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The role of FDG-PET/CT in detecting unsuspected and unknown distant metastasis in the initial staging of NSCLC

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Background/aim: Our purpose in this retrospective study was to determine the ratio of unexpected [metastases within the coverage area of thorax computed tomography (CT)] and unknown (metastases out of the coverage area of thorax CT) metastases by positron emission tomography/CT (PET/CT) in patients with newly diagnosed non-small cell lung cancer (NSCLC) who had no defined metastatic lesion, and to investigate the contribution of fludeoxyglucose (FDG)-PET/CT in metastasis staging.

Materials and methods: A total of 567 patients (489 males and 78 females, mean age 60.9 ± 10.7 years) were enrolled in this study. Among the 567 patients, a total of 156 patients who underwent PET/CT for metabolic characterization (group 1) and had solitary pulmonary nodules (group 1a, n = 39) or solitary pulmonary masses (group 1b, n = 117) and the remaining 411 patients (group 2) with NSCLC who had PET/CT performed for staging formed the basis of this study.

Results: In group 1, 5/39 (12.8%) patients with a solitary pulmonary nodule and 29/117 (24.8%) patients with a solitary pulmonary mass had distant metastases. In group 2, 129 patients of 411 (31.4%) had distant metastasis.

Conclusion: FDG-PET/CT is proven to be an effective method in detection of unsuspected-unknown metastasis, either in patients with solitary pulmonary lesion or in the initial staging of patients with NSCLC.

Key words: 18F-FDG, NSCLC, unsuspected and unknown metastases

1. Introduction

Lung cancers are one of the most common causes of death related to cancer (approximately 18%) and approximately 3,000,000 people get cancer every year (1). Non-small cell lung cancers (NSCLCs) constitute 75%–80% of all lung cancers (2). The high recurrence rate (greater than 20%) after curative resection is probably due to undetermined occult-small metastatic lesions that are present at the first diagnosis (3).

Treatment is determined predominantly by the stage of NSCLC at initial diagnosis. The accuracy of the diagnostic workup is crucial for adequate therapeutic planning. Patients with limited disease (stages I, II, and IIIA) are candidates for curative surgery. In contrast, patients with advanced disease (stages IIIB or IV) are considered to be incurable (4). In the latter group, unnecessary surgical procedures performed with a curative intent can be avoided by accurate staging, and palliative treatment options should be considered for these patients. Patients considered for surgery undergo imaging tests such as radioisotope bone scan, computed tomography (CT) of the chest and abdomen, and CT or magnetic resonance imaging (MRI) of the brain to detect metastases in order to avoid unnecessary surgery. Recently, numerous studies have indicated that the addition of positron emission tomography (PET) or PET/CT using the glucose analog 18F-fludeoxyglucose (FDG) exhibits higher diagnostic accuracy than CT alone and is also cost-effective when implemented into the staging of NSCLC (5–9).

Because PET or PET/CT is a whole-body imaging modality, it is also an efficient imaging method for assessment of thoracic and extrathoracic metastases of NSCLCs in a single session. For the patients with NSCLC, the determination rate of unknown metastases via FDG-PET or PET/CT has been found as 6%–20% (7,10–12). High sensitivity of the PET/CT in showing unexpected distant metastases may reduce unnecessary noncurative surgical procedures for NSCLC. Our purpose in this

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retrospective study is to determine the ratio of unexpected (within the coverage area of thorax CT) and unknown (outside of the coverage area of thorax CT) metastases by PET/CT in patients with newly diagnosed NSCLC who had no defined metastatic lesion in conventional thorax CT and thus to investigate the contribution of FDG-PET/CT in metastasis staging.

FDG-PET is also a highly sensitive method for assessing solitary pulmonary nodules. In a metaanalysis (n = 1474) performed by Gould et al. it was found that, in solitary lung lesions of greater than 1 cm, the sensitivity of FDG-PET was extremely high (96.8%) and the specificity was relatively low (77.8%) (13). Our other purpose in this study is to investigate the ratio of the unknown or unexpected metastases in patients with solitary pulmonary lesions (nodule or mass) who underwent PET/CT for metabolic characterization.

2. Materials and methods

2.1. PET/CT imaging and assessment protocol

PET/CT studies were performed by using a 6-slice multidetector CT integrated high-resolution PET scanner (Siemens Biograph LSO HI-REZ PET/CT, USA) on patients with a minimum 4-h fasting blood glucose level of ≤150 mg/dL and 1–1.5 h after an intravenous FDG injection.. First a topogram and then a low-dose nonenhanced CT of the region consisting of the vertex-proximal femur were taken, and finally PET images of the same region were taken. In the assessment of PET/CT imaging attenuation-corrected PET images were analyzed as a standard. Nonattenuation-corrected images were also analyzed when needed. A higher FDG uptake than physiological background activity was accepted as PET positivity. Maximum standard uptake value (SUVmax) was calculated from the most active region among the PET-positive lesions.

2.2. Patient group

A total of 567 patients (489 males and 78 females, mean age 60.9 ± 10.7 years) were enrolled in this retrospective study. Among the 567 patients, a total of 156 patients who underwent FDG-PET/CT for metabolic characterization (group 1) and had solitary pulmonary nodules (spn, group 1a, n = 39) or solitary pulmonary masses (spm, group 1b, n = 117) on thorax CT and the remaining 411 patients (group 2) with a diagnosis of NSCLC who underwent FDG-PET/CT for staging formed the basis of this study.

2.2.1. Group 1: Metabolic characterization group

The patients with a solitary lesion of ≥1 cm in the lung parenchyma, as determined by thorax CT, were evaluated by FDG-PET/CT for metabolic characterization. A total of 156 patients (35 females, 121 males, mean age 62.6 ± 10.8) who had increased FDG uptake in the lung lesion (SUVmax of ≥2.5) were included in this group. Of the 156 patients, 39 had a solitary pulmonary nodule with increased FDG accumulation (spn, group 1a, dimensions of <3 cm) and 117 patients had a solitary pulmonary mass with increased FDG uptake (spm, group 1b, dimensions of ≥3 cm) on FDG-PET/CT.

In this patient group, verification of both the FDG-positive solitary pulmonary lesion and the lesion showing increased FDG uptake suggestive of distant metastasis was performed according to the histopathological examination or clinical-radiological follow-up results. We investigated how many of these patients had histopathologically proven intrathoracic (unexpected) or extrathoracic (unknown) metastases shown by FDG-PET/CT. Since we did not aim to investigate the role of FDG-PET/CT in the characterization of solitary pulmonary lesions, verifications of PET-negative pulmonary lesions were not done.

2.2.2. Group 2: Staging group

A total of 411 patients (43 females, 368 males, mean age 60.2 ± 10.6) with histopathologically proven NSCLC who underwent FDG-PET/CT for initial staging were enrolled in this group. The patients with advanced-stage disease who had known extrapulmonary lesions suggestive of distant metastases by the time of PET scan imaging were not included in the study. Similarly, the patients with defined lesions suggesting metastasis in the contralateral lung parenchyma by thorax CT examination were also excluded from the study. In this group the patients underwent FDG-PET/CT for initial staging; the distribution of the lesions with increased FDG uptake that suggested distant metastases as shown by FDG-PET/CT was recorded as intrathoracic (unexpected) or extrathoracic (unknown) metastases. Final diagnoses of lesions with increased FDG accumulation that suggested metastases on PET/CT were made by histopathologic examination or clinical-radiological follow-up. Because the purpose of the study was not to investigate the role of PET/CT in N staging of the lung cancers, N1, N2, and N3 situations were not examined.

2.3. Statistical analysis

In the metabolic characterization groups (group 1a and group 1b), the SUVmax values and the dimensions of solitary lung lesions were compared with determination of metastasis by using the t-test. In the staging group (group 2), SUVmax values of the primary lesion and the determination of metastasis were compared by using the t-test. In the staging group, the incidence of metastasis according to the T stage of primary lesion was also compared by applying the chi-square test.

3. Results

No increased FDG uptake focus suggesting distant metastasis was observed in 32 of 39 patients with a solitary pulmonary nodule (group 1a) who were examined with FDG-PET/CT. However, true positive distant metastases were determined in 5 (12.8%) of these patients. Two of them had brain metastasis (outside of the thorax CT coverage area), 1 had metastatic lesions in ribs of the left hemithorax and metastatic lymphadenopathies (LAPs) in the left axilla (within the thorax CT coverage area), 1 patient had metastatic multiple lesions in the skeletal system and a metastatic lesion in the liver (within and outside of the thorax CT coverage area, Figure 1), and 1 patient had metastatic lesions in both adrenals and the peritoneum and metastatic multiple lesions in the skeletal system (within and outside of the thorax CT coverage area) (Table 1). On the other hand, there was a false-positive focus with increased FDG uptake suggesting distant metastasis in 2 patients (1 of them had slightly increased FDG uptake focus in the left adrenal and the other had slightly increased FDG accumulation in the left femoral neck and right scapula).

In group 1a, SUVmax value and lesion size of solitary pulmonary nodules were compared with the presence of metastases in the 32 patients who had no increased FDG uptake suggestive of distant metastases and in the 5 patients with true positive distant metastases on FDG-PET/CT by using the t-test (Table 2). The mean SUVmax of the solitary pulmonary nodules was 11.87 ± 6.65 in the 32 cases with no FDG uptake suggestive of distant metastases and 12.00 ± 2.39 in the 5 cases with true positive metastases, which was not statistically significantly different (P = 0.937). Mean lesion size was 18.25 ± 4.36 mm in cases with no FDG uptake suggestive of distant metastases and 21.80 ± 5.36 mm in cases with true positive metastases, which was not statistically significantly different (P = 0.219).

Among the 117 patients who had solitary pulmonary mass of ≥3 cm on thorax CT and who demonstrated

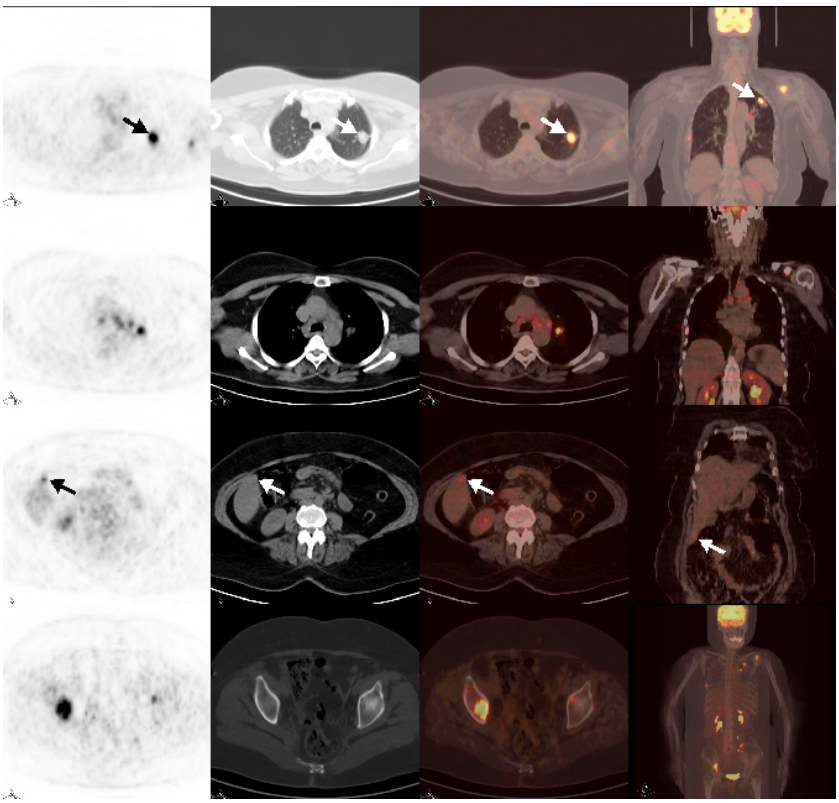

Figure 1. PET/CT images of a 59-year-old female patient with solitary pulmonary nodule in the upper lobe of the left lung determined by thorax CT. There was a hypermetabolic nodular lesion in the left upper lobe, which was compatible with primary tumor (first row). There were also metastatic hypermetabolic LAPs in the bilateral mediastinal lymphatic stations (second row). Apart from those, a hypermetabolic lesion compatible with the unknown metastasis was observed in the inferior section of the right liver lobe (third row), and unexpected and unknown metastatic lesions were determined in the skeletal system (last row).

Table 1. Distribution of metastases in the patients with solitary pulmonary nodule (spn) or solitary pulmonary mass (spm) who underwent FDG-PET/CT for metabolic characterization (Group 1).

Patient groups	Localization of distant metastasis	Number of distant metastases
Group 1a spn (n = 39)	Within the area (n = 1)	1 (n = 0)
		2 (n = 0)
		Multiple (n = 1)
	Outside of the area (n = 2)	1 (n = 2)
		2 (n = 0)
		Multiple (n = 0)
	Within + outside of the area (n = 2)	1 (n = 0)
		2 (n = 0)
		Multiple (n = 2)
Group 1b spm (n = 117)	Within the area (n = 8)	1 (n = 4)
		2 (n = 1)
		Multiple (n = 3)
	Outside of the area (n = 5)	1 (n = 1)
		2 (n = 0)
		Multiple (n = 4)
	Within + outside of the area (n = 16)	1 (n = 0)
		2 (n = 2)
		Multiple (n = 14)

Table 2. The presence of metastasis was compared with the size of the lung lesion and the SUVmax value by using the t-test in patients with solitary pulmonary nodules who underwent FDG-PET/CT for metabolic characterization (group 1a).

	Metastasis	N	Mean	Std. deviation
spn, SUVmax	-	32	11.87	6.65
	+	5	12.00	2.39
spn, size (mm)	-	32	18.25	4.36
	+	5	21.80	5.36

P = 0.937 for SUVmax, P = 0.219 for size.

increased tracer accumulation at the pulmonary lesion on FDG-PET/CT, which was performed for metabolic characterization (group 1b), 85 had no increased FDG accumulation suggestive of distant metastasis. On the other hand, distant metastasis (true positive increased FDG uptake focus) was detected in 29 patients (24.8%) (Figure 2). Of the 29 patients with true positive distant metastasis, 8 had intrathoracic, 5 had extrathoracic, and 16 had both intra- and extrathoracic distant metastases (Table 1). However, false positive increased FDG uptakes were observed in 3 patients (slightly increased FDG uptake at the 3rd rib in 1 patient, at the corpus of the 12th dorsal vertebrae in 1 patient, and at the transverse process of the 6th cervical vertebrae in 1 patient).

The detection of metastasis was compared with the SUVmax value and size of solitary pulmonary mass by using a t-test in the 85 patients who had no metastatic finding on FDG-PET/CT and in the 29 patients with true

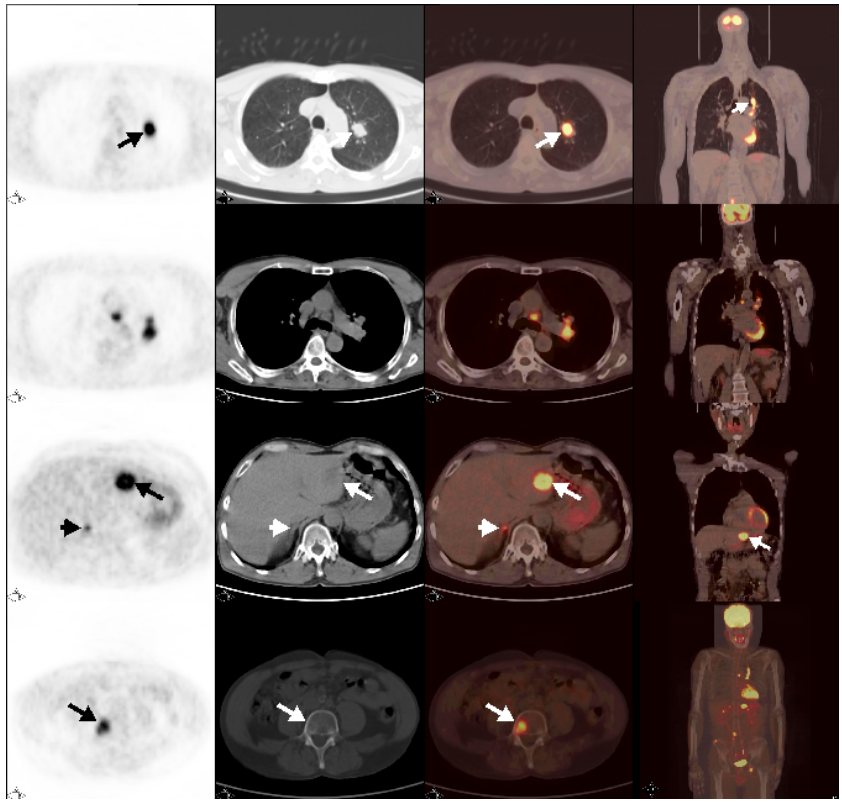

Figure 2. A 58-year-old male patient with left upper lung lobe mass who was imaged by PET/CT for metabolic characterization. In the left upper lobe, a mass with malignant hypermetabolism, indicating a primary tumor, was seen (first row). Hypermetabolic LAPs consistent with metastases were seen at the left lower paratracheal and left hilar areas in the mediastinum (second row). PET/CT images also determined unexpected metastatic hypermetabolic lesions in the left lobe of the liver and in the right adrenal (third row). Additionally, there were unexpected metastatic lesions and unknown metastatic lesions in the skeletal system (last row).

positive metastasis in group 1b (Table 3). Mean SUVmax of the solitary pulmonary mass in the 85 cases with no increased FDG uptake suggesting metastasis was 14.73 ± 6.27, while it was 14.20 ± 5.57 in the 29 cases with true positive metastasis, which did not demonstrate any statistically significant difference (P = 0.674). Mean lesion size was 48.72 ± 20.08 mm in the cases with no increased FDG uptake suggesting metastasis and 49.24 ± 17.61 mm in the cases with true positive metastasis. No statistically significant difference was found between them (P = 0.894).

Of the 411 patients with histopathologically proven NSCLC who underwent FDG-PET/CT for initial staging (group 2) and had no findings of metastasis on previously performed thorax CT, 43 had T - I, 169 had T - II, 177 had T - III, and 22 had T - IV stage tumors. In 265 of 411 patients, there was no increased FDG uptake to suggest distant metastasis. On the other hand, 17 patients had false positive increased FDG uptake suggesting distant metastasis (solitary skeletal uptake system in 5 patients, multiple skeletal uptake in 1, solitary adrenal uptake in 3, skeletal and adrenal uptake in 1, multiple skeletal and solitary other foci in 2, solitary liver uptake in 1, and uptake at the other structures in 4 patients). On the other hand, distant metastasis (true positive increased FDG uptake) was observed in 129 of the 411 patients in this group (31.4%) (Figures 3 and 4). Among these patients with distant metastasis, 42 had metastasis within the thorax area, 29 had metastasis outside the thorax area, and 58 had metastasis in both areas. The distribution of the metastatic lesions according to the T stage of the primary tumor is given in Table 4. When the frequency of metastasis was compared with the T stage of primary lung tumor using the chi-square test, we found that the frequency of metastasis increased as the T stage increase (P = 0.086) (Table 5).

The SUVmax value of the primary lung lesion and determination of metastasis was compared by applying the t-test in the 265 patients with no increased FDG uptake

Table 3. The presence of metastasis was compared with the size of the lung lesion and the SUVmax value by using the t-test in patients with solitary pulmonary mass who underwent FDG-PET/CT for metabolic characterization (group 1b).

	Metastasis	N	Mean	Std. deviation
spm, SUVmax	-	85	14.73	6.27
	+	29	14.20	5.57
spm, size (mm)	-	85	48.72	20.08
	+	29	49.24	17.61

P = 0.674 for SUVmax, P = 0.894 for size.

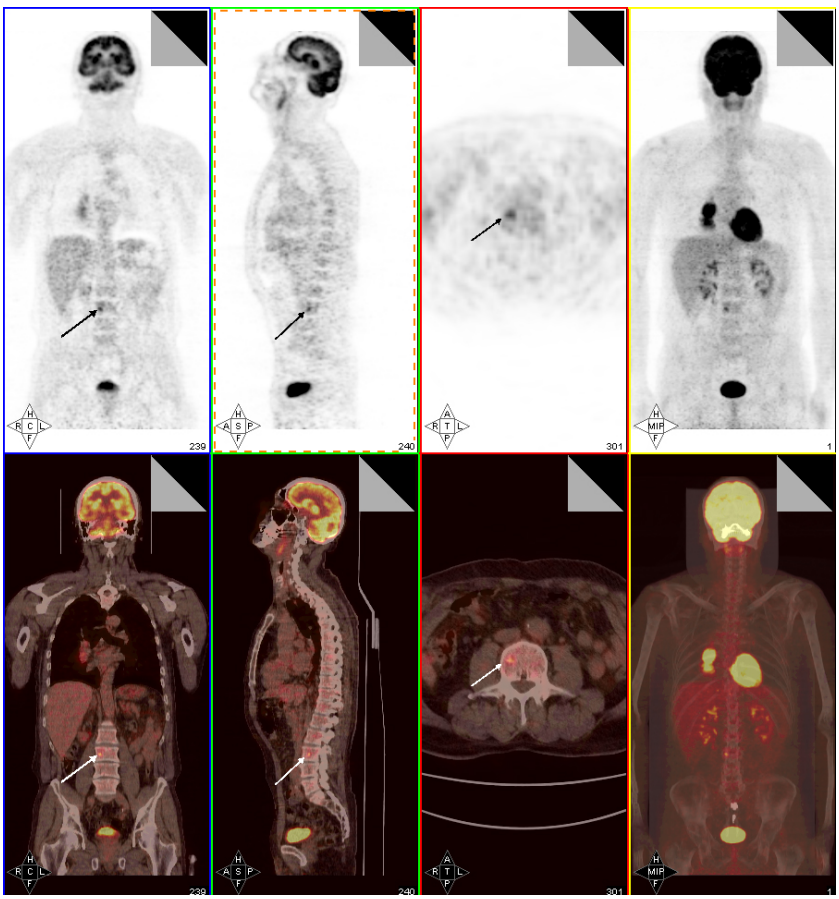

Figure 3. PET/CT images of a 62-year-old male patient with NSCLC located in the right lower lung lobe. Intense FDG uptake (right bottom corner, maximum intensity projection image) was observed in the known primary lung tumor. While there was no pathologic uptake in the N2–N3 mediastinal lymphatic stations and in the adrenals, a subcentimetric focus with slightly increased FDG uptake was determined on the right side of the L3 vertebrae corpus, suggesting metastasis. This lesion was histopathologically confirmed as metastasis.

to suggest distant metastasis and in the 129 patients with true positive metastasis (Table 6). Mean SUVmax of the primary tumor in the 265 cases with no metastasis was 16.86 ± 6.39, while it was 15.96 ± 7.11 in the 129 cases with metastasis, which did not demonstrate any statistically significant difference (P = 0.225).

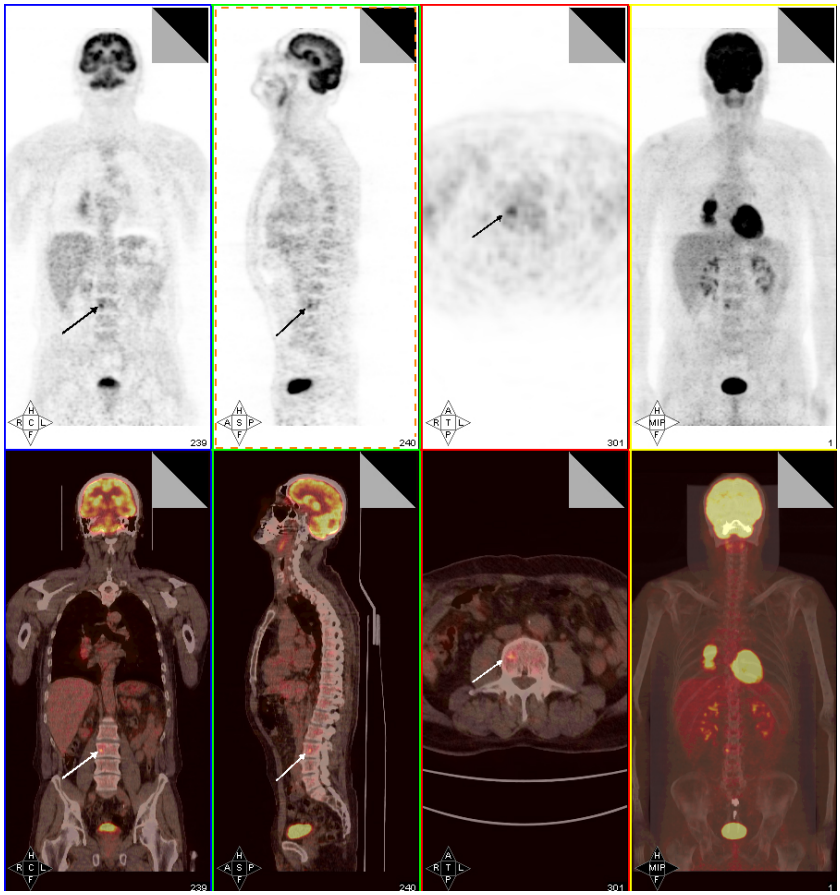

Figure 4. A 63-year-old male patient with diagnosis of NSCLC who underwent PET/CT for staging. Thorax CT showed a mass lesion at the superior segment of the right lower lobe and N2 mediastinal lymph nodes. PET/CT images demonstrated hypermetabolic lesion at the known tumoral lesion (first row). There were also metastatic LAPs with intense hypermetabolism at the right hilar and subcarinal region in the mediastinum (second row). Additionally, bilateral metastatic lesions in the adrenals (third row) and multiple metastatic lesions in the skeletal system (last row) were noted.

4. Discussion

The accurate demonstration of metastasis in NSCLC is essentially important for the selection of the best possible treatment modality and prognosis assessment. The presence of distant metastasis (M1) takes the patient to stage IV, where palliation is indicated instead of curative treatments. Approximately 20% of patients who undergo treatment for localized disease will develop metastases later because of unknown-undetected metastases that were actually present during the initial staging (3). In other words, the 5-year survival rate of less than 60% after curative surgical interventions was mostly due to undetermined distant metastasis in the initial period. Distant organ metastasis was found in 40% of the patients at initial diagnosis. The most common extrathoracic metastatic regions were the brain (43%), adrenals (40%), liver (40%), bone (33%), kidneys (23%), and abdominal lymph nodes (30%) (14,15). Generally contrast-enhanced thorax CT is used for the staging of lung cancers (16,17). However, the sensitivity, specificity, and accuracy of this method are limited. Because FDG-PET can image the whole body in a single session it is an efficient method for finding unexpected metastases of lung cancers (18). It has been reported that FDG-PET has higher sensitivity, specificity, and accuracy when compared to contrast-enhanced CT in NSCLC staging (19–23).

In the studies in which the efficiency of FDG-PET/CT in determination of distant metastases in NSCLC was assessed, it was found that the best noninvasive method was FDG-PET/CT (11,24–27). Unknown metastases were determined by FDG-PET/CT in 10%–20% of cases with NSCLC (7,11,12). In our study, PET/CT detected unexpected-unknown distant metastases in 163 of 567 patients (28.8%).

Table 4. Metastases distribution according to the T stage in the patients with NSCLC diagnosis who underwent FDG-PET/CT imaging for initial staging (group 2).

Stage	Localization of distant metastasis	Number of distant metastases
T - I (n = 43)	Within the area (n = 2)	1 (n = 1)
		2 (n = 0)
		Multiple (n = 1)
	Outside of the area (n = 0)	1 (n = 0)
		2 (n = 0)
		Multiple (n = 0)
	Within + outside of the area (n = 5)	1 (n = 0)
		2 (n = 0)
		Multiple (n = 5)
T - II (n = 169)	Within the area (n = 15)	1 (n = 11)
		2 (n = 2)
		Multiple (n = 2)
	Outside of the area (n = 12)	1 (n = 8)
		2 (n = 1)
		Multiple (n = 3)
	Within + outside of the area (n = 24)	1 (n = 0)
		2 (n = 7)
		Multiple (n = 17)
T - III (n = 177)	Within the area (n = 22)	1 (n = 13)
		2 (n = 6)
		Multiple (n = 3)
	Out of the area (n = 15)	1 (n = 9)
		2 (n = 0)
		Multiple (n = 6)
	Within + outside of the area (n = 25)	1 (n = 0)
		2 (n = 1)
		Multiple (n = 24)
T - IV (n = 22)	Within the area (n = 3)	1 (n = 1)
		2 (n = 2)
		Multiple (n = 0)
	Outside of the area (n = 2)	1 (n = 1)
		2 (n = 0)
		Multiple (n = 1)
	Within + outside of the area (n = 4)	1 (n = 0)
		2 (n = 0)
		Multiple (n = 4)

Table 5. Comparison of the metastases frequencies according to the T stage of the primary lesion using the chi-square test in the patients (group 2) who underwent FDG-PET/CT for initial staging.

T stage		Initial staging		Total
		Metastasis –	Metastasis +	
I	n	36	7	43
	%	83.7	16.3	100.0
II	n	118	51	169
	%	69.8	30.2	100.0
III	n	115	62	177
	%	65.0	35.0	100.0
IV	n	13	9	22
	%	59.1	40.9	100.0
Total	n	282	129	411
	%	68.6	31.4	100.0

Table 6. Comparison of determination of metastases and the SUVmax value of the primary lesion by using the t-test in group 2 patients.

	Metastasis	n	Mean	Std. deviation
Primary Tm SUVmax	-	265	16.86	6.39
	+	129	15.96	7.11

P = 0.225.

In the determination of distant metastasis in non-small cell lung cancers it was reported that the sensitivity of FDG-PET/CT was 90%–100% and its specificity was 79.2%–96.4% (28-31). In a metaanalysis that investigated the role of FDG-PET in detection of distant metastasis, the sensitivity, specificity, and accuracy values were found to be 94%, 97%, and 96%, respectively (10). The accuracy of detecting distant metastases by FDG-PET and FDG-PET/CT, except in the brain, was found to be higher than that of other imaging modalities (32). Because intense FDG uptake is normally seen in the brain cortex, the efficiency of FDG-PET is low in the detection of brain metastases. FDG-PET can detect unexpected brain metastasis in only 0.4%–1.5% of cases (33,34). However, current PET/CT systems are expected to have higher detection rates because of their higher resolution limit. In our study, PET/CT detected brain metastasis in 5 of the group 1 patients (3 of whom had isolated brain metastasis) and 12 of the group 2 patients (6 of whom had isolated brain metastasis).

FDG-PET has superior sensitivity and specificity than CT in the detection of liver, bone, and extrathoracic lymph node metastasis as well as secondary malignity (25,35). The sensitivity, specificity, and false negativity of FDG-PET/CT in detecting adrenal metastasis were 98%, 92%, and 3.8%, respectively (36–38). We demonstrated unknown adrenal metastasis in 9 [isolated adrenal metastasis in 3 patients (2 unilateral, 1 bilateral)] patients in group 1 and 38 [12 patients with isolated adrenal metastasis (10 unilateral, 2 bilateral)] patients in group 2 by PET/CT.

In a study with a limited number of patients, the sensitivity and specificity of PET in the determination of liver metastases in NSCLC was reported as 100% (39). In our study, 6 of the group 1 patients (isolated liver metastasis in 1 patient) and 22 of the group 2 patients (isolated brain metastasis in 2 patients) had liver metastasis.

FDG-PET/CT was also found to be a beneficial method in the determination of bone metastases and its efficiency in the determination of sternum and vertebra metastases

was higher than that with CT (40). Bone scintigraphy has high sensitivity and low specificity in determining metastases, but it is limited to the skeletal system. The sensitivity of bone scintigraphy in osteolytic metastases is also low. When compared to a bone scan, FDG-PET was reported to have higher specificity and comparable sensitivity in the determination of bone metastases (41). In our study, 18 of the group 1 patients (2 of them within the coverage area of thorax CT, 2 outside of the coverage area, and 14 within and outside of the coverage area) and 83 of the group 2 patients (18 of them within the coverage area of thorax CT, 15 outside of the coverage area, and 50 within and outside of the coverage area) had bone metastases. In a study comparing bone scintigraphy and FDG-PET in the detection of bone metastasis in newly diagnosed lung cancers, the sensitivity, specificity, and accuracy of FDG-PET were found to be superior to bone scintigraphy (42). In another study, it was shown that FDG-PET/CT has higher sensitivity, specificity, and positive/negative predictive values in the determination of bone metastases than bone scintigraphy (43). In light of such data, it can be predicted that FDG-PET/CT may replace bone scintigraphy in the determination of bone metastases of lung cancers.

Unexpected distant metastasis were found in 8% of stage I tumor, 18% of stage II tumor, and 24% of stage III tumor patients in a series with various disease stages by using PET (39,44,45). In our study, metastases were determined in 7 of 43 (16.3%) cases with T - I stage, 51 of 169 (30.2%) cases with T - II stage, 62 of 177 (35.0%) cases with T - III stage, and 9 of 22 (40.9%) cases with T - IV stage by FDG-PET/CT performed for initial staging. It is remarkable that the incidence of metastasis increases as the T stage increases. However, this was not found to be statistically significant, probably because of the unequal distribution of the patient numbers in each stage.

It was reported that using FDG-PET in the staging of potentially operable non-small cell lung cancers prevented unnecessary thoracotomies in 20% of cases (46). FDG-PET/CT was superior to conventional methods in determining unknown metastasis in lung cancers and upstages the disease in 25%–40% of cases (5,47). Additionally, increased FDG uptake in PET or PET/CT images is not specific to metastasis. It is known that FDG can accumulate in various inflammatory processes, as well. In our study, false positive increased FDG uptake was seen in 5 (3.2%) of 156 patients in the metabolic characterization group. On the other hand, in the staging group, false positive increased FDG uptake was observed in 17 (4.1%) of 411 patients. Therefore, it is required to be more careful in assessing especially solitary lesions, cases with low SUVmax values (low FDG accumulation), and cases in which corresponding CT images are incompatible and upstage the disease by PET/CT. Histopathological verification should be made in order to avoid false positive results.

There were 2 limitations to our study. The first limitation is that histopathological confirmation of FDG positives for all lesions was not available. Most of the cases were verified by clinical or radiological methods. The second limitation is that the rate of false negative PET/CT was not examined because the PET/CT study was not compared with any other imaging modality such as whole-body bone scan, CT, MRI, or sodium fluoride-PET.

In conclusion, being a whole-body imaging modality, PET/CT is an effective imaging method in the assessment of both thoracic and extrathoracic lesions in only one session. Demonstration of distant metastases in NSCLCs is crucial to determine treatment modality and prognosis, and it generally leads to nonsurgical and palliative therapies instead of curative treatments. Determining unexpected metastatic lesions with FDG-PET/CT imaging performed for benign/malignant differential diagnosis of solitary lung lesions, and detecting unexpected-unknown metastatic lesions in patients with a diagnosis of NSCLC who underwent FDG-PET/CT for staging, proves that FDG-PET/CT is an extremely useful imaging method in assessing lung lesions and planning the treatment for lung cancers. Thus, FDG-PET/CT imaging should be performed in the evaluation of all pulmonary lesions with suspicion of malignancy and in the initial staging of all patients with a diagnosis of NSCLC.

References

1. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. Lancet 2000; 355: 479–485.

2. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. Lung Cancer 2001; 31: 123–137.

3. Pantel K, Izbicki J, Passlick B, Angstwurm M, Häussinger K, Thetter O, Riethmüller G. Frequency and prognostic significance of isolated tumour cells in bone marrow of patients with non-small-cell lung cancer without overt metastases. Lancet 1996; 347: 649–653.

4. Silvestri GA, Gould MK, Margolis ML, Tanoue LT, McCrory D, Toloza E, Detterbeck F; American College of Chest Physicians. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007; 132: 178S–201S.
5. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koëter GH, Fidler V, Pruim J, Groen HJ. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000; 343: 254–261.
6. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, Schicha H. Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results. Eur J Nucl Med 2000; 27: 1598–1609.
7. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, van Velthoven PC, Comans EF, Diepenhorst FW, Verboom P et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002; 359: 1388–1393.
8. Herder GJ, Kramer H, Hoekstra OS, Smit EF, Pruim J, van Tinteren H, Comans EF, Verboom P, Uyl-de Groot CA, Welling A et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. J Clin Oncol 2006; 24: 1800–1806.
9. Sogaard R, Fischer BM, Mortensen J, Hojgaard L, Lassen U. Preoperative staging of lung cancer with PET/CT: cost-effectiveness evaluation alongside a randomized controlled trial. Eur J Nucl Med Mol Imaging 2011; 38: 802–809.
10. Hellwig D, Ukena D, Paulsen F, Bamberg M, Kirsch CM. Meta-analysis of the efficacy of positron emission tomography with F-18-fluorodeoxyglucose in lung tumors. Basis for discussion of the German Consensus Conference on PET in Oncology 2000. Pneumologie 2001; 55: 367–377.
11. Lardinois D, Weder W, Roudas M, von Schulthess GK, Tutic M, Moch H, Stahel RA, Steinert HC. Etiology of solitary extrapulmonary positron emission tomography and computed tomography findings in patients with lung cancer. J Clin Oncol 2005; 23: 6846–6853.
12. Verhagen AF, Bootsma GP, Tjan-Heijnen VC, van der Wilt GJ, Cox AL, Brouwer MH, Corstens FH, Oyen WJ. FDG-PET in staging lung cancer: how does it change the algorithm? Lung Cancer 2004; 44: 175–181.
13. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001; 285: 914–924.
14. Quint LE, Tummala S, Brisson LJ, Francis IR, Krupnick AS, Kazerooni EA, Iannettoni MD, Whyte RI, Orringer MB. Distribution of distant metastases from newly diagnosed non-small cell lung cancer. Ann Thorac Surg 1996; 62: 246–250.
15. Prokop M, Galanski M. Spiral and Multislice Computed Tomography of the Body. Stuttgart, Germany: Thieme; 2003.
16. Schrevens L, Lorent N, Dooms C, Vansteenkiste J. The role of PET scan in diagnosis, staging, and management of non-small cell lung cancer. Oncologist 2004; 9: 633–643.
17. Little AG, Stitik FP. Clinical staging of patients with non-small cell lung cancer. Chest 1990; 97: 1431–1438.
18. Vesselle H, Pugsley JM, Vallieres E, Wood DE. The impact of fluorodeoxyglucose F 18 positron-emission tomography on the surgical staging of non-small cell lung cancer. J Thorac Cardiovasc Surg 2002; 124: 511–519.
19. Gupta NC, Graeber GM, Rogers JS 2nd, Bishop HA Comparative efficacy of positron emission tomography with FDG and computed tomographic scanning in preoperative staging of non-small cell lung cancer. Ann Surg 1999; 229: 286–291.
20. Scott WJ, Gobar LS, Terry JD, Dewan NA, Sunderland JJ. Mediastinal lymph node staging of non-small-cell lung cancer: a prospective comparison of computed tomography and positron emission tomography. J Thorac Cardiovasc Surg 1996; 111: 642–648.
21. Steinert HC, Hauser M, Allemann F, Engel H, Berthold T, von Schulthess GK, Weder W. Non-small cell lung cancer: nodal staging with FDG PET versus CT with correlative lymph node mapping and sampling. Radiology 1997; 202: 441–446.
22. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verschakelen JA, Nackaerts KL, Mortelmans LA. Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non-small cell lung cancer: a prospective analysis of 50 cases. Leuven Lung Cancer Group. Chest 1997; 112: 1480–1486.
23. Bury T, Paulus P, Dowlati A, Corhay JL, Weber T, Ghaye B, Schoffers J, Limet R, Albert A, Rigo P et al. Staging of the mediastinum: value of positron emission tomography imaging in non-small cell lung cancer. Eur Respir J 1996; 9: 2560–2564.
24. Lardinois D, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, von Schulthess GK, Steinert HC. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003; 348: 2500–2507.
25. De Wever W, Vankan Y, Stroobants S, Verschakelen J. Detection of extrapulmonary lesions with integrated PET/CT in the staging of lung cancer. Eur Respir J 2007; 29: 995–1002.
26. De Wever W, Ceyssens S, Mortelmans L, Stroobants S, Marchal G, Bogaert J, Verschakelen JA. Additional value of PET-CT in the staging of lung cancer: comparison with CT alone, PET alone and visual correlation of PET and CT. Eur Radiol 2007; 17: 23–32.
27. Cerfolio RJ, Ojha B, Bryant AS, Raghuveer V, Mountz JM, Bartolucci AA. The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with nonsmall cell lung cancer. Ann Thorac Surg 2004; 78: 1017–1023.

28. Yi CA, Shin KM, Lee KS, Kim BT, Kim H, Kwon OJ, Choi JY, Chung MJ. Non-small cell lung cancer staging: efficacy comparison of integrated PET/CT versus 3.0-T whole-body MR imaging. Radiology 2008; 248: 632–642.

29. Quaia E, Tona G, Gelain F, Lubin E, Pizzolato R, Boscolo E, Bussoli L. Integrated fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT compared to standard contrast-enhanced CT for characterization and staging of pulmonary tumors eligible for surgical resection. Acta Radiol 2008; 49: 995–1004.

30. Tsushima Y, Tateishi U, Uno H, Takeuchi M, Terauchi T, Goya T, Kim EE. Diagnostic performance of PET/CT in differentiation of malignant and benign non-solid solitary pulmonary nodules. Ann Nucl Med 2008; 22: 571–577.

31. Hau NH, Ravel AC, Duclos A, Giammarile F, Souquet PJ. FDG-PET-CT and the diagnosis of malignancy of pulmonary nodules and mass lesions. Rev Mal Respir 2008; 25: 33–41.

32. Rankin SC. The role of positron emission tomography in staging of non-small cell lung cancer. Target Oncol 2008; 3: 149–159.

33. Krüger S, Buck AK, Mottaghy FM, Hasenkamp E, Pauls S, Schumann C, Wibmer T, Merk T, Hombach V, Reske SN. Detection of bone metastases in patients with lung cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 2009; 36: 1807–1812.

34. Posther KE, McCall LM, Harpole DH Jr, Reed CE, Putnam JB Jr, Rusch VW, Siegel BA. Yield of brain 18F-FDG PET in evaluating patients with potentially operable non-small cell lung cancer. J Nucl Med 2006; 47: 1607–1611.

35. Ludwig V, Komori T, Kolb D, Martin WH, Sandler MP, Delbeke D. Cerebral lesions incidentally detected on 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography images of patients evaluated for body malignancies. Mol Imaging Biol 2002; 4: 359–362.

36. Wiering B, Ruers TJ, Krabbe PF, Dekker HM, Oyen WJ. Comparison of multiphase CT, FDG-PET and intra-operative ultrasound in patients with colorectal liver metastases selected for surgery. Ann Surg Oncol 2007; 14: 818–826.

37. Metser U, Miller E, Lerman H, Lievshitz G, Avital S, Even-Sapir E. 18F-FDG PET/CT in the evaluation of adrenal masses. J Nucl Med 2006; 47: 32–37.

38. Brady MJ, Thomas J, Wong TZ, Franklin KM, Ho LM, Paulson EK. Adrenal nodules at FDG PET/CT in patients known to have or suspected of having lung cancer: a proposal for an efficient diagnostic algorithm. Radiology 2009; 250: 523–530.

39. Kumar R, Xiu Y, Yu JQ, Takalkar A, El-Haddad G, Potenta S, Kung J, Zhuang H, Alavi A. 18F-FDG PET in evaluation of adrenal lesions in patients with lung cancer. J Nucl Med 2004; 45: 2058–2062.

40. Marom EM, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Coleman RE, Herndon JE, Patz EF Jr. Staging non-small cell lung cancer with whole-body PET. Radiology 1999; 212: 803–809.

41. Nakamoto Y, Osman M, Wahl RL. Prevalence and patterns of bone metastases detected with positron emission tomography using F-18 FDG. Clin Nucl Med 2003; 28: 302–307.

42. Bury T, Barreto A, Daenen F, Barthelemy N, Ghaye B, Rigo P. Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non-small cell lung cancer. Eur J Nucl Med 1998; 25: 1244–1247.

43. Cheran SK, Herndon JE 2nd, Patz EF Jr. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. Lung Cancer 2004; 44: 317–325.

44. Song JW, Oh YM, Shim TS, Kim WS, Ryu JS, Choi CM. Efficacy comparison between (18)F-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small-cell lung cancer. Lung Cancer 2009; 65: 333–338.

45. MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A, Ware RE, Ball DL. High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. Int J Radiat Oncol Biol Phys 2001; 50: 287–293.

46. Eschmann SM, Friedel G, Paulsen F, Reimold M, Hehr T, Scheiderbauer J, Budach W, Kotzerke J, Bares R. Impact of staging with 18F-FDG-PET on outcome of patients with stage III non-small cell lung cancer: PET identifies potential survivors. Eur J Nucl Med Mol Imaging 2007; 34: 54–59.

47. Reed CE, Harpole DH, Posther KE, Woolson SL, Downey RJ, Meyers BF, Heelan RT, MacApinlac HA, Jung SH, Silvestri GA et al. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. J Thorac Cardiovasc Surg 2003; 126: 1943–1951.

48. [No authors listed.] Pretreatment evaluation of non-small-cell lung cancer. The American Thoracic Society and The European Respiratory Society. Am J Respir Crit Care Med 1997; 156: 320–332.

49. Opoka L, Kunikowska J, Podgajny Z, Błasińska-Przerwa K, Burakowska B, Oniszh K, Gola M, Langfort R, Rudziński P, Bestry I et al. Staging of non-small cell lung cancer using CT and integrated PET-CT. Pneumonol Alergol Pol 2013; 81: 5–15.