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Staging of non-small cell lung cancer using CT and integrated PET-CT

Ocena zaawansowania niedrobnokomórkowego raka płuca metodą tomografii komputerowej i pozytonowej tomografii emisyjnej skojarzonej z tomografią komputerową

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Abstract

Introduction. Lung cancer is the leading cause of death from cancer in developed countries. Radiological imaging methods are the basic methods in early diagnosis of this disease. TNM classification is a very important tool for optimal treatment in non-small lung cancer (NSCLC). Conventional radiological techniques allow the evaluation of the stage on the basis of anatomical changes only, while PET-CT provides information about the biochemical processes that may precede anatomical changes. The aim of this study was to compare the accuracy and sensitivity of CT and PET-CT in the staging of NSCLC.

Material and methods. The study was conducted on a group of 99 patients with NSCLC diagnosed at the National Tuberculosis and Lung Diseases Research Institute in the period from January 2008 to May 2010. CT and PET-CT were performed in all patients. Histological or cytological examination of the material obtained from biopsy, bronchoscopy, mediastinoscopy, and intraoperatively was the reference test. TNM classification was performed independently after CT and PET-CT.

Results and conclusions. It has been shown that PET-CT is a more accurate and sensitive method than CT in the staging process in NSCLC. PET-CT allowed the correct classification of the T, N, M, and total TNM in, respectively, 97%, 95%, 99%, and 89% of cases, while for CT it was, respectively, 95%, 84%, 84%, and 68% ($p = 0.0002$).

Key words: lung cancer, PET-CT, TNM, staging

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Introduction

High mortality in lung cancer patients makes it one of the most significant healthcare issues in most countries. Lung cancer is the most common malignancy and causes most malignancy-related deaths worldwide [1–4]. No significant improvement in therapy outcome has been obtained as yet, despite constant progress in diagnostics and treatment [5–9]. Five-year overall survival rate for lung cancer patients in the USA is currently 16%, whereas in Europe the respective index is 10%. Poland is one of the countries with highest incidence and mortality rates due to this disease.

The rate of increase in both morbidity and mortality due to lung cancer has been slowing down in the last decade as compared to previous ones. There are many factors implicated in increasing incidence of the disease, including, in first place, widespread tobacco smoking. Increasing life expectancy, industry-related environmental pollution, genetic factors, and dietary habits also play important roles in the etiology of lung cancer.

Differences in incidence of lung cancer depend on age, sex, ethnic background, and geographical location. The choice of therapeutic strategy and prognosis in non-small lung cancer (NSCLC) depend on disease stage.

In the 1990s, studies on low-dose computed tomography (CT) in early detection of lung cancer in high-risk patients were initiated. Similary to classical radiological modalities, low emission dose CT permits detection of smaller and less advanced lesions. Preliminary data from studies on low-dose CT screening for lung cancer showed similar mortality rates to non-screened patients, with 4.4 deaths per 1,000 persons per year [10, 11].

Screening yields a high percentage of false positive results, which in turn lead to many unnecessary invasive procedures [12].

However, one of the most recent publications showed a decrease in mortality in patients screened by low dose CT, which may change earlier views on the issue [13].

The TNM classification (tumour, node, metastasis), defined by the American Joint Committee on Cancer (AJCC), is a tool of utmost importance in prognostic assessment and choice of optimal therapeutic strategy. Adequate diagnostic procedures performed according to the TNM principles for NSCLC are crucial for best treatment outcomes.

The TNM classification is based on assessment of tumour size, involvement of regional lymph nodes, and presence of distant metastases. In NSCLC, surgery is performed in stages IA, IB, IIA, and IIB disease as well as in selected patients with stage IIIA disease.

Computed tomography (CT) is a technique applied for NSCLC staging on a routine basis, enabling accurate assessment of tumour size, status of regional lymph nodes, and potential distant metastases within the investigated anatomical areas. The role of CT is, however, limited in the assessment of mediastinal lymph nodes since morphological staging criteria, based on measurement of lymph node dimensions, include no information on the potential presence of so-called micrometastases. Evaluation of lymph node groups is currently performed using positron emission tomography (PET) in lung cancer patients with CT-negative mediastinal lymph nodes under qualification for surgery. This modality enables detection of metastases in normally-sized mediastinal lymph nodes. The PET-CT scanning combines the advantages of modalities, permitting accurate anatomical assessment and a more sensitive evaluation of metabolic tissue activity. This method provides information on biochemical phenomena that may precede the appearance of identifiable anatomical lesions. Combined PET-CT scanning began to replace independent CT and PET assessments from 2001.

The aim of the study was to compare the diagnostic accuracy of multidetector-row computed tomography and PET-CT in staging of lung cancer.

Material and methods

The study population included 99 patients with NSCLC (tumour size of more than10 mm), diagnosed in the National Tuberculosis and Lung Diseases Research Institute in Warsaw between January 2008 and May 2010. Staging was performed according to the principles of the 6th edition of the TNM classification, which was edited in 2007. The PET-CT investigations were performed in two institutions: Euromedic, Warsaw (centre A; GE Discovery STE device) and the Department of Nuclear Medicine of the Medical University of Warsaw (centre B; Siemens Biograph Truepoint64 device). Radiopharmaceutical fluoro- 2deoxy-D-glucose (FDG) was administered intravenously in each patient prior to PET-CT scanning. The measured activity of FDG was 320–400 MBq in centre A and 250–450 MBq in centre B.

Radiopharmaceuticals were administered 45 minutes prior to PET-CT scanning in centre A and 60 minutes before onset of the procedure in centre B. An additional scanning session (so-called delayed scan) was performed in selected patients diagnosed in centre B; this scanning covered thoracic

field only and was performed after 120 minutes. Standardized uptake value (SUVmax) in the tumour was assessed during the PET-CT scan. Additional measurements of SUVmax 120 minutes after administration of radiopharmaceutical were performed in 25/27 patients (92.6%) at centre B. Threshold value for benign lesions was set at or below 2.5, as described in the literature. The results of the PET-CT scanning were evaluated by specialists in nuclear medicine.

Single phase CT scanning after contrast medium administration, using spiral scanning technique, was performed in all the studied patients. All thoracic CT scans were taken at the National Tuberculosis and Lung Diseases Research Institute in Warsaw using the Siemens Somatom Sensation 16-detector-row device, and evaluated by specialists in radiology.

The TNM classification was assigned independently after PET-CT and CT. The result of the histopathological tissue examination was used for reference in each patient. Tissue and cell samples for morphological evaluation were obtained through mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or from intraoperative sampling (so-called frozen section). All samples were evaluated by specialists in pathomorphology.

The combined radiological staging data were then compared with histopathological findings, and basic diagnostic accuracy parameters were calculated for PET-CT and CT.

Calculations were based on data charts according to the statistical test theory. These included patients with positive (T+) and negative (T–) results of the given test in subjects with or without the disease:

— TP (true positives): number of patients having the disease, in whom the result of the test was positive, i.e. representing true positive results;
— FP (false positives): number of patients not having the disease, in whom the result of the test was positive, i.e. representing false positive results;
— FN (false negatives): number of patients having the disease, in whom the result of the test was negative, i.e. representing false negative results;
— TN (true negatives): number of patients not having the disease, in whom the result of the test was negative, i.e. representing true negative results.

The obtained results of radiological assays were compared to reference test findings. Results were arranged in the table, including TP, TN, FP, and FN results. Then, in order to evaluate the diagnostic accuracy of the method, the following parameters were calculated: sensitivity (Se), specificity (Sp), accuracy (Acc), level of reliability of positive result (LR+), level of reliability of negative result (LR–), and diagnostic odds ratio (DOR), all expressed with 95% confidence intervals (CI). The sign test was applied for comparing the diagnostic accuracy of respective tests. This test concerns related variables when the results of both CT and PET-CT in a given patient are similar. Statistical analysis was performed using the Statistica for Windows 6.5 software.

Results

The mean age in the studied group of 99 patients with primary lung carncer was 64.2 years (41–88 years). Men comprised 70.7% of the patients in this group.

The location of the lesion was precisely described in each patient. The tumour was located in the right upper lobe in 37/99 patients (37.3%), in the right lower or median lobe in 22/99 persons (22.2%), in the upper left lobe in 25/99 cases (25.2%), and in the left lower lobe in 15/99 subjects (15.1%).

The main tumour dimension was measured for all 99 patients. Mean tumour size was 41.7 mm. Tumours were then divided in two groups — having between 10 mm and 30 mm in diameter, and of more than 30 mm in size.

Lymph node dimensions were measured along their short axis. During FDG PET-CT scan, the SUV value for each tumour was assessed. Sixty out of 99 studied patients were operated on, with resection of all lymph node groups accessible during the procedure. In two patients, surgical procedure followed chemotherapy. Histopathological analysis of all 99 tumours revealed 27 cases of adenocarcinoma (27.3%) and 30 cases of squamous cell carcinoma (30.3%), whereas in 42 patients (42.3%) the diagnosis of "non-small cell cancer not otherwise specified" was made.

Computed tomography scanning was performed in 99 patients, of which 59 persons were already diagnosed with lung cancer during previous investigation, and a further 40 persons were referred for diagnostics of focal lung lesions but had no diagnosis as yet. Analysis of SUVmax values was performed separately in centres A and B. The obtained mean SUVmax values in the respective centres after the first phase investigations were 7.5 (A) and 7.6 (B) for adenocarcinoma, 11.7 (A) and

Table 1. Details of accuracy of tumor (T) status: CT compared with integrated PET-CT and pathological staging (pT), no statistically significant difference between CT and PET-CT

Correctly staged	CT/CT	PET-CT	pT
T1	28	28	28
T2	49	50	51
T3	10	10	11
T4	7	8	9
Total (99)	94/99 (95%)	96/99 (97%)	99 (100%)

17.3 (B) for squamous cell carcinoma, and 8.6 (A) and 13.9 (B) for non-small cell cancer NOS. In the delayed phase test, the mean value of SUVmax measured in centre B was 14.9 for adenocarcinoma, 17.9 for squamous cell carcinoma, and 18.8 for non-small cell cancer NOS. All tumour types demonstrated increased FDG uptake during the second phase evaluation. No increase in FDG uptake within the lesion (FN) was observed in 3 patients (3.0%)

The following surgical procedures were performed: lobectomy — 47/60 patients (78.3%), bilobectomy in 3/60 patients (5.0%), and pneumonectomy in 10/60 subjects (16.6%).

Adenocarcinoma was the most common type of tumour in the operated patients, concerning 92.6% of subjects (25/27).

In 39 patients (39.3%) no surgical resection was performed due to the presence of distant metastases, poor general condition, or lack of patient consent for surgery. Staging was assigned according to the sixth edition of the TNM classification presented by Union for International Cancer Control (UICC) in December 2006, and by AJCC in June 2007.

T descriptor

Tumour size was assigned using the greatest identified dimension of the lesion. According to the intraoperative assessment, T1 stage was assigned in 28 patients (28.2%), T2 in 51 persons (51.5%), T3 in 11 cases (11.1%), and T4 in one subject (1.0%). The T descriptor was assigned correctly by CT in 94 patients (94.9%), and by PET-CT in 96 subjects (96.9%). Incorrect T-stage assignment by CT occurred in 5 persons (5.0%), including one T1 patient (3.6%), three T2 subjects (5.9%), and one T4 patient (11.1%). Incorrect T-staging by PET-CT was noted in three persons, including two T2 patients (3.9%) and one person with a T4 tumour (9.1%).

Overall analysis revealed that four CT and three PET-CT investigations showed a smaller tumour size as compared to pathological staging (pTNM). Underestimation of the tumour size was due to intraoperatively detected infiltration of nearby structures, including main vessels, which had not previously been identified by imaging techniques. One CT investigation suggested a bigger tumour size as compared to intraoperative data. Overestimation of the tumour size was due to infiltration of the nearby structures, previously described in CT but not confirmed by the surgeon. Tumour size was underestimated by CT assessment in 4.0% of cases in the entire group, and by PET-CT in 3.0% of cases. Overestimated values were found in 1.0% of cases, as assessed by CT (Tab. 1).

N-descriptor

Regional lymph node involvement was ultimately described as N0 in 51 patients (51.5%), N1 in 23 cases (23.2%), N2 in 18 cases (18. 2%), and N3 in 7 cases (7.1%). Correct N-staging was provided by CT scanning in 83 patients (83.8%) and by PET-CT in 94 patients (94.9%). Incorrect staging of this parameter was observed in 16 patients (16.2%) after CT investigation and in five persons (5.1%) after PET-CT scanning. Underestimation of nodal involvement by CT was observed in 11 patients (FN), and overestimation in five patients (FP). Following PET-CT scanning, the N-descriptor was underestimated in three patients (FN), and overestimated in two patients (FP).

Sensitivity of the PET-CT test was 0.94, and that of CT was 0.76. This means that the probability of positive PET-CT result in patients having regional nodal metastases is 94% (95% confidence interval [CI]: 83–98), and the respective value for CT testing is 76% (95% CI: 61–86). Specificity of PET-CT investigation was 0.96, which means that the probability of a negative imaging result in a patient having no nodal metastases is 96% (95% CI: 87–99). Specificity of computed tomography testing was 0.90. Thus, the probability of a negative CT result in a patient in whom reference test shows no presence of mediastinal lymph node metastases is 90% (95% CI: 80–96).

The calculated value of the reliability index of a positive result by PET-CT scanning was 24.8. Therefore, the probability of obtaining a positive CT finding in a patient having nodal metastases is 24.8 times higher than the respective probability in a subject with no lymph node engagement. Respective index calculated for CT diagnostics was 8.2, which means that the probability of a positive CT finding is 8.2 times higher in a patient having metastases to lymph nodes than it is in a person in whom histopathological analysis disclosed no presence of tumour cells in lymph nodes.

Accuracy of CT imaging in lymph node evaluation was 84% (95% CI: 75–90), whereas the respective value for FDG PET-CT was 95% (95% CI: 89–99). Reliability index of a negative PET-CT result was 0.1, which means that the probability of obtaining a negative radiology result in a patient who does have nodal metastases is only 0.1 of the probability of that of a patient having metastases. The reliability index of a negative CT result was 0.3, which means that the probability of obtaining a negative radiology result in a patient who does have nodal metastases is only 0.3 of the probability of that of a patient having metastases. The calculated diagnostic accuracy for PET-CT was 95% (95% CI: 89–99), and the respective index for CT was 84% (95% CI: 75–90). The difference between those two values was statistically significant (p = 0.0055).

Diagnostic odds ratio for PET-CT was 248, and for CT was 27.3; therefore, the probability of correct staging for the N-descriptor is nine times higher when using PET-CT than it is for CT alone. In order to correctly N-stage one more patient having lung cancer, PET-CT scanning must be performed instead of CT in nine persons. Positive predictive value (PPV) was 87.2% for CT; therefore, the probability of true nodal engagement in a patient having enlarged mediastinal lymph nodes is 87.2% (95% CI: 72–94). Negative predictive value (NPV) for CT was 81.7%, which means that the probability of not having nodal metastases for a person with no nodal enlargement visualised by CT is 81.7% (95% CI: 70–89). The positive predictive value for PET-CT was 95.5%. Therefore, the probability that a patient with increased mediastinal lymph node uptake has metastases in this region is 95.5 (95% CI: 85–99).

The negative predictive value for the same diagnostic modality was 94.4%, which is also the probability rate of absence of metastases in a patient in whom no increase in FDG uptake was observed in mediastinum (95% CI 85; 98) (Tab. 2).

Table 2. Sensitivities, specificities, positive likelihood ratio (LR+), negative likelihood ratio (LR–), accuracy, diagnostic odds ratio (DOR), positive predictive values (PPV), negative predictive values (NPV) for the detection of malignant lymph nodes (N) of CT and integrated PET-CT, statistically significant difference between CT and PET-CT (p = 0.0055)

	CT/CT	PET-CT
Se (95% CI)	76% (61; 86)	94% (83; 98)
Sp (95% CI)	90% (80; 96)	96% (87; 99)
Lr+	8,2	24,8
Lr–	0,3	0,1
Acc (95% CI)	84% (75; 90)	95% (89; 99)
DOR	27,3	248
PPV	87% (72; 94)	96% (85; 99)
NPV	82% (70; 89)	94% (85; 98)

M-descriptor

Distant metastases were detected in 18 patients (18.2%). Computed tomography scanning results suggested the presence of metastases outside the mediastinum (M1) in seven subjects. Of those, three had false positive results (metastases to contralateral lung, to adrenal glands or bone), and in four cases the results were truly positive, with brain, contralateral lung, adrenal gland, or bone metastases present. The suggestion of M1 stage was made by PET-CT in 19 cases. A false positive result was identified in one person, with suspected contralateral lung metastasis. True positive results were found in 18 patients, including bone metastases in 7 persons, contralateral lung engagement in 4 persons, adrenal gland metastases in 3 persons, supraclavicular lymph node metastases in 2 persons, and axillary lymph node engagement and brain metastases in one person each. Computed tomography scanning underestimated the M-stage in 13 patients (13.1%) and overestimated it in three subjects (3.0%).

There were no cases of M-stage underestimation by PET-CT, but in one patient M-staging was overestimated (1.0%). Based on these data, the correct M-staging was more common when using PET-CT (98 patients) as compared to CT alone (83 patients). Correct M-staging by CT was obtained in 83 subjects, which yielded an accuracy of 83.8% (95% CI: 75–90). When using PET-CT, correct M-staging was achieved in 98 patients, with an accuracy of 98.9% (95% CI: 95–100). The difference between these values was statistically significant (p = 0.0012) (Tab. 3).

Table 3. Details of accuracy of metastatic (M) status: CT compared with integrated PET-CT and pathological staging (pM), statistically significant difference between CT and PET-CT (p = 0.0012)

	CT/CT	PET-CT	pM	CT/CT	PET-CT	pM
M status	M0	M0	M0	M1	M1	M1
Total	92	80	81	7	19	18

Table 4. Overall staging at CT and integrated PET/CT in patients with lung cancer: correctly staged (1), overstaged (2), understaged (3),statistically significant difference between CT and PET-CT (p = 0.0002)

	CT/CT	CT/CT	CT/CT	PET-CT	PET-CT	PET-CT
	1	2	3	1	2	3
Histological type						
Adenocarcinoma	21	4	2	22	4	1
Squamous	20	3	7	27	0	3
Subtype not defined	26	2	14	39	3	0
Total	67 (68%)	9	23	88 (89%)	7	4

Total TNM stage

Most patients in the studied group were assigned to TNM stage I, following assessment by CT, PET-CT, and pTNM. Computed tomography alone provided correct staging in 67/99 patients (67.7%), and PET-CT in 88/99 subjects (88.9%). The calculated diagnostic accuracy was 68% for CT (95% CI: 58–76) and 89% for PET-CT (95% CI: 81–94). The difference was statistically significant.

Computed tomography alone was most accurate for TNM staging in patients assigned to stage IA or IB, and the least accurate for stage IV patients. As for PET-CT, the greatest accuracy was noted for stages IA, IIIA, and IV (Tab. 4).

Discussion

Surgery remains the main radical treatment option in non-small cell lung cancer. Radiological assessment, tumour biopsy, and staging according to TNM classification should be performed prior to the planned operative intervention. Correct staging is a prerequisite for optimal and successful treatment [14].

Surgical intervention is aimed at radical resection, and lobectomy remains a standard in non-small cell cancer. Segmentectomy may be performed in peripheral lesions of low stage but only if the patient has contraindications for radical surgery.

A tumour is considered resectable if it can be separated from the surrounding structures. The estimated sensitivity and specificity of computed tomography in the assessment of thoracic wall infiltration is 38–87% and 40–90%, respectively [15]. Imaging by PET-CT often permits differentiation between neoplastic infiltration and uninvolved surrounding structures. In the presented study, correct T-staging was more often achieved by PET-CT (96/99 patients) than by CT alone (94/99 patients). Accuracy of PET-CT staging was 96.9% and that of CT was 94.9%, with no statistically significant difference.

Computed tomography is not sufficiently specific in the assessment of involved mediastinal lymph nodes. This diagnostic modality enables good visualisation of lymph node location, shape, and dimensions, and can be used for identification of appropriate lymph nodes for biopsy [16, 17]. Most authors consider 10 mm as the threshold value of the lymph node size, along its shortest axis [18, 19]. More precise assessment can be performed when using different thresholds for respective lymph node groups, as delineated by the American Thoracic Society [20]. For example, 13 mm along the shorter axis is an upper limit for lymph nodes situated below the tracheal bifurcation and for pretracheal ones. With this threshold respected, the number of false positive results is decreased.

Not only the size but also the location of involved lymph nodes is of prognostic significance [21]. Stage N1 lymph nodes can most often be removed during the operation, but this can be technically difficult if they adhere to the pulmonary artery; pneumonectomy is the best option in such cases.

An important aspect in N-staging accuracy is the histological type of the tumour. Mori et al. found that lymph nodes containing metastases of lung adenocarcinoma are often normal in size in CT pictures [22]. A higher CT sensitivity for N-staging was observed for squamous cell carcinoma.

To sum up, the applicability of CT and PET-CT in the assessment of mediastinal lymph nodes depends on the lymph node dimensions, location, and type of tumour. A report from the Institute for Clinical Evaluative Sciences (ICES) points out the importance of PET-CT in nodal staging in patients with lung cancer, which is superior to that of CT. The combined modality is useful for assessment of lymph node metastases, irrespective of their size [23, 24]. However, many authors reported a high number of false positive results of nodal staging by PET-CT [25]. Fewer false positive results were observed for lymph nodes in upper mediastinum. It should be remembered that inflammatory changes in lymph nodes can give false positive results in PET-CT scans, which can potentially disqualify patients eligible for surgery.

In the presented study, the calculated diagnostic accuracy of PET-CT for N-staging was 95% (95% CI: 89–99), and the respective value for CT was 84% (95% CI: 75–90), with a statistically significant difference ($p = 0.0055$).

Metastases from lung cancer pose a serious diagnostic dilemma and may be found in various organs. Thus, whole body PET-CT scanning facilitates correct M-staging.

Focal lesions are often detected in ipsi- or contralateral lung in patients having lung cancer. Adequate assessment of additional focal lung lesions in patients with non-small cell lung cancer is of utmost importance in therapeutic strategy planning.

Those additional lesions can be of benign (non-neoplastic) character and may represent another primary lung cancer or metastases from lung cancer or from the malignancy localised in another organ. Caretta et al. performed a histopathological analysis of additional focal lung lesions associated with lung cancer [26]. One of the more intriguing findings was the presence of intrapulmonary lymph nodes, identified histopathologically. Many other lesions turned out to be of post-inflammatory character, radiologically imitating cancer metastases.

These authors suggest that scrupulous investigation of accessory lung lesions is indicated in all patients considered for surgery.

In the presented study, only four patients (4/99) had contralateral lung metastases. Computed tomography correctly identified one of them, whereas PET-CT detected all the lesions.

Horejs reported that in 25% of patients with low stage lung cancer (no regional lymph node metastases) distant metastases could be found by CT [27, 28].

Metastases to adrenal glands, liver, brain, bones, or lymph nodes are a common finding in patients with lung cancer. Numerous reports from literature suggest that even patients with no clinical signs or symptoms should be investigated for potential metastases from lung cancer. Adenocarcinoma gives distant metastases more frequently than other histological types of NSCLC [29, 30]. Squamous cell carcinoma, however, often gives distant metastases at a later timepoint [31]. Any clinical information can be of great help for radiologists for interpretation of the obtained pictures.

In the presented study, adrenal gland metastases from primary lung cancer were identified in 3/99 patients (3%). Computed tomography yielded two true positive, and PET-CT three true positive results.

Adrenal glands are organs of particular importance as they can harbour many benign lesions (adenomas, hyperplastic changes) that imitate cancer metastases [32].

Metastases in adrenal glands can most often be detected in thorax CT, if only the organs are within the analysis gate. The presence of adrenal metastases can be detected by CT in 5–10% of patients [33, 34]. The lesions are mostly unilateral, with bilateral metastases detected in not more than 3% patients. Adrenal gland adenomas are common findings and can be identified in 2–10% of subjects in the general population [35]. These can be erroneously interpreted as cancer metastases. An adrenal focal lesion of density less than 10 HU before contrast medium administration, with more than 50% contrast elimination after 10 minutes, as compared to elimination after 1 min, is believed to be of benign character [36, 37]. Magnetic resonance imaging (MRI) is another diagnostic modality that can be used for the investigation of adrenal glands. Similarly to CT, MRI pictures of adrenal glands visualise fatty tissue contained in the organ, with potential focal lesions. In cases of equivocal CT and MRI findings, PET-CT scanning can be of value, as it determines the metabolic activity of any identified lesion. If PET-CT scans yield unclear pictures, biopsy of the adrenal gland is the only available investigation left for verification of the lesion character. Removal of the metastatically affected adrenal gland can prolong the patient's life or even be curative [38].

In the presented study, brain metastases were identified by CT and MRI in a single patient out of all 99 subjects (1%). The diagnosis was made before PET-CT scan.

Brain metastases from lung cancer may be present in as many as 18% of patients [39, 40], with most of them presenting neurological symptoms. Kormas et al. found that 6% of patients with non-small cell lung cancer, with no neurological symptoms, had brain metastases. These were identified at the beginning of diagnostic procedures in 3% of patients, and in a further 3% of subjects brain metastases were found a year later, during follow-up [41]. Ferrigno and Buccheri reported the presence of brain metastases in as many as 15% of patients with low stage lung cancer [42]. Brain metastases can be invisible in CT pictures [43, 44], and MRI is perceived as a more accurate and sensitive diagnostic modality.

Similarly to adrenal gland metastases, surgical removal of an isolated brain metastatic focus can prolong life or be curative in patients with resectable lung cancer [45, 46].

In the current study, bone metastases were found in 7/99 patients (7%). Computed tomography yielded one true positive result; bone structures harbouring metastatic lesions were not investigated radiologically in the remaining six patients. Combined PET-CT scan returned seven true positive results.

Most patients with bone metastases complain of pain, which suggests tumour spread. However, bone metastases may remain asymptomatic in 40% of patients [47, 48]. In any patient with pain symptomatology, scintigraphy and MRI should be considered, along with measurement of alkaline phosphatase activity [49–51]. Scintigraphy has a high sensitivity in this setting (90%) but with lower specificity (61%) [52, 53]. False positive results of scintigraphy or PET-CT scans can be due to local tissue degeneration as well as the presence of inflammatory or posttraumatic lesions. False positive PET-CT findings can be found even in some patients with osteolytic lesions [54]. Nevertheless, FDG PET-CT is believed to be the optimal diagnostic modality for detection of bony metastases undetected by other methods, and is superior to CT and scintigraphy in skeletal system investigation [55]. It is commonly suggested that FDG PET-CT scanning should be performed routinely as part of non-small cell lung cancer staging [56].

Positron emission tomography combined with computed tomography is of great value in the detection of metastatic lesions, particularly in adrenal glands and the skeletal system. Verhagen et al. [57] reported the presence of metastases detected by PET-CT in 15% of paients, where other diagnostic modalities showed no abnormalities.

In the presented study, extrapulmonary lymph node metastases were also found, including lesions in supraclavicular lymph nodes in two persons, and in the axillary lymph node in another patient.

Those lymph nodes were described as normal (not enlarged) in CT scans but identified as metastatic foci in PET-CT due to increased FDG uptake.

High accuracy of PET-CT in M-staging was observed in the presented study (98.9%) as compared to CT alone (83.8%).

Cerfolio et al. investigated the accuracy of PET-CT in staging in non-small cell cancer in 129 subjects [58]. The accuracy of positron emission tomography combined with computed tomography was superior to that of CT alone in the assessment of both T and N-descriptors as well as in overall TNM staging, with statistically significant differences.

Lardinois et al. also compared PET-CT with CT, and found the former modality to be more accurate in staging for T, N, and M descriptors [59].

Shim et al. demonstrated that PET-CT is significantly more accurate in N-staging and overall TNM staging but not superior to CT in the assessment of tumour size (T-descriptor) [60]. Similar results were found in the presented study.

Many authors consider PET-CT and CT to have similar accuracy in TNM staging but point to superior PET-CT results in the assessment of mediastinal lymph nodes (N-stage).

Van Tinteren et al. included PET-CT into routine diagnostics, and observed a reduction in the number of unnecessary procedures from 41% to 21%. According to Viney et al., PET-CT scanning results affect the choice of therapeutic procedures in 20% of stage I or II patients but do not reduce the number of thoracotomies performed, since results of PET-CT scanning are not sufficient for disqualification from surgery. Australian researchers reclassified 14% of patients following PET-CT scanning [61]. In the presented study, PET-CT investigations were conclusive for nonresectability of the lesion in 22/99 patients (22%).

Similarly to the previously mentioned reports, the authors of the presented study noted a significant reduction in unnecessary thoracotomy procedures following investigation by PET-CT.

In the presented study, PET-CT scanning demonstrated nonresectability of the lesion in 22/99 patients (22%).

Herder et al. did not observe statistically significant differences in TNM stage between pa-

tients who underwent PET-CT scanning and those who did not [62].

However, differences were observed between the duration and cost of diagnostic procedures. Average duration of diagnostic sequence decreased from 23 to 14 days, and the number of patients requiring more than one investigation for lymph node assessment was aslo significantly lower.

False positive results of PET-CT scanning can be obtained in cases of infections or inflammatory lesions.

Therefore, all positive PET-CT scan results should be, if possible, verified histopathologically. Potential candidates for surgery, with positive PET-CT lymph node scans should be biopsied through mediastinoscopy for definitive confirmation of metastatic lymph node involvement. Verification should also be performed in cases of any suspected extrathoracic lesions found by CT, MRI, or scintigraphy. False negative results are observed mainly if nodal, pulmonary, or other metastatic lesions are of small size.

In the presented study, increased FDG uptake was not found in malignant tumours in PET-CT scans in three patients (3%) (FN). In two of those, the tumour was histologically of adenocarcinoma type, and in the remaining patient the lesion was 11 mm in diameter.

According to Nomori et al., PET-CT cannot detect metastatic lesions smaller than 4 mm [63].

Conflict of interest

The authors declare no conflict of interest.

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