiation of benign and malignant solitary pulmonary nodules. More than half of patients with a solitary lung nodule are exposed to an unnecessarily and heavy surgery such as thoracotomy (Mack et al., 1993). PET images are evaluated primarily in visual (qualitative) basis and then processed in semi-quantitative measurements. The foci showing increased activity according to the backgrounds and surrounding tissues are evaluated in visual assessment. SUVmax is used as a parameter in semiquantitative assessment. SUVmax values greater than 2.5 to 3 may suggest probability of pulmonary and mediastinal malignancies. However, there is no definite diagnostic SUVmax values. In the present study, 3 patients with radiologically solid masses and with high SUVmax values (4.4, 5.1 and 8.3) in PET-CT, were diagnosed as tuberculosis after surgery. The final diagnosis of another case with a 4.2 SUVmax level was a neural benign tumor named schwannoma.

Gonzalez Stawinski and colleagues compared PET-CT findings with mediastinoscopy results in staging of 202 lung cancer patients in a study, they reported the sensitivity and the specificity of

PET-CT as 64.4 and 77.1%, respectively (Gonzalez et al., 2003). A meta-analytic assessment was made with the wide range of focal lung lesions (n = 1474). FDG-PET sensitivity was found as 83 to 100% (average = 96%), and specificity was found as 50-100% (average = 73.5%). While only a small pulmonary nodules less than 3 cm (n = 450), the sensitivity of FDG-PET was considered as 93.9%, and the specificity was 85.8% in an average (Gould et al., 2001). These results are favorable with our study findings. FDG-PET may cause false-positive results (10 to 25%) in several infections particularly granulomatous diseases which include activated macrophages. The most common causes of false-positivities are tuberculosis, sarcoidosis, coccidioidomycosis, aspergillosis, and some other infections. Thus, FDG-PET is not much effective in terms of positive predictive value, and FDG uptake highlights the need for histological diagnosis of nodules. On the other hand, FDG-PET may show false-negative results (average 5 to 8%) in bronchioloalveolar carcinoma, carcinoid tumors, some of the tumors having low metabolic activity due to high content of mucin, smaller nodules than 1 cm (especially < 6 mm) and hyperglycemic patients. In order to avoid false positive PET induced incorrect up staging or misdiagnosis of tumor, patients need to be confirmed with mediastinoscopy or other invasive procedures (Sonmezoglu, 2005). Dewan

et al. evaluated PET findings and histopathological diagnosis in 30 PET positive patients, they were diagnosed as malignant in 20 cases and benign in 10 patients, they found false positive PET-CT in two cases and false negative report in only one patient (Dewan et al., 1993). Kurul and colleagues reported false positive PET-CT examinations in tuberculosis and false-negative results in metastatic thyroid cancer (Kurul et al., 2007). Eroglu et al. reported PET-CT values in lung cancer surgery. 32 of 172 excised mediastinal lymph node stations were malignant. Sensitivity, specificity, positive and negative predictive values of PET-CT were found as 65.6, 86.4, 52.5 and 91.7%, respectively. Due to high false positive results in positron emission tomography, suspected mediastinal stations should be verified by biopsy of metastases (Eroglu et al., 2007). Positron emission tomography has been in reported over 90% of the specificity and sensitivity for demonstrating benign nodules (Patz et al., 1993; Lowe et al., 1998), a meta-analysis of 40 studies found the overall sensitivity (96.8%) and specificity (77.8%) in detection of malignant nodules (Gould et al., 2001). The nodules which have low FDG uptake levels are considered benign because of PET's high specificity. However, the slow-growing malignancies (bronchoalveolar carcinoma, carcinoid, etc.) and uncontrolled hyperglycemia may cause false-negativities. Lv et al. made a

meta-analytic study and concluded that: In the patient-based data analysis, the pooled weighted sensitivity was 0.76 (95% CI: 0.65 to 0.84) and the pooled weighted specificity was 0.88 (95% CI: 0.82 to 0.92). In the mediastinal lymph node based data analysis, the pooled sensitivity was 0.68 (95% CI: 0.56 to 0.78) and the pooled specificity was 0.95 (95% CI: 0.91 to 0.97) (Lv et al., 2011). Integrated PET with CT is a relatively accurate noninvasive imaging technique, with excellent specificity for mediastinal lymph node staging in patients with NSCLC. In the present study, we determined lower predicted values than the other studies in determining hilar and mediastinal lymph node metastasis with FDG-PET. Nevertheless, current evidence suggests that we should not depend on the results of PET/CT completely for mediastinal lymph node staging in patients with NSCLC. Because the speed of tumor growth is proportional to its energy consumption, it is considered that the higher the metabolic activity of a lesion, the less likely its malignancy if it was stable in size over time (Wan et al., 2010). In meta-analysis, the sensitivity and specificity of PET in diagnosing single pulmonary nodules and masses is found to be 96 and 78%, respectively. In mediastinal staging, the sensitivity and specificity of PET is estimated to be 83 and 92%. In order to achieve high diagnostic values from PET. Recently, PET and PET/CT have become increasingly integrated in therapy planning and evaluation: response evaluation during and after chemotherapy, restaging after neoadjuvant therapy, planning of radiotherapy and detection of recurrent disease are all examples of emerging indications for PET and PET/CT in managing patients with lung cancer (Fischer et al., 2006).

It is a general comment that active infections or inflammatory processes (like tuberculosis, histoplasmosis, and sarcoidosis, etc.) can lead to false FDG-PET positivities (Hartman, 2005; Lowe et al. 1998; Yilmaz et al., 2005 and Erasmus et al. 1998). It is possible to determine malignant nodules by the combination of spiral CT and PET studies with high probability. This method is recommended for patients who have low to medium cancer probability not for the patients who have low or high probability of malignancy. Some different methods were investigated to reduce PET's limitations, especially in countries with a high prevalence of tuberculosis (due to a false positive). In a comparative study, cancer and tuberculosis cases were investigated by 11C-choline and FDG methods, and both the cancer and tuberculosis had a high SUV with FDG (standardized uptake value), high SUV values were found for only cancer patients by 11C-choline, the SUV value was found low in cases of tuberculosis (Hara et al 2003). Therefore, this method was useful for differentiation of malignancy- and TB (Kartaloglu, 2008). Hsieh et al. reported that 11C-methionine-PET seems more specific and sensitive when compared with 18F-FDG-PET for the purpose of differentiating benign and

malignant thoracic nodules or masses. In spite of the false-positive results of 18F-FDG-PET, 11C-methionine-PET was true negative in four cases with chronic inflammatory nodules and three cases of pulmonary tuberculosis. The possibility of an FDG-avid lesion being malignant is decreased if it shows a negative result by 11C-methionine-PET (Hsieh et al., 2008).

Differentiating lung cancers from tuberculoma is a difficult and important clinical entity because granuloma has nonspecific radiographic appearance and its bacteriological confirmation is very difficult. Coexistent lymphadenopathy makes diagnosis more complicated. It may be possible to distinguish patients with tuberculoma from those with lung cancer by serial FDG-PET examination before and after specific treatment of antituberculous treatment for several months (Suzuki and Takeda, 2011).

Thoracal surgery is very dangerous for patients with active pulmonary tuberculosis. It is suggested that positive FDG PET/CT findings should be interpreted with caution in tuberculosis-endemic regions (Zheng et al., 2011).

## Conclusions

The present study suggests that FDG-PET is a useful technique in mediastinal and hilar lymph node staging and diagnosing patients with NSCLC. However, because FDG-PET has a lower specificity and positive predictive value for evaluating lymph nodes in patients with inflammatory diseases or previous pulmonary tuberculosis, even when such complications are inactive or healed, care should be taken during lymph node staging and giving decision to thoracal surgery.

This study would suggest that FDG-PET alone is not sufficiently accurate to replace biopsy techniques in the evaluating of tuberculomas and NSCLC cases. Tuberculomas should be followed by antituberculous treatment and serial FDG-PET examinations.

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