

RESEARCH ARTICLE

Performance of Integrated FDG-PET/CT for Differentiating Benign and Malignant Lung Lesions -Results from a Large Prospective Clinical Trial

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Abstract

Purpose: The purpose of the study was to evaluate prospectively whether integrated 2-deoxy-2-[¹⁸F]fluoro-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) is more accurate for determination of malignancy in newly diagnosed pulmonary lesions compared to separate interpretation of CT and FDG-PET.

Procedures: Two hundred and seventy-six patients with newly diagnosed lung lesions underwent FDG-PET/CT. Helical CT, FDG-PET, and FDG-PET/CT were interpreted separately to determine the performance of each imaging modality. Histopathology served as reference in all patients, and in further 60 patients, a benign lesion was verified at follow-up (mean follow-up of 1,040 days).

Results: Histology revealed malignant lung tumors in 216 of 276 patients. With PET and PET/CT, a significantly lower number of lesions were classified as equivocal compared to CT alone ($p < 0.001$). Assuming that equivocal lesions are benign, performance of diagnostic tests was as follows: sensitivity, specificity, and accuracy for CT was 94, 75, and 90%, for PET 97, 83, and 94% ($p = 0.021$), and for PET/CT 96, 87, and 94% ($p = 0.010$). Assuming that equivocal lesions are malignant, sensitivity, specificity, and accuracy for CT was 99, 37, and 86%, for PET 99, 77, and 94% ($p < 0.001$), and for PET/CT 98, 68, and 92% ($p = 0.002$). PET and PET/CT showed the highest concordance ($K = 0.912$; confidence interval 0.866–0.958). In lesions less than or equal to 3 cm, there was a significant difference in the performance of PET alone and multidetector row CT as well as PET/CT and multidetector row CT ($p = 0.007$), irrespective if equivocal findings were judged as malignant or benign.

Conclusion: For differentiation of benign from malignant lung lesions, integrated FDG-PET/CT imaging was significantly more accurate than CT but not FDG-PET. The addition of metabolic imaging (FDG-PET) to morphological imaging (CT) leads to an increase in specificity and significantly reduced equivocal findings and is therefore recommended to further specify newly diagnosed lung lesions.

Key words: NSCLC, PET/CT, PET, MDCT, Lung tumor

Introduction

In daily clinical practice, determination of newly formed pulmonary lesions with noninvasive imaging modalities remains challenging. Tissue histopathology represents the gold standard for evaluation of indeterminate lung lesions, and biopsy of the lesion is usually required to obtain a definite diagnosis. However, depending on the anatomic location of pulmonary lesions (i.e., central lesions or tumors in close proximity to large vessels), endoscopic or transthoracic computed tomography (CT)-guided core biopsy of the lung is not possible in all patients. Moreover, invasive techniques can frequently not be performed in patients with comorbidities and are sometimes also associated with complications. Therefore, a noninvasive imaging modality with high diagnostic accuracy is desirable. The reliable detection of inflammatory consolidation mimicking a tumor helps to avoid surgical interventions such as thoracotomy. Additionally, early diagnosis of a malignant tumor is one of the most important prognostic factors [1, 2].

Chest radiography and multidetector row CT (MDCT) are the most commonly used imaging modalities to diagnose and differentiate pulmonary lesions. Although MDCT has a high spatial resolution and enables multiplanar reconstructions, the differentiation of benign from malignant lung tumors remains difficult in cases presenting without typical morphological features [3, 4]. Inflammatory consolidations can mimic a malignant tumor resulting in a reduced specificity. On MDCT, morphologic criteria such as spicules of the tumor, tumor invasion into surrounding tissue, or inhomogenous contrast enhancement are employed for making a diagnosis. Considering contrast enhancement within the tumor, MDCT achieves an accuracy up to 85% for detecting lung cancer [5, 6].

Positron emission tomography with the glucose analog 2-deoxy-2- ^{18}F fluoro-D-glucose (FDG-PET) is now increasingly performed for differentiation of suspicious lesions detected by chest X-ray or CT [7]. The accuracy for differentiation of malignant from benign tumors was reported to be as high as 90% [8–10]. On the other hand, FDG is not a tumor-specific radiotracer and accumulates also in inflammatory lesions. Moreover, FDG-PET provides imprecise anatomic localization of lesions [11]. Integrated FDG-PET/CT combines the advantages of morphological and functional imaging, and it was shown recently that PET/CT is significantly more accurate for T- and N-staging of lung cancer than CT or FDG-PET when interpreted separately. However, a significant improvement in accuracy regarding differentiation of benign from malignant lung tumors has not been demonstrated in a larger patient series [12, 13].

FDG-PET/CT was compared to MDCT alone and FDG-PET alone regarding the differentiation of benign from malignant lung tumors. Additionally, potential reasons for misinterpretation of lesions at FDG-PET/CT were evaluated.

Materials and Methods

Patient Cohort

From January 2003 to February 2006, 276 patients (201 men, 75 women; mean age 64.3 years [SD 11.9 years, range 38–86 years]) with a lung lesion newly diagnosed at conventional chest radiography and/or MDCT suspicious for a malignant primary underwent integrated FDG-PET/CT after giving written informed consent. In this prospective study, PET/CT has been included as an additional imaging test before biopsy of the lesion and histological evaluation was performed. All patients were included consecutively and underwent bronchoscopy including fine-needle aspiration or core biopsy. If bronchoscopic biopsy was not practicable, transthoracic CT-guided biopsy of the lesion was performed. Because negative biopsy cannot exclude a malignant tumor, clinical follow-up also served as reference for benign lesions. Patients with a history of extrapulmonary malignant disease had been excluded from the series.

Two hundred and seventy-six patients fulfilled the inclusion criteria. In 216 patients (78.2%), a malignant tumor was diagnosed. In 60 patients (21.7%), lung lesions turned out to be benign. In 35 patients, lesion size could not be measured because of a diffuse lesion growth, e.g., parahilar location. In the remaining 241 lesions, mean lesion size was 41 mm (range 7–140 mm; standard deviation ± 24 ; 10th percentile = 17 mm, 90th percentile = 76 mm). Histological diagnoses of all malignant tumors are shown in Table 1. Benign lesions consisted out of chondrohamartoma ($n=3$), hamartoma ($n=1$), schwannoma ($n=1$), glomus tumor ($n=1$), lipoma ($n=1$), solitary fibrous tumor ($n=1$), teratoma ($n=1$), bronchogenic cyst ($n=2$), inflammatory lesions (bronchitis, chronic pneumonia, cryptogenic organizing pneumonia, asbestosis, fibrosis; $n=9$), or tuberculosis ($n=1$). Other benign lesions were not further classified ($n=39$).

Integrated FDG-PET/CT

Before examination, blood glucose level had to be below 150 mg/dl. FDG-PET/CT was performed using a modern hybrid scanner (General Electric Discovery LS, General Electric Medical Systems, Milwaukee, USA). MDCT and PET emission data were acquired from the base of the skull to the mid-thigh. Image acquisition started 60 min after intravenous injection of 370 to 550 MBq of FDG, adapted to the body weight of the patient. MDCT was performed after intravenous injection of 120 ml contrast medium (Ultravist 300[®], Schering, Berlin, Germany). An 80-ml bolus (flow 3 ml/s) was injected, and the scan was started with a delay of 60 s. During the scan, additional 40 ml of contrast medium was administered to optimize contrast in pulmonary vessels. MDCT was acquired with the following parameters: 140 kV, 160 mAs, slice thickness 5 mm, increment 4.25 mm, pitch 1.5, and rotation time 0.5 s. For matching of MDCT slices and PET slices, CT was acquired in a middle respiratory position. Directly after MDCT, the PET acquisition was started. Acquisition time was 4.5 min per bed position (five to eight bed positions per patient). During imaging of the chest, shallow breathing was instructed. Each position had 35 scanning planes with a 14.6 cm longitudinal field of view and a one-slice overlap between scanning positions. ^{18}F FDG-PET images were reconstructed using MDCT attenuation correction and an ordered subset expectation maximization algorithm (28 subsets, two iterations, loop filter with a full-width at half-maximum [FWHM] of 3.91 mm, postfilter with an FWHM of 6.5 mm, 128 \times 128 image matrix, pixel-size 4.29 mm). MDCT

Table 1. Histological diagnosis of all malignancies

Histological diagnosis	<i>n</i> (%)
Nonsmall cell lung cancer	182 (84.3)
Small cell lung cancer	15 (6.9)
Carcinoid tumor	11 (5.0)
Large cell carcinoma	3 (1.4)
Mesothelioma	3 (1.4)
Pulmonary sarcoma	1 (0.5)
Signet ring cell carcinoma	1 (0.5)
Total number of malignant tumours	216

Distribution of histological diagnosis of all malignancies ($n=216$). Given are the absolute number n and percentage (%).

images were converted into linear attenuation coefficients for the 511 keV energy radiation as implemented in the system. MDCT and PET images were matched and fused into transaxial images (thickness 4.25 mm) using a workstation and software provided by GE Healthcare (Xeleris, General Electric Medical Systems).

Image Analysis

All images were analyzed using a digital reading workstation (Entegra or Xeleris, General Electric Medical Systems). Despite the fact that ^{68}Ge attenuation-corrected data might produce fewer artifacts than MDCT attenuation correction [14], the latter approach was used because of superior image quality of PET and reduced examination time.

All prospectively performed PET/CT scans have been re-evaluated by two readers blinded to the clinical and histological data. In a randomized order, imaging data were uploaded to a Xeleris or Entegra workstation by a medical doctorate. Evaluation of all images was performed in separate reading sessions for CT alone and PET alone. All CT images were interpreted ahead of PET reading. Therefore, the PET images were interpreted with the knowledge of the CT findings. In another session, combined PET/CT images were evaluated.

Analysis of MDCT was performed by two radiologists with an experience of more than 6 years in chest imaging. PET scans were evaluated by two experienced nuclear medicine physicians, and PET/CTs were analyzed by one radiologist and one nuclear medicine physician. Reading was always performed in consensus in case of differing results.

Image Interpretation

The physician had to assess the likelihood of malignancy for each lung lesion using a five-point scale (1=definitely malignant, 2=probably malignant, 3=indeterminate, 4=probably benign, 5=definitely benign), and respective findings were recorded by

Table 2. MDCT findings in comparison to histology

Histology	MDCT			Total
	Malignant	Equivocal	Benign	
Malignant	203	12	1	216
Benign	15	23	22	60
Total	218	35	23	276

MDCT findings (malignant tumor, equivocal finding, benign lesion) in comparison to histology for all patients ($n=276$). Given are the absolute number of patients.

Table 3. PET findings in comparison to histology

Histology	PET			Total
	Malignant	Equivocal	Benign	
Malignant	209	4	3	216
Benign	10	4	46	60
Total	219	8	49	276

PET findings (malignant tumor, equivocal finding, benign lesion) in comparison to histology for all patients ($n=276$). Given are the absolute number of patients.

consensus. If the readers were unable to interpret the lesion as malignant (1, 2) or benign (4, 5), respective lesions were recorded as 'equivocal.' For understanding the underlying reasons for misinterpretations at FDG-PET/CT, all equivocal findings ($n=15$) were re-evaluated with knowledge of the final histological diagnosis.

Criteria for interpreting lesions as benign at MDCT were well-defined pulmonary tumors, lesions with calcifications or fat, consolidations with low or missed contrast enhancement, and tumors without infiltration in surrounding tissue. Calcifications were considered as a benign pattern if the calcification was diffuse, central, or laminar or the calcification had a popcorn configuration [15]. The following CT criteria were used for malignant tumors: presence of tumor spicules, blurred margins, invasion into vessels or into surrounding tissue or bronchial tubes, and inhomogeneous contrast enhancement of the tumor. In the present study, contrast enhancement of the tumor was evaluated by visual interpretation. If there was no normal lung parenchyma between the tumor and normal airway structures or an irregular bronchial wall, an infiltration of trachea or large bronchial tubes was suspected. Criteria for a mediastinal tumor infiltration was replacement of mediastinal fat by soft tissue mass or a mass invading mediastinal structures [6].

Malignancy was diagnosed at FDG-PET in case of any focally increased FDG uptake in projection of the lung parenchyma, which was higher compared to the normal uptake of the mediastinum. Lesions were interpreted as benign if there was no focal FDG uptake in the lung or faint, diffuse uptake of FDG.

Criteria for evaluation of integrated FDG-PET/CT were based on the criteria already described for CT and FDG-PET. With PET/CT, we aimed at further increasing the accuracy of assessing the malignancy based on the addition on the CT scan. Because FDG-PET shows false-positive findings in inflammatory lesions [16], typical inflammatory lesions at CT were regarded benign despite increased FDG uptake. Because FDG-PET shows also false-negative findings especially in small tumors less than 10 mm because of partial volume effects and

Table 4. PET/CT findings in comparison to histology

Histology	PET/CT			Total
	Malignant	Equivocal	Benign	
Malignant	208	4	4	216
Benign	8	11	41	60
Total	216	15	45	276

PET/CT findings (malignant tumor, equivocal finding, benign lesion) in comparison to histology for all patients ($n=276$). Given are the absolute number of patients.

Table 5. Determination of malignancy with MDCT, PET, and PET/CT assuming that equivocal findings are benign

Imaging method	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)	Accuracy % (CI)
MDCT	94 (0.899–0.968)	75 (0.621–0.853)	93 (0.889–0.961)	78 (0.647–0.875)	90 (0.857–0.932)
PET	97 (0.934–0.987)	83 (0.715–0.917)	95 (0.918–0.978)	88 (0.763–0.949)	94 (0.903–0.964)
PET/CT	96 (0.928–0.984)	87 (0.754–0.941)	96 (0.928–0.984)	87 (0.754–0.941)	94 (0.908–0.967)

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and confidence intervals (CI) for determination of malignancy with MDCT, PET, and PET/CT ($n=276$) assuming that equivocal findings are benign.

tumors with rare histologies such as bronchioloalveolar carcinoma or pulmonary carcinoid, FDG-negative lesions were regarded malignant when the lesion was highly suspicious or of a typical malignant tumor. If CT was indeterminate and FDG-PET showed a focal lesion with a high FDG uptake, the tumor was regarded as malignant.

Statistical Analysis

The sensitivity, specificity, positive and negative predictive values as well as the accuracy for detection of malignant lung lesions were calculated for MDCT alone, FDG-PET alone, and integrated FDG-PET/CT. For each of these parameters, the 95% confidence intervals (CI) were calculated. For these analyses, equivocal findings were once assumed as benign and once as malignant to calculate best- and worst-case scenarios.

Weighted K coefficients (Cicchetti–Allison weights) were performed to analyze concordance of each of two methods, where equivocal findings were kept in a separate category. The McNemar test was performed to analyze if the number of equivocal findings are significantly different between the three imaging modalities. This comparison has been performed for the all lung lesions ($n=276$) and in a separate calculation for lung lesions less than or equal to 3 cm ($n=106$) as well as for masses greater than 3 cm ($n=135$). In 35 patients, tumors could not be clearly delineated from neighboring normal structures and were not included in this calculation.

Results

The results concerning determination of malignancy of an intrapulmonary lesion in comparison to histology are shown for each imaging modality in Tables 2, 3, and 4. Benign histology was further confirmed by follow-up data. Mean follow-up of patients was 1014 days (range 18–1747 days). Two deaths occurred in the group of patients with suspected benign lesions not related to malignant disease. At the end of the observation period, median overall survival was not reached.

Assuming that all equivocal findings were benign nodules, the results are as follows (Table 5): The sensitivity, specificity, positive and negative predictive values as well as accuracy for MDCT alone are 94 (CI 0.899–0.968), 75 (CI 0.621–0.853),

93 (CI 0.889–0.961), 78 (CI 0.647–0.875), and 90% (CI 0.857–0.932). With PET alone, the sensitivity and specificity were 97 (CI 0.934–0.987) and 83% (CI 0.715–0.917), the positive and negative values were 95 (CI 0.918–0.978) and 88% (CI 0.763–0.949), and the accuracy was 94% (CI 0.903–0.964). With PET/CT, the sensitivity was 96% (CI 0.928–0.984), the specificity increased to 87% (CI 0.754–0.941), the positive and negative positive values were 96 (CI 0.928–0.984) and 87% (CI 0.754–0.941), and the accuracy reached a value of 94% (CI 0.908–0.967).

The McNemar test indicated significantly higher accuracy of FDG-PET compared to contrast-enhanced CT ($p=0.021$). PET/CT was also significantly more accurate compared to CT ($p=0.010$). However, there was no significant difference between PET and PET/CT ($p=0.710$).

Assuming that all equivocal findings represent malignant tumors, the following results were obtained (Table 6): With MDCT alone, sensitivity and specificity were 99 (CI 0.975–0.999) and 37% (CI 0.246–0.501), the positive and negative values were 85 (CI 0.799–0.892) and 96% (CI 0.781–0.999), and the accuracy was 86% (CI 0.812–0.898). With PET alone, the values were as follows: sensitivity 99% (CI 0.959–0.997), specificity 77% (CI 0.639–0.866), positive and negative positive values 94 (CI 0.899–0.966) and 94% (CI 0.831–0.987), and accuracy 94% (CI 0.903–0.964). The sensitivity, specificity, positive and negative predictive value as well as the accuracy for PET/CT were 98 (CI 0.953–0.995), 68 (CI 0.550–0.797), 92 (CI 0.875–0.950), 91 (CI 0.788–0.975), and 92% (CI 0.879–0.946).

The McNemar test indicated significantly higher accuracy of PET compared to CT ($p<0.001$). PET/CT was significantly more accurate compared to CT ($p=0.002$). PET/CT was also significantly more accurate than PET ($p=0.034$).

Equivocal Findings

With MDCT alone, 13% (35 of 276 patients) of all lesions were classified as equivocal, with PET alone 3% (8 of 276 patients),

Table 6. Determination of malignancy with MDCT, PET, and PET/CT assuming that equivocal findings are malignant

Imaging method	Sensitivity % (CI)	Specificity % (CI)	ppv % (CI)	npv % (CI)	Accuracy % (CI)
MDCT	99 (0.975–0.999)	37 (0.246–0.501)	85 (0.799–0.892)	96 (0.781–0.999)	86 (0.812–0.898)
PET	98 (0.959–0.997)	77 (0.639–0.866)	94 (0.899–0.966)	94 (0.831–0.987)	94 (0.903–0.964)
PET/CT	98 (0.953–0.995)	68 (0.550–0.797)	92 (0.875–0.950)	91 (0.788–0.975)	92 (0.879–0.946)

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and confidence intervals (CI) for determination of malignancy with MDCT, PET, and PET/CT ($n=276$) assuming that equivocal findings are malignant.

Table 7. Comparison of all imaging methods (pair sign) using the McNemar test for patients with lesions greater than 3 cm ($n=135$); given are p values for equivocal findings judged as malignant or benign

Imaging methods	Equivocal findings=malignant	Equivocal findings=benign
PET vs MDCT	0.179	0.045
PET vs PET/CT	— ^a	0.317
PET/CT vs MDCT	0.317	0.083

^aThere were no discordant findings.

and with PET/CT 5% (15 of 276 patients), respectively. The difference was statistically significant for MDCT and PET ($p<0.001$) as well as for MDCT and PET/CT ($p<0.001$).

Comparison of MDCT, PET, and PET/CT

PET and PET/CT showed the highest concordance for the interpretation of malignancy of an intrapulmonary tumor ($K=0.912$; CI 0.866–0.958), irrespective of the size of the lung lesions. The concordance of MDCT and PET was low ($K=0.658$; CI 0.569–0.747). MDCT and PET/CT showed a moderate concordance regarding differentiation of malignant from benign lung tumors ($K=0.726$; CI 0.646–0.806).

Tables 7 and 8 demonstrates a separate analysis regarding lesion size. For lesions larger than 3 cm, only PET and MDCT showed a significant difference regarding determination of malignant tumors if all equivocal findings were interpreted as benign ($p=0.045$). Neither with PET nor with PET/CT pulmonary lesions were judged as equivocal when lung masses had a size greater than 3 cm.

There was a significant difference between FDG-PET and MDCT ($p=0.001$ when equivocal findings were interpreted as malignant; $p=0.033$ when equivocal findings were interpreted as benign) as well as between PET/CT and MDCT ($p=0.007$) for lesions less than or equal to 3 cm irrespective if equivocal findings were interpreted as malignant or benign.

Pitfalls Leading to Misinterpretation at FDG-PET/CT

In 15 patients, PET/CT returned equivocal findings. In four patients with histologically proven nonsmall cell lung cancer, PET/CT could not detect a malignant tumor because of the polygonal configuration of the surrounding parenchymal lesion caused by retention pneumonia. [¹⁸F]FDG uptake was increased in these lesions but not focal.

In seven patients with benign lesions, PET showed a moderate [¹⁸F]FDG uptake. A polygonal parenchymal opacity was detected by MDCT. In five of these patients, core biopsy showed a chronic pneumonia. In one patient each, tuberculosis or cryptogenic organizing pneumonia was proven by histology. In another patient, extensive pleural fibrosis related to asbestosis was misinterpreted at PET/CT as pleural mesothelioma (PET was negative).

In three patients, there was no elevated FDG uptake at PET, but a tumor was visible at MDCT. Therefore, malignancy could not be excluded by PET/CT. All these tumors were histologically proven benign tumors (two hamartomas and one chondrohamartoma; Fig. 1).

In eight patients (2.9%), all three imaging modalities lead to an incorrect diagnosis (Fig. 2).

Discussion

Prediction of the biologic potential of a newly diagnosed intrapulmonary lesion on chest radiography is mandatory for the adequate therapeutic management. A noninvasive method offering high accuracy in distinguishing between benign and malignant tumors is highly desirable to avoid unnecessary invasive procedures or oncologic interventions. Integrated FDG-PET/CT may add important clinical information compared to FDG-PET alone or CT alone. PET/CT has been suggested for superior tumor staging in a large variety of cancers. However, the clinical utility of PET/CT regarding evaluation of indeterminate lung lesions has not been clearly defined.

In this prospective clinical trial, we could demonstrate that FDG-PET alone as well as combined imaging of PET and MDCT provides the highest accuracy for differentiating benign and malignant pulmonary lesions; this could be shown for all pulmonary lesions as well as in the subgroup of patients with lesions less than or equal to 3 cm. This is most likely explained by the contribution of FDG-PET, which has a higher specificity than morphologically based imaging modalities such as MDCT [10]. The sensitivity of FDG-PET for the determination of malignant lung nodules was similar to that of integrated PET/CT (209 of 216 patients [95%] vs 208 of 216 patients [96%]). There was a tendency of lower specificity of PET/CT (41 of 60 patients [68%]) compared to PET (46 of 60 patients [77%]). Because of the typical morphological criteria, inflammatory consolidations could be identified as correlates for increased glucose consumption in benign tumors. Moreover, indeterminate findings could be significantly reduced using FDG-PET or fused FDG-PET/CT images. Because hybrid imaging is now the standard of clinical PET, FDG-PET/CT turns out to be the method of choice for noninvasive assessment of indeterminate pulmonary lesions.

Table 8. Comparison of all imaging methods (pair sign) using the McNemar test for patients with lesions less than or equal to 3 cm ($n=106$); given are p values for equivocal findings judged as malignant or benign

Imaging methods	Equivocal findings=malignant	Equivocal findings=benign
PET vs MDCT	0.001	0.033
PET vs PET/CT	0.059	0.655
PET/CT vs MDCT	0.007	0.007

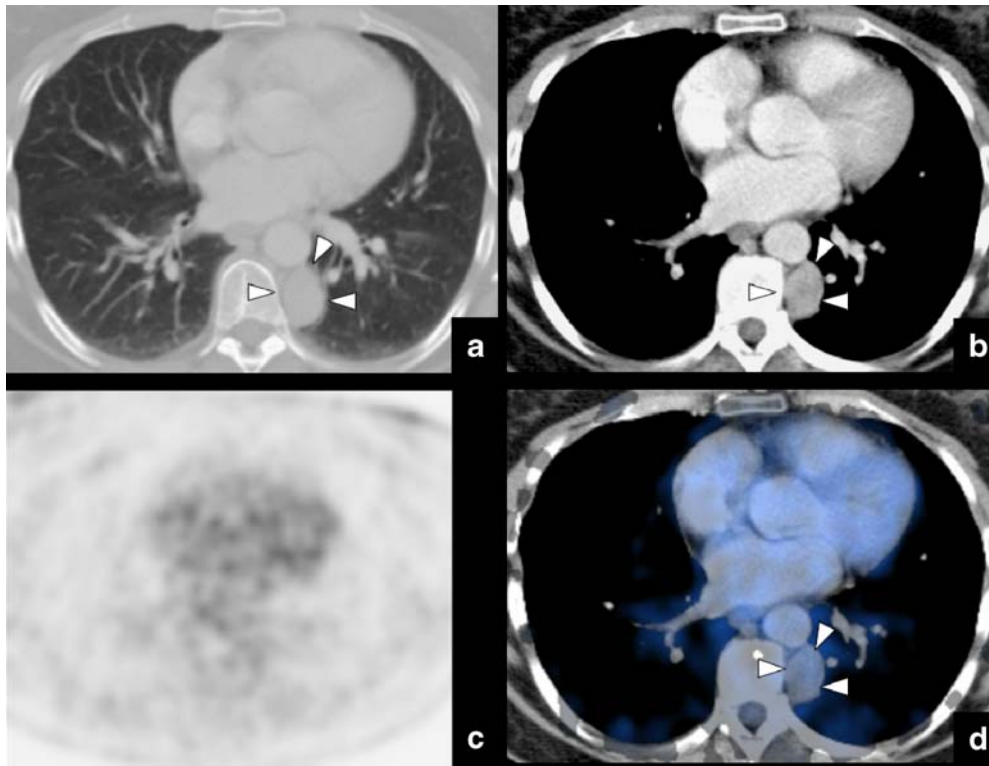


Fig. 1. MDCT (**a + b**), PET (**c**), and PET/CT (**d**) of a patient with a solid lung tumor (*arrowheads*). The lesion showed a low contrast enhancement on MDCT but no increased FDG uptake. PET/CT could not distinguish between a benign lesion and a carcinoid tumor. Hamartoma was proven by histology.

PET/CT showed a very high sensitivity for detection of malignant tumors but is still inferior to histology. Surgical resection remains therefore the reference method for the diagnostic workup of an unclear lung lesion. However, in patients with comorbidity, surgery may be delayed in case of a negative FDG-PET.

MDCT uses typical morphologic features for lesion characterization. Additionally, intravenous application of contrast agent increases sensitivity in predicting the malignancy of a tumor. Contrast enhancement of more than 20% indicates a malignant tumor [5]. By dynamic MDCT, accuracy values more than 90% were described in the literature [17]. The most benefit of contrast-enhanced MDCT is to define and localize a pathologic lesion [18]. In the present study, equivocal findings were observed most frequently at MDCT. A value of 13% was significantly higher than the number of indeterminate lesions present at FDG-PET or integrated PET/CT. The differentiation of an intrapulmonary tumor and surrounding structures remains often difficult at MDCT especially in cases with atelectasis or active inflammation, as they may also present with contrast enhancement [19]. This is one reason for the lower specificity of MDCT for lesion characterization [20]. With MDCT alone, it is frequently impossible to distinguish between a central tumor with subsequent atelectasis from

atelectasis caused by an inflammatory consolidation. Other morphologic alterations such as circular atelectasis or polygonal pulmonary opacities can mimic intrapulmonary tumors at MDCT. In these cases, MDCT findings are interpreted as equivocal.

In our study, FDG-PET as well as PET/CT could significantly reduce the number of equivocal findings. No lesion larger than 3 cm was classified as equivocal with PET as well as with PET/CT. Surprisingly, the addition of MDCT to FDG-PET led to more equivocal findings with PET/CT compared to PET alone (3 vs 5%, nonsignificant) in lung lesions less than or equal to 3 cm. A potential reason for this observation is that at PET/CT, readers tended to interpret pulmonary lesions as malignant, although the consolidation showed no pathologic uptake of FDG. As indicated by our study, equivocal findings on MDCT showing only weak or missing uptake of FDG are most frequently benign lesions, and a short-term follow-up may be appropriate. This strategy could avoid unnecessary surgical interventions [21, 22].

Calculation of standardized uptake values (SUV) of tumoral FDG uptake has been utilized as a quantitative index to better differentiate between benign from malignant tumors. Several studies described a direct correlation between the maximum FDG SUV within the lesion and the likelihood of malignancy [23, 24]. However, in carcinoid

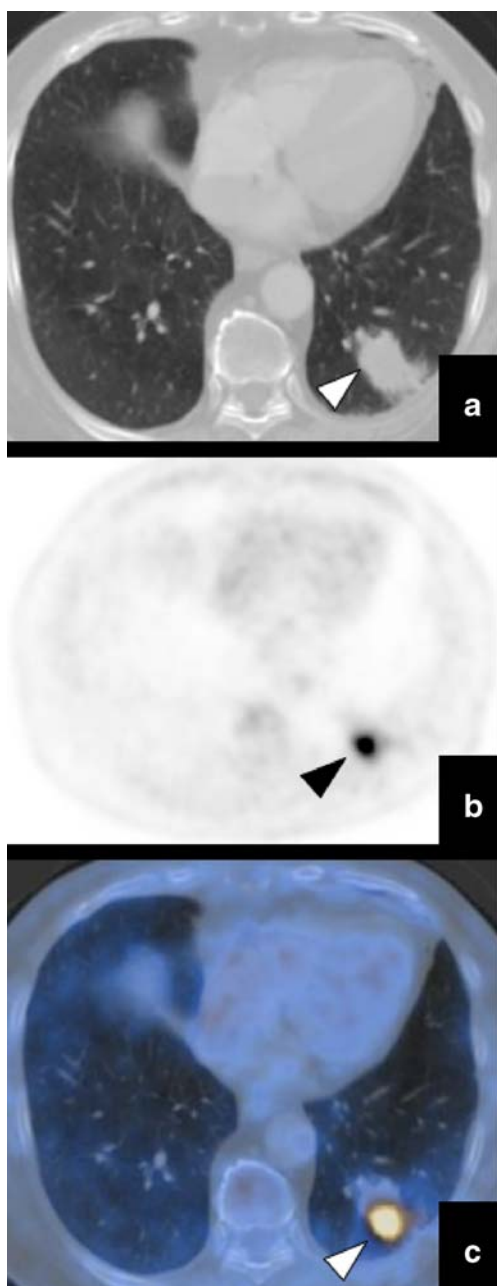


Fig. 2. Solitary pulmonary nodule (*arrowheads*) in the left lower lobe suspicious for malignancy. Presentation of the lesion at MDCT (**a**) and at PET (intense focal FDG-uptake, **b**). Integrated PET/CT is demonstrated in (**c**). All three imaging modalities indicated a malignant tumor, whereas histology revealed pneumonia with carnification.

tumors or bronchiolo-alveolar carcinoma, the SUV is often low, which causes a reduced sensitivity of FDG-PET in these tumor entities [25].

In the present study, malignancy was suspected in case of focally increased [^{18}F] FDG uptake, which was markedly higher compared to a mediastinal blood pool. Visual comparison of tumor uptake to the mediastinal blood pool has been suggested as a standard criterion to differentiate

between benign and malignant tumors. The use of SUVs is still not part of the routine clinical workup of lung lesions. Respective SUVs were not documented in individual patients because it was reported that semiquantitative analysis of FDG-PET data is not superior to visual analysis regarding determination of malignancy [26, 27]. Furthermore, recent publications indicate that a quantitative analysis of FDG SUV as a criterion for characterization of pulmonary tumors does not improve accuracy compared to visual interpretation [15]. Recently, dual time point imaging has been suggested to further increase specificity of PET [28]. Using a threshold of FDG-SUV greater than 2.5 and increasing uptake in the time course as criteria, benign and malignant pulmonary nodules could be differentiated with an accuracy of up to 92%. However, FDG is not a tumor-specific radiopharmaceutical and can also accumulate in inflammatory cells causing false-positive findings. It remains to be determined if calculation of SUVs can increase the accuracy of PET or PET/CT for interpreting lung lesions.

Specificity of integrated FDG-PET/CT was not superior compared to FDG-PET alone. The high specificity of 93% for malignancy on MDCT described by Yi et al. [17] could not be reproduced in our series. This is probably related to patient selection and a smaller patient cohort, different CT protocols (no dynamic CT scans), and different evaluation criteria such as tumor enhancement/washout regarding Hounsfield units utilized in the series of Yi et al.

There are a couple of new CT developments such as computed-aided diagnosis systems suggesting an improvement of accuracy with integrated PET/CT [29]. However, the concrete benefit remains to be determined.

This study has several limitations. Evaluation of MDCT focused on the lung lesions only and potential pathologic findings such as distant metastases or the presence of suspicious mediastinal lymph nodes may increase the accuracy for malignancy using MDCT and FDG-PET/CT. The influence of these features on the final diagnosis of a lung tumor was not evaluated. All images were evaluated blinded without any information about patient's history or risk factors. The likelihood of malignancy because of preknown malignant tumors in patients' histories have not been taken into account. It is also well known that the [^{18}F] FDG uptake of a pulmonary mass and therefore the diagnostic accuracy for determination of malignancy depend on tumor size and decrease especially for lesions smaller than 10 mm [17, 21]. Furthermore, our series predominantly consists of patients with indeterminate lung lesions suspicious for a malignant tumor. Therefore, the prevalence of malignant tumors in the present series is as high as 78%.

Conclusion

FDG-PET and PET/CT were the most precise imaging modalities for detecting malignancy in newly diagnosed lung lesions. The addition of metabolic imaging is therefore recommended for the clinical workup of indeterminate lung

tumors. Compared to helical CT, the number of equivocal findings could be significantly reduced by PET and integrated PET/CT. Surprisingly, there was a nonsignificant or only marginal increase in accuracy using fused PET/CT images indicating that the addition of morphological information to metabolic data does not necessarily cause a significant improvement of accuracy. In patients with equivocal findings at MDCT or [¹⁸F]FDG-PET, PET/CT most frequently determines the correct diagnosis, and short-term follow-up should be performed to avoid unnecessary surgical interventions. A lung biopsy should be performed in all solid pulmonary lesions with an increased FDG uptake irrespective of the morphology on MDCT.

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