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Staging of recurrent and advanced lung cancer with ^{18}F-FDG PET in a coincidence technique (hybrid PET)

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Summary

The aim of this study was to evaluate [^{18}F]fluorodeoxyglucose (^{18}F-FDG) imaging of recurrent or inoperable lung cancer using a hybrid positron emission tomography (PET) device of the third generation. Examinations were compared with the results of conventional staging. Thirty-six patients suffering from recurrent or primarily inoperable lung cancer (29 men, seven women; age 64.8 $\pm$ 12.0 years) were examined using hybrid PET (Marconi Axis γ-PET^2) 60 min after injection of 370 MBq ^{18}F-FDG. The data obtained were reconstructed iteratively. All patients received a computed tomography (CT) scan using either the spiral or multislice technique. All lesions suspicious for primary or recurrent tumour were verified by biopsy; mediastinal lymph nodes were considered as malignant, when positive histology or a small axis diameter of greater than 1 cm measured with CT in addition to progression of clinical course was found. Distant metastases were diagnosed by CT and bone scintigraphy. Using hybrid PET all lesions showed a focally elevated glucose metabolism. Lymph node involvement of the ipsilateral peribronchial and hilar station (N1) was identified in 24/26 cases (92%), in 26/29 cases (90%) of ipsilateral central manifestation (N2) and in 11/13 (85%) cases of central contralateral or supraclavicular lymphatic infestation (N3). Pulmonary spread in hybrid PET was found in 4/8 cases (50%), whereas mainly lung metastases with a diameter of 1.5 cm and smaller were missed. Pleural involvement diagnosed by CT was verified in 4/5 patients. All four patients with bony metastases in conventional staging also presented with positive findings in hybrid PET (8/9 lesions). Concordance with conventional staging was found in 28/36 of patients (78%). In 4/36 patients (11%) unknown sites of tumour were detected leading to therapeutic consequences in three patients after radiological confirmation. Hybrid PET would have led to an understaging in four cases (11%), resulting theoretically in inefficient treatment in two patients. Hybrid PET for ^{18}F-FDG imaging in the staging of recurrent or primarily inoperable lung cancer supplied equal (78%) or more information (11%) compared to conventional staging procedures. Using the information of hybrid PET alone, 11% of the patients would have been understaged. We conclude that hybrid PET has the potential for use as an additional staging tool in this subgroup of patients, providing supplementary information compared to conventional staging modalities. (© 2003 Lippincott Williams & Wilkins)

Keywords: lung cancer, coincidence imaging, hybrid PET, ^{18}F-FDG.

Introduction

In Germany, more than 40 000 deaths are caused by lung cancer every year. About one third of male and about 10% of female cancer mortality is related to this diagnosis [1]. The majority of patients presents with an inoperable stage of disease because of local infiltration of vital organs, contralateral mediastinal lymph node involvement or distant metastases. Radio- or systemic chemotherapy or a combination of both are the treatments of choice for this group of patients [2, 3].

The established staging modalities consist of computed tomography (CT) of the chest and abdomen for

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assessment of morphological and anatomical details of the primary tumour and for the investigation of the most frequent sites of lymphatic and haematogenic spread (mediastinum, pleura, lungs, liver, adrenal glands). For the detection of bony metastases skeletal scintigraphy with ^{99m}Tc labelled phosphonates is performed additionally. The definitive diagnosis has to be established by biopsy.

As a functional imaging modality, positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (^{18}F-FDG) supplies information about the glucose metabolism of tissues [4, 5]. Since malignant tumour cells show elevated FDG uptake, primary tumours and their metastases can be visualized in a whole-body examination, providing usefulness for initial diagnosis and staging. Various reports from the last decade fortify the impact of FDG PET in the management of bronchial carcinoma [6–11].

A major disadvantage of dedicated PET scanning is the relatively high cost. Since the early 1970s there have been first trials to modify gamma cameras for the use of positron emitting radionuclides, and since 1994 dual-head cameras with an optional coincidence mode for the registration of annihilation photons are commercially available. Besides imaging with low energy radionuclides (e.g. ^{99m}Tc, ^{123}I) these systems offer an inexpensive opportunity to conduct FDG examinations [12]. With respect to lung cancer, mainly two topics of interest have been investigated so far: the assessment of significance of solitary pulmonary nodules and the staging of mediastinal lymph nodes [13–15]. Little is known so far about the clinical impact of whole-body staging and its impact on the management of patients with advanced bronchial carcinomas [16–18].

The aim of this study was to evaluate ^{18}F-FDG imaging of recurrent or inoperable lung cancer using a hybrid PET device of the third generation. Examinations were compared with the results of conventional staging (chest, abdominal CT and bone scintigraphy).

Patients, material and methods

A patient group of 36 patients with recurrent or primarily inoperable lung cancer (Table 1) (seven women and 29 men, mean age 64.8 ± 12.0 years, range 39–88 years) was investigated, consisting of three patients with small cell lung cancer (SCLC; all of them with a limited disease stage) and 33 with non-small cell lung cancer (NSCLC; 20 squamous cell carcinomas, seven adenocarcinomas and six undifferentiated or large cell carcinomas).

After an overnight fasting period (>12 h) 300–370 MBq ^{18}F-FDG were injected in a peripheral vein. Hybrid PET acquisition was started 60 min post-injection on a dual-head gamma camera with coincidence option (Axis γ-PET^2 AZ, Marconi Medical Systems, Cleveland, OH) in list mode using an axial filter. The patients were examined from the base of the skull to the pelvis in two or three bed positions (40 min per bed position; field of view per bed position, 42 cm; angular range, 180°; 60 steps, 40 s per step). Data were rebinned into a 128×128 matrix, and reconstructed iteratively (four iterations, low-pass post-filtering, cut-off value 0.25). Uniform attenuation correction according to Chang's first-order method was applied to all data. Using appropriate software, whole-body images were created and represented in sagittal, coronal and transversal slice orientation.

For the purpose of (re)-staging all patients underwent bone scintigraphy (550 MBq ^{99m}Tc-DPD, dicarboxypropane diphosphonate) and CT of the chest and abdomen in spiral or multislice technique (Siemens Somatom Plus 4, Marconi Mx 8000) after intravenous administration of a non-ionic contrast agent. Axial slices were used for interpretation.

The thoracic and abdominal CT scans were interpreted separately by two experienced radiologists

Table 1. Characteristics of the 36 patients with recurrent or inoperable lung cancer included in the study.

Characteristic	*Number of patients (or years)*
Gender (number of patients)	
Female	7
Male	29
Median age (years)	
Median	65
Range	39–88
SD	12.0
History (number of patients)	
Small cell carcinoma	3
Squamous cell carcinoma	20
Adenocarcinoma	7
Large cell or undifferentiated carcinoma	6
Newly diagnosed vs recurrent disease (number of patients)	
Newly diagnosed disease	26
Recurrent disease	10
Tumour stage (number of patients)	
T1-4N0M0	6
T1-4N0M1	1
T1-4N2M0	13
T1-4N2M1	4
T1-4N3M0	3
T1-4N3M1	9

blinded to the PET findings. Hybrid PET and bone scans were analysed by two experienced nuclear medicine physicians. Lesions were classified pathologically if focally increased tracer uptake surpassing the normal range of the surrounding tissue was noticed. If the observers disagreed about a lesion, a consensus was obtained for definite interpretation of the FDG scan. For semiquantitative analysis, regions of interests (ROIs) were drawn around the focally increased uptake of the primary lesion and at the contralateral shoulder girtle as background ROI. The ratio of lesion-to-background counts (maximum lesion versus background; L/B ratio) was calculated. The results were generated for the assessment of correlation between tumour size and intensity of FDG uptake and did not influence the scan interpretation.

The hybrid PET findings were compared to the sum of the other staging modalities. If there were still unclear results, selective examination of the interesting region was performed (e.g. cervical CT) or earlier image files were reappraised. All staging examinations were performed in a period not exceeding 2 weeks before or after the hybrid PET study (and without any tumour specific therapy during this time), but most of the staging procedures were completed during 1 week.

Results were confirmed by histology. Mediastinal or distant lesions were corroborated by mediastinoscopy or by radiological follow-up investigations.

The study was approved by the competent authorities in accordance with the ethical standards laid down in the Declaration of Helsinki.

Results

Primary lesions

On the basis of visual analysis 36/36 primary lesions showed a focally increased uptake in the hybrid PET investigation (Figs 1 and 2). There was a weak positive correlation between lesion size and the intensity of FDG accumulation ($r = 0.36$) (Fig. 3).

After the CT scans had been examined 34/36 (94%) of the lesions were considered as malignant; in two cases the presence of scar tissue was revealed.

Lymph node metastases

Lymph node involvement of the ipsilateral peribronchial and hilar station (N1) was identified in 23/26 cases (89%;

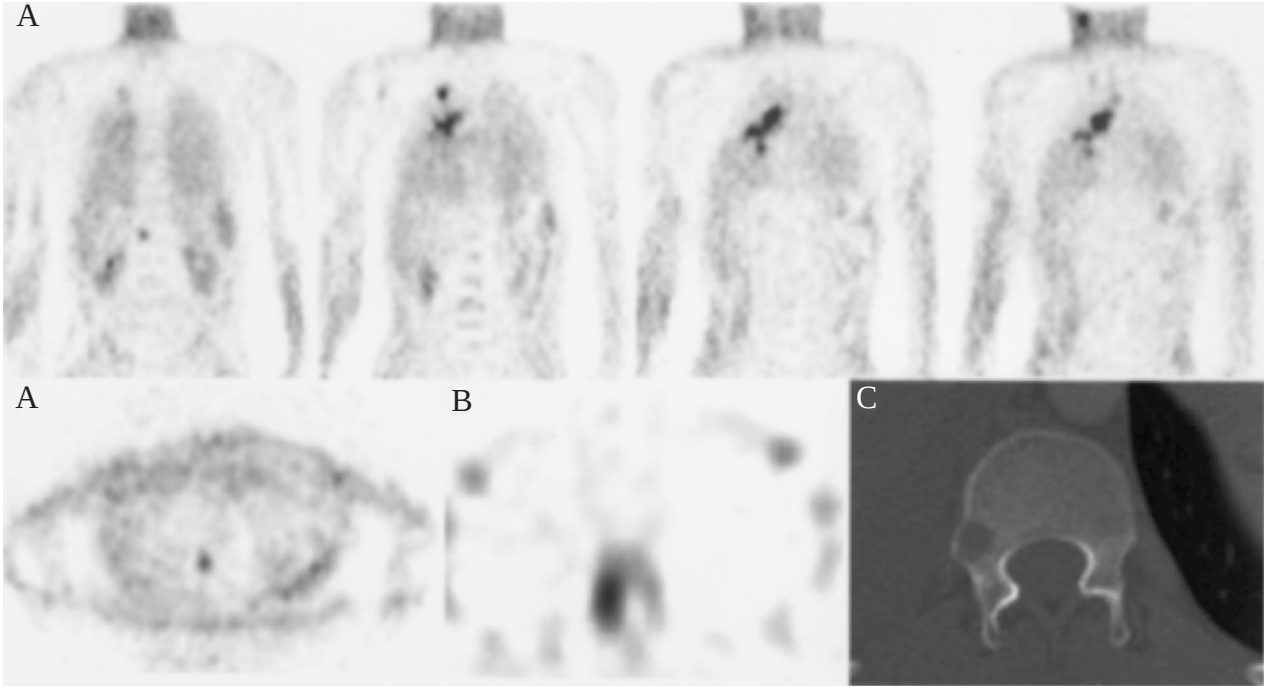

Fig. 1. Hybrid fluorodeoxyglucose positron emission tomography (FDG PET) (A) of a 39-year-old male patient with adenocarcinoma of the apical right lobe of the lung with extensive metastatic involvement of peribronchial, hilar, central mediastinal and cervical lymph nodes. A small metastasis to the right pedicle of 12th thoracic vertebra (panel C: computed tomography in bone window; diameter of the lytic lesion 1.1 cm) shows good dermarcation with hybrid PET and bone scintigraphy single photon emission computed tomography (B) as well.

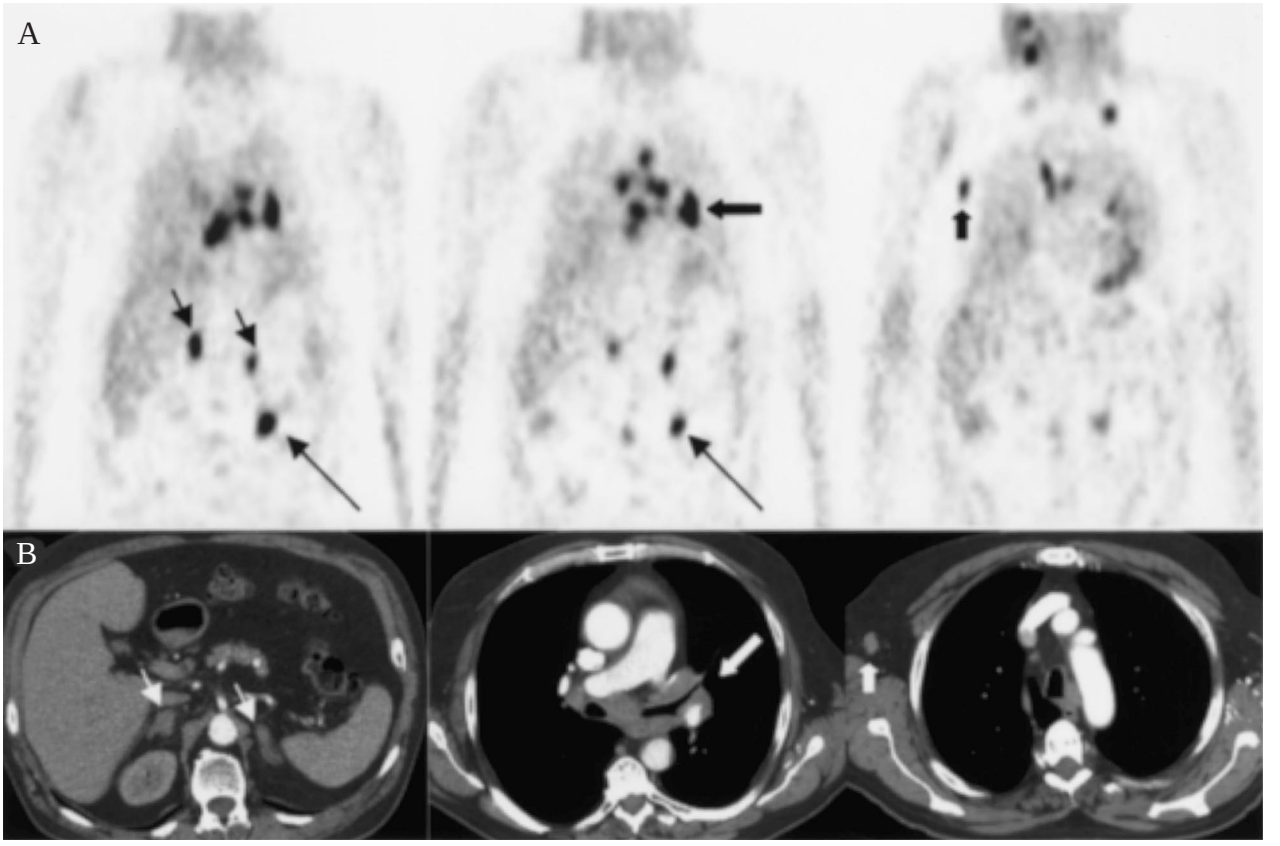

Fig. 2. Hybrid FDG PET (A) and multislice computed tomography (CT) (B) showing a 63-year-old male patient with a squamous cell carcinoma infiltrating the left main bronchus (long fat arrows) with metastatic involvement of bilateral mediastinal, scalenic and cervical lymph nodes. Additionally, spread to the right axilla was detected (short fat arrows, right column) by the FDG investigation, this lesion could be confirmed retrospectively by CT. Also, adrenal metastases can be seen (short arrows), the caudal hot spot on the left side (long arrow) is caused by renal activity.

CT 25/26, 96%). According to the TNM (T-primary tumour, N-regional lymph nodes, and M-distant metastasis) classification continuous extension of the primary tumour towards ipsilateral peribronchial or hilar lymph nodes was considered N1 positive [19]. The short axis diameters of the false negative lymph nodes in hybrid PET were 0.8 cm, 1.1 cm and 0.9 cm, respectively. Right positive hybrid PET findings which were missed in CT occurred in two patients. One presented with recurrent disease accompanied by fibrotic tissue after primary resection. Another had multiple lymph nodes, all smaller than 1 cm (maximum 0.9 cm).

The involvement of ipsilateral mediastinal and/or subcarinal lymph nodes (N2) correlated with positive PET findings in 26/29 cases (90%; CT 27/29, 93%). The lymph nodes not visible on the PET scan presented with measurements of 1.0 cm, 1.2 cm and 1.8 cm, respectively.

Metastases to contralateral mediastinal, hilar and/or bilateral scalene or supraclavicular lymph nodes (N3) showed a positive hybrid PET scan in 11/13 cases (85%; diameters of the false negative lesions, 1.1 cm and 1.6 cm; CT showed all N3 lymph nodes at initial examination).

Pulmonary/pleural metastases

Pulmonary spread in eight patients was accompanied by a positive hybrid PET finding in four cases (50%), whereas in three patients with multiple round lesions with a diameter of 1.5 cm or less, hybrid PET was false negative. In one patient pulmonary metastases suspected in CT could be ruled out by a negative hybrid PET which was confirmed by follow-up.

Involvement of the pleura was found in five patients by CT of chest. In four cases (80%) the FDG examination also revealed a pathological finding. The false negative hybrid PET appeared in a patient with adenocarcinoma who, in the CT, presented with an extensive affection of the left pleura (maximum thick-

ness, 0.9 cm). In this case the FDG examination also showed a relatively low uptake of the primary tumour as well as a false negative result of a mediastinal lymph node metastasis.

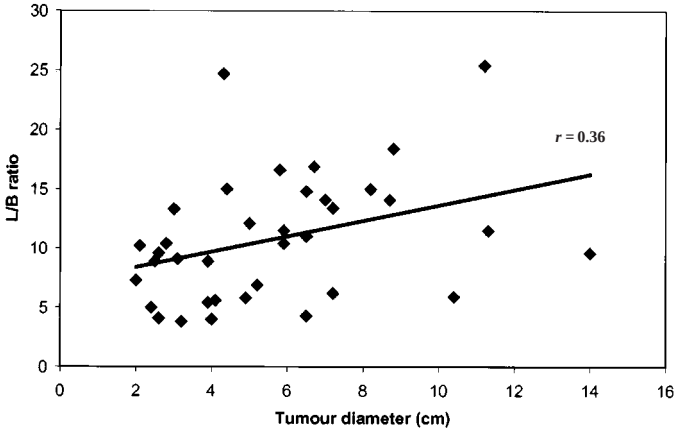

Fig. 3. The relation ($r = 0.36$; Pearson correlation coefficient) between tumour size (maximum diameter) and intensity of uptake (L/B ratio, lesion-to-background ratio).

Bony metastases

In three patients nine bony metastases were found by conventional staging. Eight of the lesions were also detected by hybrid PET (sensitivity 89%) (Fig. 1). The false negative finding in one patient was located in a rib. In another patient, a hybrid PET finding suspicious for metastatic spread in the pelvic skeleton remained unconfirmed.

Other sites of metastatic disease

One solitary liver metastasis was found with hybrid PET which was missed by abdominal computed tomography; the lesion could be identified in the follow-up CT scan (Fig. 4). In a second case, a suspicious CT finding in the liver had no correlation in the hybrid PET investigation. Follow-up produced no evidence of malignancy.

Similarly to the low incidence of hepatic spread in our patient group, a positive PET finding of adrenal metastases was found in concordance to CT (Fig. 2) only in one case.

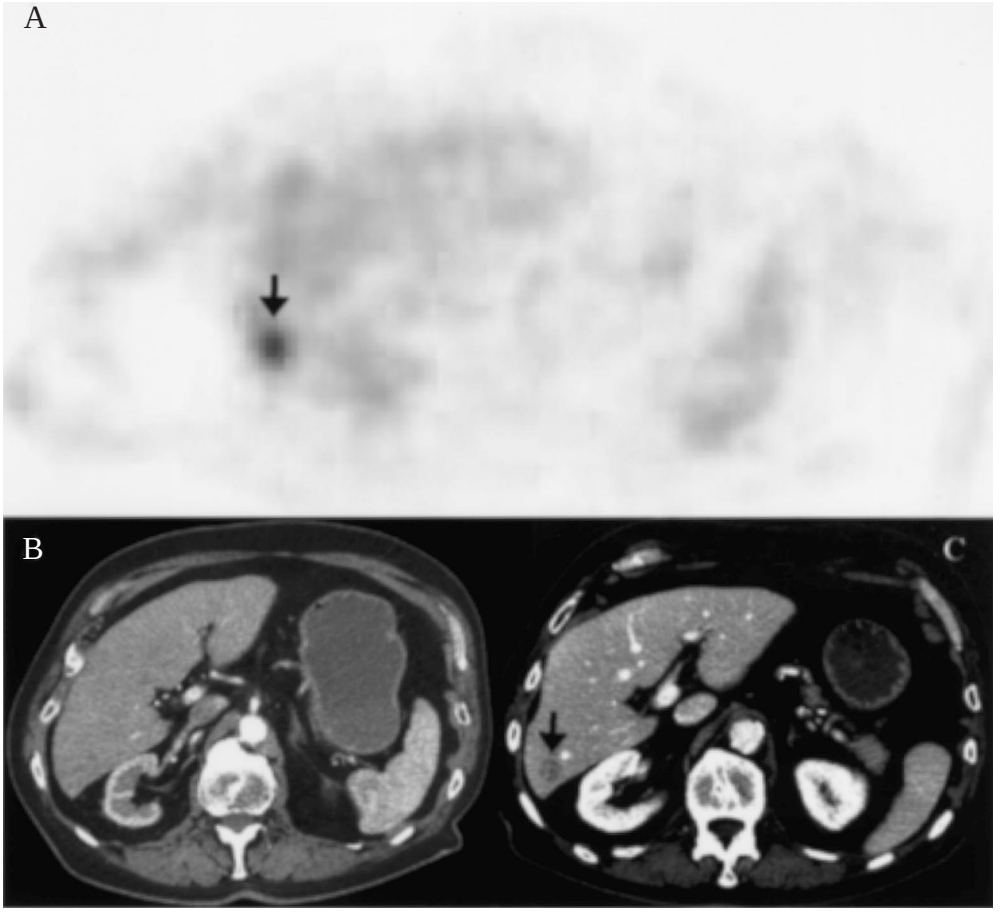

Fig. 4. Hepatic metastasis (arrow) detected by FDG PET in the coincidence technique (A) and abdominal CT (C; with portal venous contrast) but missed by the earlier thoracal CT including the upper abdomen (B).

In one patient, hybrid PET revealed a finding suspicious for malignancy of the large bowel in two repeated studies. This potential lesion could not be affirmed, because colonoscopy was refused by the patient and abdominal CT and sonography supplied equivocal findings.

Unknown cervical lymph node involvement cranial of the hyoid was discovered by hybrid PET in three patients and confirmed by CT (Figs 1, 2).

Comparison of hybrid PET to the sum of conventional staging modalities

Concordance with conventional staging methods was found in 28/36 of patients (78%), in 4/36 (11%) unknown and radiologically confirmed sites of tumour were detected. Consequently, equal or superior diagnostic information was achieved by hybrid PET in 32/36 (89%) of patients. These findings led to therapeutic consequences in three patients. In four patients (11%) hybrid PET alone would have resulted in an understaging, with the theoretical consequence of inefficient treatment in two patients.

Discussion

FDG PET has been described as being of significant impact for the initial diagnosis and the staging of lung cancer [6–9, 20–26]. Although it is known to be superior to conventional imaging modalities (i.e. CT) with respect to mediastinal staging and the detection of distant metastases, and is potentially cost effective at present [21], its availability as a widely used clinical tool is still limited [21, 27]. One important precondition is the availability of a cyclotron for synthesizing ^{18}F-FDG. In Germany, as in many other western countries, this problem was solved by a commercial delivery system [28, 29]. A more restrictive factor is the high cost associated with a dedicated PET camera system. This has raised interest in the use of single photon emission computed tomography (SPECT) cameras for the detection of the high energy photons resulting from positron decay. After a series of comparative studies of SPECT with 511 keV collimation and dedicated PET systems it became obvious that the sensitivity for the detection of lesions smaller than 2 cm was very low and therefore a clinical impact for oncological studies was not to be expected [12, 30, 31]. This is the main reason that gamma cameras which are capable of detecting coincidental events caused growing interest and prevailed over the collimator based technique [32, 33].

The lower image quality of these devices, compared to dedicated PET scanners was improved by stepwise modifications. In particular, the capacity of count rates could be raised markedly (e.g. Picker Prism 2000 XP-PCD: 8 kcounts/s trues; Marconi Axis γ-PET^{2}AZ: 30 kcounts/s trues). There is little evidence whether hybrid PET can play a role in the context of oncological studies known to be proven indications for dedicated FDG PET. With respect to head and neck tumours Ak *et al*. [13] and Dresel *et al*. [34] reported similar results for both techniques. Relating to other malignancies, such as lung cancer and lymphoma, data are insufficient to draw definite conclusions. Generally, a lesion size greater than 15 mm generates a comparable diagnostic result, whereas in smaller tumours the sensitivity decreases for hybrid PET [13, 15, 17, 34, 35]. Our study raises the question whether hybrid PET is appropriate for diagnostic purposes in patients with inoperable or recurrent lung cancer.

As an important presupposition, for the purpose of staging, every primary or recurrent bronchial carcinoma in our series presented with a focally increased glucose metabolism, the smallest of which was 2.0 cm. These data correspond with the current literature reporting false negative findings mainly in lesions smaller than 1.5 cm and in bronchio-alveolar carcinoma, a histological subentity of adenocarcinoma not occuring in our collection [15, 17, 36, 37]. The comparative poor dependency between FDG uptake and lesion size (Fig. 3) correlates with the observation of Vesselle *et al*. [22] showing the influence of other factors. These were proliferation markers and tumour differentiation on the intensity of tracer accumulation.

The interpretation of results concerning mediastinal lymph node involvement was difficult for two reasons. (1) In many cases it was not possible to determine the absolute number of nodes, since metastatic disease frequently leads to tumour conglomerates. (2) Surgical assessment by mediastinoscopy to confirm the diagnosis of hybrid PET was not performed in patients suffering from advanced or recurrent tumour disease. Although the sensitivity of hybrid PET (N1, 89%; N2, 90%; N3, 85%) was higher than reported figures of about 60–70% concerning sensitivity while using–single time–chest CT based on the size criterion (short axis diameter >1 cm) [9, 21], we found no superiority in comparison to morphological imaging. One possible explanation is that our patient group with advanced or recurrent disease presented with a higher prevalence of mediastinal involvement than study groups dealing mostly with newly diagnosed patients [7, 25]. In agreement with other studies our results show that it is difficult to detect small lymph node metastases with hybrid PET [15, 17]. In one case, even a malignant mediastinal lymph node with a size of 1.8 cm diameter was not detected. We anticipate that the contrast in this anatomical region is too low for

the demarcation of smaller pathological changes, which is a requirement for the nodal staging in bronchial carcinoma. With these uncertainties, camera based FDG PET examinations cannot yet be rated as equivalent to dedicated systems in the assessment of nodal involvement in lung cancer [7]. The results of former studies finding a similar overall diagnostic accuracy of dedicated and hybrid FDG PET – mainly using a second generation device – concerning the nodal status cannot be confirmed [13, 15].

However, the detection of unknown metastases (three of 36 cases, 8%) to cervical lymph nodes cranial of the hyoid, which have to be rated as M1-lesions, was a main aspect of our study, since these findings led to a significant modification of the therapeutic strategy (e.g. extension of the radiation field).

Acceptable results were obtained in cases of carcinomatous pleurisy. Only one out of five patients with pleural lesions was misjudged by hybrid PET. These figures are similar to studies performed with dedicated PET systems investigating indeterminate pleural processes [38]. With regard to pulmonary spread there were discrepant findings between CT and hybrid PET in 50% of cases (four of eight patients). Even though false negative lesions had diameters of 1 cm or less it is evident that the constellation of small, non-specific pulmonary nodules in CT cannot be sufficiently ascertained by camera based PET. Particularly in cases with relevant clinical consequences (stage III/IV; radiation therapy vs. chemotherapy) the clinical value of hybrid PET is limited, even when small sized lung nodules, which are positive in CT, were diagnosed true negative by hybrid PET. One major reason may also be the contrast between lesion and surrounding tissue. Since no transmission measured attenuation correction was applied, the pulmonary signal was almost as intensive as the hepatic FDG accumulation.

Metastases to the skeleton detected by the conventional staging modalities were found with hybrid PET in 8/9 lesions (89%), whereas one additional lesion suspicious for metastatic spread to the pelvic skeleton remained unconfirmed. No patient would have been understaged concerning the ossary M stage. These results correlate well with a recent report on the diagnostic power of hybrid PET using FDG detecting skeletal involvement in patients with breast carcinoma [39].

Metastatic spread to the adrenal glands and to the liver was correctly diagnosed with hybrid PET, while CT detected the hepatic lesion only during follow-up. One suspicious lesion detected by CT, and not visible by hybrid PET, was also ruled out as cancerous by follow-up. The number of metastases in our patient group is small which makes it difficult to draw conclusions. However, our results indicate that hybrid PET may be equally powerful as dedicated PET for the detection of metastatic disease to the adrenal glands and with limitations (higher background) also for hepatic involvement.

Hybrid PET detected previously unknown distant metastases in 11% of the cases. Similar results were reported by Hellwig *et al*. [7] in a meta-analysis (12%) including 13 studies on whole-body staging of bronchial carcinoma by means of dedicated FDG PET. Therefore, it is suggested that hybrid PET supplies equivalent information about the M stage of bronchial carcinoma when compared to dedicated PET.

Because of the fact that in 11% of the cases hybrid PET would have led to an understaging of patients by missing lymph node involvement our results do not support a modification of conventional staging modalities at this time. As mentioned above, the crucial rationale seems to be unfavourable contrast between lesion and background, whereas insufficient resolution does not appear to be a disadvantage when compared to dedicated PET. An attenuation correction applied to the data using a transmission map is thought to have a large impact on image quality especially in examining lungs and mediastinum. Recent improvements in camera based PET devices include the possibility for measured attenuation correction. Even if our experience on imaging lung cancer with this updated PET systems is still limited, results are very encouraging.

There are some limitations of our study that should be addressed. It would have been ideal to have simultaneous images of the patients with a dedicated PET system, to clearly establish the efficacy of the coincidence technique in comparison to that of ring PET systems. A second scan using a dedicated system would have required an additional injection of ^{18}F-FDG because both systems are placed in different locations. This was not feasible due to ethical reasons. In addition, there is a high prevalence of disease which may favour sensitivity and makes specificity difficult to assess. However, the aim of the study was to compare hybrid PET to other imaging modalities which were also performed under the same condition of prevalence, therefore making them comparable.

Conclusion

Using hybrid PET for ^{18}F-FDG imaging in the staging of recurrent or primarily inoperable lung cancer supplied equal (78%) or more information (11%) compared to conventional staging procedures (CT and bone scintigraphy), 11% of the patients would have been understaged using the information of hybrid PET alone. Although we found no superiority of the method in the judgement of

mediastinal involvement we conclude that hybrid PET of the third generation has the potential to be used as an additional staging tool in this subgroup of patients with advanced disease, providing supplementary information. This applies primarily for the staging of distant metastases.

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