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Original Paper

18F-FDG Whole Body Positron Emission Tomography (PET) in Patients with Unknown Primary Tumours (UPT)

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The management of patients with unknown primary tumours (UPT) often includes a large number of radiographical studies and invasive procedures, but the occult primary tumour is detected in less than 25%. In this prospective study we explored whether non-invasive whole body PET scans using FDG (18-F-fluorodeoxyglucose) are of clinical value in detection of UPT. Whole-body FDG-PET scans were performed in 20 patients following standard staging procedures according to histology. PET results were verified either histologically or by the clinical course of the disease. 11 patients had neck metastases (5 squamous cell, 5 adenocarcinomas and 1 poorly differentiated carcinoma). The remaining patients had metastases located in bone (3), bone marrow (1), brain (1), pericardium (1), skin (1), pleura (1) and chest wall (1). All metastatic lesions were visible with PET. In 13 patients PET suggested the site for the primary tumour and this was verified in 9 (45%), either histologically or by the clinical course of disease. 8 of these had primary lung cancer and 1 had carcinoma at the basis of the tongue. In most patients PET had no treatment related implications. 3 patients with non-small cell lung cancer (NSCLC) received chemotherapy prompted by the PET result. The rest received either radical radiotherapy to the head and neck region (7), palliative radiotherapy to the metastatic lesion (8), chemotherapy based on signet ring cell carcinoma in bone marrow (1) or no therapy (1). These results indicates that PET is useful in UPT preceding expensive and invasive diagnostic procedures and can result in a faster diagnosis in approximately one third of the patients who then avoid unnecessary extensive procedures. Furthermore, a larger proportion of patients will receive treatment aimed at the correct diagnosis. A prospective cost-effectiveness analysis of PET in this setting is warranted

Key words: 18-F-fluorodeoxyglucose (FDG), positron emission tomography (PET), unknown primary tumour
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INTRODUCTION

THE INCIDENCE of unknown primary tumours (UPT) is between 0.5% and 6.5% [1, 2]. Only 15–20% of newly diagnosed cancer patients with metastatic disease from an unknown primary tumour have radiological and nuclear medical imaging of their lungs, bones, brain, kidneys, and gastrointestinal tract [3], and common diagnostic procedures are rarely able to detect the occult primary tumour. The most convincing demonstration of the inability of radiological studies to locate the primary site in patients with metastatic non-squamous carcinomas of unknown origin is the report by Nystrom and colleagues [4]. In their study of 266 patients, upper and lower gastrointestinal series, intravenous pyelograms and chest radiographs were performed as part of the diagnostic evaluation. Of a total of 136 patients who had no postmortem examination, the authors were able to confirm the primary tumour in only 22. Furthermore, of the remaining 130 patients who had autopsies, 25 were found to have

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false-positive X-ray studies for the primary site. Not only were the majority of studies negative, but many of the positive reports proved to be false-positive. In addition, chest X-rays thought to be characteristic of primary lung cancer frequently represented metastatic lesions (43%).

The large number of radiological studies in patients with UPT can be time consuming and costly. Despite extensive examinations, the primary tumour will never be found in the majority of cases (70–80%), and in most patients only palliative treatment can be offered. A majority of the patients suffer from advanced gastrointestinal cancer or lung cancer for which cure is rare [1]. Accordingly a thorough examination for treatable tumours is most appropriate and cost-effective. In patients with adenocarcinomas this includes prostate, breast, ovary, endometrial and thyroid cancer. In cases of undifferentiated tumours this includes lymphomas, germ cell tumours and neuroendocrine tumours. In patients with squamous cell carcinoma in the upper two thirds of the neck region an extensive examination for head and neck cancer should be performed. However, even such dedicated exploration for a primary tumour employ many radiological studies. This emphasises the need for a simple and better method.

Positron emission tomography (PET) is a non-invasive procedure and whole-body PET with the tracer 18-F-Fluoro-2-deoxy-glucose (FDG) has proven very sensitive in a variety of cancers [5, 6], including head and neck cancer [7], lung cancer [8], breast cancer [9], lymphomas [10], colorectal cancer [11] and melanomas [12]. The method is based on the increased glycolytic activity in cancer cells [13]. FDG is a glucose analogue entering the cell parallel to glucose. However, after phosphorylation no further degradation takes place and FDG is trapped in the tissue and this is utilised in the study of tumours [14]. When FDG decays, annihilation with an electron takes place, resulting in emission of two 511 keV gamma photons in opposite direction. After coincident detection and reconstruction, areas of focal increased FDG uptake can be visualised in axial, coronal and sagittal planes.

This prospective study was carried out in order to investigate the value of FDG whole-body PET in patients with UPT after extensive standard diagnostic procedures. The purpose was to investigate whether PET was able to localise the primary tumour and thereby reduce the number of examinations performed in this group of patients. This might save the patients for expensive and unnecessary invasive examinations and even lead to improved treatment.

PATIENTS AND METHODS

Patients

20 patients referred to Rigshospitalet, Copenhagen University Hospital, from April 1996 to September 1997 were enrolled. A signed informed consent was obtained from all the patients and the study was approved by the local ethical committee. The patients were consecutively referred to the Finsen Centre from county hospitals after have performed routine diagnostic procedures as discussed below. Patients from the local area had diagnostic tests performed at the National University Hospital, Rigshospitalet. Inclusion criteria were aged 18–75 years with biopsy proven metastatic malignant disease and an unknown primary tumour following complete physical examination, X-ray and/or computer tomography (CT) examinations and routine laboratory evaluation.

Diagnostic procedures

The diagnostic procedures were performed according to the primary histology of the metastases (Table 1). Endoscopic head and neck examinations were performed at specialised departments with the patients fully anaesthetised.

Positron emission tomography

PET was performed with a GE Advance PET scanner (General Electric Medical Systems, Milwaukee, Wisconsin, U.S.A.). Data was collected in multiple, continuous transaxial 4.25 mm thick slices. The axial field of view was 15 cm and the resolution in the axial plane (FWHM) was 5 mm. All patients fasted at least 6 h prior to the PET study. 40 min after injection of 10 mCi FDG (350–400 MBq) in a cubital vein the patient emptied the bladder and was placed in the scanner. Static emissions in 2-D acquisition were obtained with 7–8 consecutive frames, each of 5 min emission, from the level of the proximal femur to the vertex of the cranium. A transmission scan for attenuation correction was not performed.

All PET scans were performed within 4 weeks after initial diagnostic procedures. Images were reconstructed in a 256×256 transaxial matrix and resliced in coronal and sagittal slices with a spacing of 4.25 mm. A semiquantitative analysis of FDG uptake was not performed. Artifactual and physiological soft tissue FDG accumulation was taken into account during the visual interpretation of PET [15] by nuclear medicine specialists with significant PET experience (AE and LF). At the time of visual interpretation relevant correlative

Table 1. *Diagnostic procedures according to histology*

Histology	Diagnostic procedures
Adenocarcinoma	
Female	Mammography, palpation of the thyroid gland and neck thyroid scintigraphy, gynaecological examination, abdominal ultrasonography or CT.
Male	Serum-PSA, palpation of prostate and mammae region, palpation of the thyroid gland and neck and thyroid scintigraphy.
Squamous cell carcinoma	
Cervical	Extensive oto-rhino-laryngeal exploration, fibreoptic endoscopy and cervical CT.
Inguinal	Abdominal CT, cystoscopy and anoscopy.
Poorly differentiated carcinoma	
Age < 60 years	Abdominal and thoracic CT, serum HCG-β and AFP.

CT, computed tomography; PSA, prostate specific antigen; HCG, human chorionic gonadotropine; AFP, alpha-fetoprotein.

Table 2. Patient characteristics

Patient no.	Gender	Age (yrs)	PS	Histology	Localisation of metastases
1	Female	52	0	SCC	Cervical lymph node
2	Female	64	2	PDAC	Pericardium
3	Male	64	1	SCC	Cervical lymph node
4	Male	44	2	PDAC	Subcutis
5	Female	51	1	PDC	Bone (humerus)
6	Female	47	1	WDAC	Brain
7	Male	47	1	PDA	Bone (femur)
8	Female	61	1	PDC	Cervical lymph node
9	Female	74	1	PDA	Cervical and axillary lymph node
10	Female	75	1	PDA	Cervical lymph node
11	Female	34	2	PDA	Supraclavicular lymph node
12	Male	26	2	WDA*	Bone marrow
13	Female	27	2	PDC	Pleura
14	Female	52	1	WDA	Supraclavicular and axillary lymph node
15	Male	57	1	WDA	Bone (scapula)
16	Male	35	1	SCC	Cervical lymph node
17	Male	69	1	PDA	Chest wall (anterior)
18	Male	57	1	SCC	Cervical lymph node
19	Female	56	0	SCC	Cervical lymph node
20	Male	62	1	SCC	Cervical lymph node

SCC, squamous cell carcinoma; PDA, poorly differentiated adenocarcinoma; PDC, poorly differentiated carcinoma; WDA, well differentiated adenocarcinoma; PS, performance status. *Signet ring carcinoma.

information concerning histology and location of metastatic lesions were available. Pathological uptake was described as focal areas visual in all three planes with the same coordinates (x, y, z), and, if a suspected lesion was confirmed as the primary tumour, either histologically or during follow-up, the PET result was defined as true-positive (TP). If a suspected lesion could not be confirmed, the PET result was defined as false-positive (FP). If PET was negative, but the primary was later identified, the PET result was defined as false-negative (FN), whereas PET was defined as not confirmed (NC) if the primary remained unknown. PET was defined as true-negative (TN) if no primary site was suggested, although the suspected metastatic lesion had pathological FDG uptake, and this turned out to be the primary tumour.

Further diagnostic procedures were guided by the PET results. Areas of increased focal uptake were verified histologically if the result could indicate a treatment with curative or significant palliative potential. Otherwise, the patients were followed regularly at the referring hospital until death or a verification was obtained by the clinical course of the disease. At the end of the study all radiographs were reviewed by an experienced specialist in diagnostic radiology.

Table 3. The results of the PET evaluation of site of the primary tumour

Patient no.	Site of metastasis	Suggested primary site	Therapy	Confirmed primary tumour	PET result
1	Pericardia	Lung	No	Lung	TP
2	Bone	Lung	No†	Lung cancer	TP
3	Neck	Lung	No†	Lung cancer	TP
4	Neck	Lung	No†	Lung cancer	TP
5	Neck	Lung	CT	Lung cancer	TP
6	Pleura	Lung	CT	Lung cancer	TP
7	Neck	Lung	CT	Lung cancer	TP
8	Bone	Lung	No†	Lung cancer	TP
9	Neck	Tongue	RT	Tongue	TP
10	Neck	Tongue	RT	Not found	FP
11	Subcutis	Thyroid	No	Pancreatic cancer	FP
12	Neck	Ventricle	RT	Not found	FP
13	Neck	Tongue	RT	Not found	FP
14	Brain	None	No†	Not found	NC
15	Bone	None	No†	Not found	NC
16	Neck	None	RT	Not found	NC
17	Neck	None	RT	Not found	NC
18	Neck	None	No*	Tongue	FN
19	Thorax	None	No†	Mesothelioma	TN
20	Bone	None	CT	Gastric cancer	FN

*The patient received standard radiotherapy when the primary tumour was found and staged as T1N2bM0 †Palliative radiotherapy only. RT, radiotherapy; CT, chemotherapy; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive; NC, not confirmed.

RESULTS

20 patients were included in the study. Table 2 shows age, sex, histology and localisation of the metastases. The majority of the patients (55%) presented with metastatic cervical lymph nodes, 6 with squamous cell carcinoma and 5 with adenocarcinoma. The metastatic lesions were clearly visible with PET in all patients and additional suspected lesions were detected in 4 patients. However, these were not histologically confirmed. In 13 patients (65%) PET suggested a location for the primary tumour (Table 3) and this was confirmed in 9 patients (pts 1–9), either histologically, in 3 patients, or during the clinical course of the disease, in the latter 6 patients. 6/9 patients with a true-positive PET had a previously performed CT which was negative. In the other 3 patients plain X-rays were negative and a CT was not performed. After a radiological review the PET diagnosis was retrospectively confirmed by CT or plain X-ray in 2 patients with primary adenocarcinoma of the lung (Figure 1).

8 of the 9 patients had a primary lung cancer and 1 had a histologically confirmed primary carcinoma of the lingual base (Figure 2). Of 4 patients with a false-positive finding (pts 10–13), 2 were suspected of having a primary tumour in the tongue, 1 in the ventricle and 1 in the thyroid gland. The latter had a normal neck ultrasonography. This patient (pt. 11)

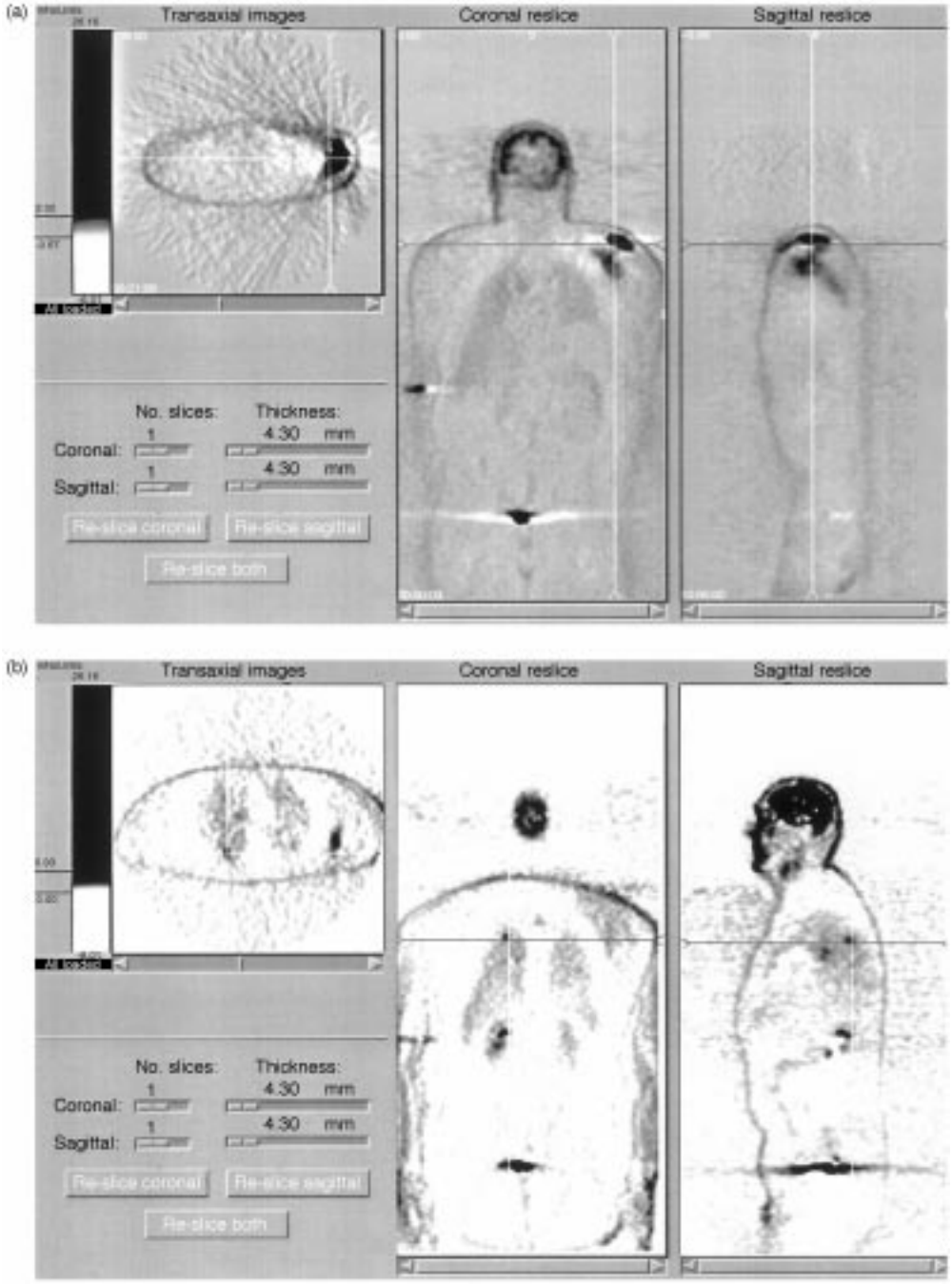

Figure 1. (a) Transaxial, sagittal and coronal PET image of a patients with metastatic adenocarcinoma of the left scapula (a) and a primary lung cancer in the right upper lobe (b) indicated by focal increased FDG uptake (+). Physiological FDG uptake is seen in the brain, salivary glands, kidney and bladder.

presented with multiple subcutaneous metastases, a biopsy showed adenocarcinoma. All the subcutaneous metastases were visible with PET, but the patient died shortly afterwards due to rapid progression. A primary pancreatic carcinoma was found at autopsy. The other 3 patients received invasive endoscopic procedures with biopsies which were negative.

In 4 patients (pts 14–17) neither PET nor the clinical course revealed the primary tumour and in 3 patients (pts 18–20) in which PET was unable to identify a primary lesion the primary tumours were identified later. One of these patients (pt 18) had a squamous cell carcinoma of the lingual base. This patient had a metastatic squamous cell carcinoma of a cervical lymph node and was initially offered radiation therapy, but refused. During follow-up the primary tumour emerged and the patient received radiotherapy resulting in complete remission. Another patient (pt 19) had a poorly differentiated adenocarcinoma in the thoracic wall. This lesion was visible with PET, but no location of the primary tumour was suggested. During the clinical course the lesion penetrated the thoracic wall and turned out to be a primary pleural mesothelioma, and PET was, therefore, considered true-negative.

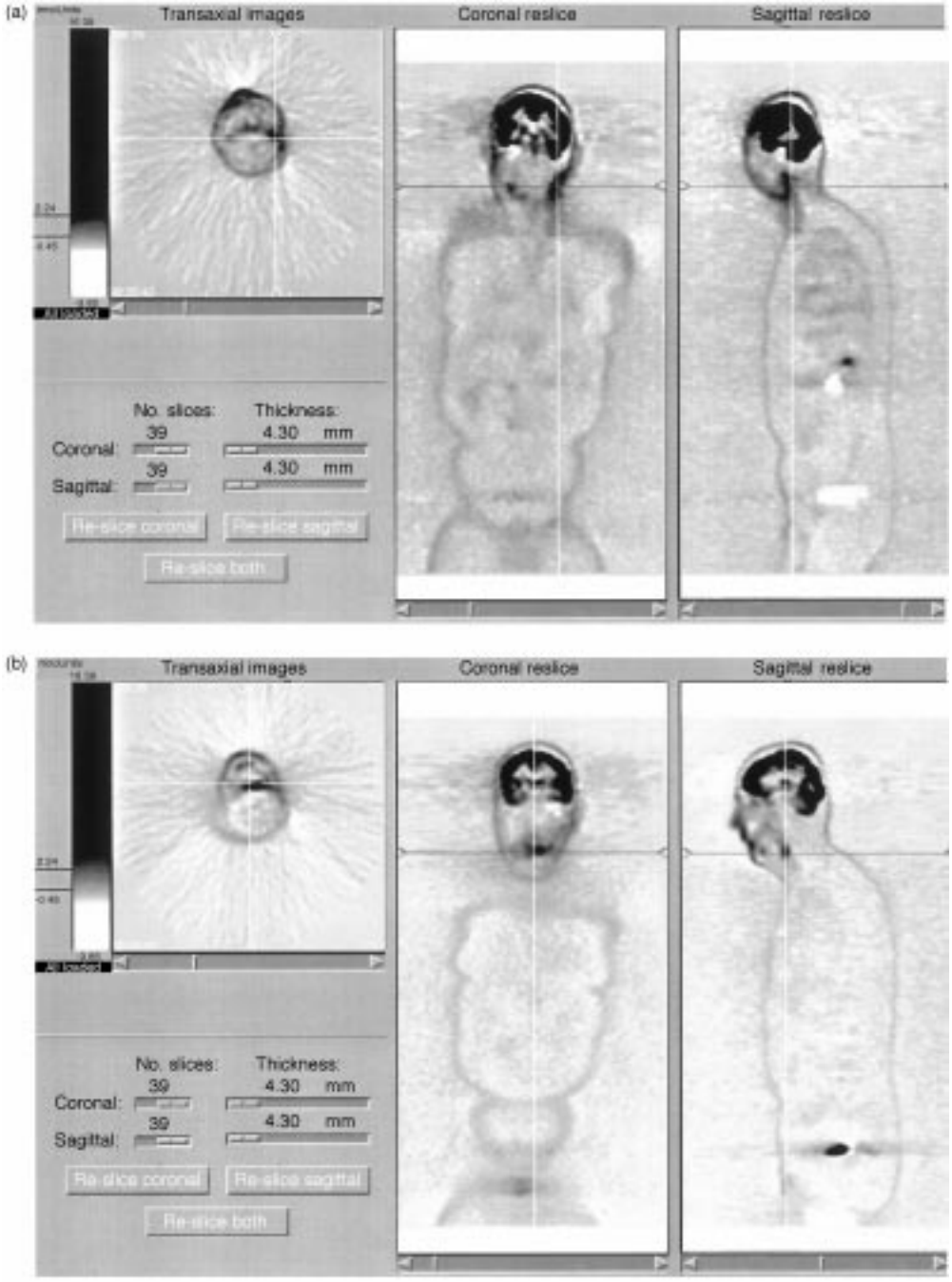

Figure 2. (a) Transaxial, sagittal and coronal PET image of a patient with metastatic lymph nodes in the neck region (+) and no finding of a primary after initial head and neck examination including diagnostic endoscopy. (b) Focal increased FDG indicated a primary tumour at the lingual base (+) which was histologically confirmed after repeated diagnostic endoscopy. Physiological FDG uptake is seen in the brain salivary glands and bladder.

In most patients the PET result had no treatment related implications. In 2 patients therapy was omitted because of rapid deterioration. 7 patients received palliative radiotherapy to the metastatic lesion. 5 patients with metastatic squamous cell carcinoma and 1 patient with poorly differentiated carcinoma in the cervical lymph nodes received bilateral radiotherapy targeting wide head and neck fields of more than 60 Gy whereas one patient refused radiotherapy until a primary tumour was found in the tongue during follow-up. The remaining 4 patients with metastatic cervical lymph nodes had adenocarcinomas or poorly differentiated carcinoma. In all these cases the metastases were localised in the lower cervical region and in 2 of these combined with axillary lymph node metastases. A primary lung cancer was identified by PET and confirmed during the clinical course in all 4 cases. These lesions were localised centrally in 2 patients and in the upper lobe in 2 patients. 2 of these received combination chemotherapy and experienced tumour regression. Another patient who presented with pleural adenocarcinoma also had a primary lung cancer identified by PET and received combination chemotherapy. In the latter 3 patients the treatment decision was guided by the PET result. This was also the case in 1 patient who received reduced radiation fields after a primary tumour in the lingual base was identified by PET and confirmed histologically (Figure 2).

DISCUSSION

Patients with unknown primary tumours often undergo various extensive investigations, which will result in prolonged hospitalisation and discomfort, often with no benefit for the patients. False-positive finding may lead to unnecessary invasive procedures, and even though UPT represents only 0.5–6.5% of all cancer the expenses may be substantial. A restrictive selective search for treatable tumours is most appropriate and cost effective.

In this study a PET scan correctly identified the primary tumour in 9 patients (45%). In all included patients metastatic disease was histologically confirmed prior to inclusion, and no radical excisions were performed. All the metastatic sites could be identified on the PET scans. This indicates that in an unselected group of patients with unknown primary tumours, a PET scan has at least the same possibility of detecting the primary tumour as a CT scan. It has previously been shown that a CT scan is superior to plain X-ray studies, and has resulted in improving the likelihood of locating the primary tumour site from approximately 8% to over 30%. MacMillan and coworkers [16] were able to locate the primary site in 17 of 46 patients using abdominal CT scan and this was superior to ultrasonography. Karsell and co-workers [17] confirmed these results by demonstrating a clinically occult primary site in 31 of 98 patients (31.6%) with CT scanning. In addition the false positive rate was only 6%. In the present PET study the false-positive rate was 20%. In 6 of 9 patients with a true-positive PET scan, a previous performed CT scan was negative. In the latter 3, the chest X-ray was negative, but chest CT was not performed.

One of the reasons that neither CT scan nor PET scan is able to locate the primary tumour in a high proportion of cases might be due to either very small primary tumours or primary tumour involution. The quality of the CT scanner may also be of importance. The newer and faster spiral CT scanners have higher spatial resolution compared to conventional CT scanners which were used in this study.

Post mortem examinations performed in patients with unknown primary tumours has shown that approximately 20% of the patients will have a pancreatic carcinoma and 20% a lung cancer [18]. In the present study at least 31% had a lung cancer. None of these are curable, but chemotherapy may prolong survival [19] and is considered standard treatment in advanced NSCLC in most oncology centres.

The patients in this study was selected by the referring hospitals and the denominator is unknown. The diagnostic procedures used were according to the guidelines of the Danish Society of Internal Medicine and Danish Society of Medical Oncology. Only patients with negative findings were referred to the Finsen Centre and consecutively enrolled if written informed consent was achieved.

In a recent study of FDG-PET in 13 patients with UPT and cervical metastases the primary tumour was found in only 4 patients [20]. Thus, in approximately one third of the patients, PET can identify the primary tumour after extensive diagnostic endoscopic procedures have been performed.

Patients with cervical metastases usually receive extensive radiotherapy and the field target and fractionation is more or less the same whether a primary tumour of the head and neck region is found or not. However, if the primary tumour is found outside this region this treatment may be of no benefit to the patients, i.e. cervical radiotherapy is not indicated if the primary tumour is a primary lung cancer. The present data do not indicate whether true-positive PET scans resulted in improved survival. Treating earlier possibly could be beneficial, but the clinical impact of PET is more likely to reduce the time to diagnosis and spare the patients from unnecessary invasive examinations. However, false-positive PET scans may also result in extraordinary invasive examinations which, in fact, may outweigh the benefit gained by PET.

Standardised uptake values (SUV) from PET were not calculated in this study. This requires transmission scans for attenuation correction and is more time consuming. Additionally, interpatient and intrapatient variations may occur. The plasma glucose levels may affect SUV and not only body weight, but also fat content play a role for the uptake of FDG [21–23]. Also, the time to reach a plateau of the FDG concentration may differ from tumour to tumour [24] and artifactual or physiological uptake may reach SUV levels similar to pathological levels [15]. False-positive FDG uptake cause difficulties in the visual interpretation, but this is not reduced by application of SUV. Multitracer PET studies may reduce this problem [25], but will also make PET more time consuming and expensive. Visual interpretation of PET is more feasible in this group of patients. Semiquantitative estimates of FDG uptake is not always necessary when PET is used diagnostically. However, pancreatic cancer and other deep structures of the body may be missed when attenuation scan is not performed, and it is very important to be aware of the morphological appearance of benign structures, and the visual interpretation must be made with caution [26]. A recent report of lesion-to-background ratios in 24 fasting patients with various tumours indicated that attenuation-corrected and uncorrected images were equally sensitive in detection lesions [27]. The efficacy of non-attenuated whole-body FDG images was similar to the ratios of attenuated corrected images [27].

In our study the PET evaluations were made by experienced specialists in nuclear medicine. Symmetric FDG uptake in the buccal region or uptake in the intestines, heart,

various muscles groups and urinary tract were not considered pathological.

Our results indicate that whole-body PET with FDG may be useful in patients with UPT. Initial patient history, clinical examination, chest X-ray and histological examination including immunohistochemistry may be sufficient in some of the cases. We propose that whole-body PET should be performed prior to further diagnostic procedures.

In Denmark, the cost of one whole-body FDG PET examination is approximately US$1000–1500 which is comparable to the cost of a regional MRI or a similar advanced diagnostic imaging procedure. As one whole body PET scan with FDG can reveal even small tumours and metastases the PET scanning is less expensive and cumbersome compared with the cost of hospitalisation during invasive endoscopic procedures, including anaesthesia and radiographical examinations, such as ultrasound, CT or MRI. Using PET will result in a faster diagnosis in one third of the patients, and it is likely that the majority of these patients will avoid unnecessary and expensive diagnostic radiological or invasive procedures. Furthermore, a few patients will receive a treatment that is aimed at the correct diagnosis resulting in an improved chance of cure. However, a detailed prospective analysis of the cost-effectiveness of PET in patients with UPT is needed to settle this issue.

1. Daugaard G. Unknown primary tumours. *Cancer Treat Rev* 1994, **20**, 119–147.
2. Hainsworth JD, Wood AJJ, Greco A. Treatment of patients with cancer of an unknown primary site. *New Engl J Med* 1993, **329**, 257–263.
3. Panza N, Lombardi G, Rosa MD, Pacilio G, Lapenta L, Salvatore M. High serum thyroglobulin levels, diagnostic indicators in patients with metastases from unknown primary sites. *Cancer* 1987, **60**, 2233–2236.
4. Nyström JS, Wiener JM, Wolf RM, Bateman JR, Violoa MV. Identifying the primary site in metastatic cancer of unknown origin: inadequacy of roentgenographic procedures. *JAMA* 1979, **241**, 381–383.
5. Hoh CK, Hawkins RA, Glaspy JA, *et al.* Cancer detection with whole-body PET using 2-(^{18}F)fluoro-2-deoxy-D-glucose. *J Comput Assist Tomogr* 1993, **17**, 582–589.
6. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991, **32**, 623–648.
7. Laubenbacher C, Saumweber D, Wagner-Manslau C, *et al.* Comparison of fluorine-18-fluorodeoxyglucose PET, MRI and endoscopy for staging head and neck squamous-cell carcinomas. *J Nucl Med* 1995, **36**, 1747–1757.
8. Patz EF, Lowe VJ, Hoffman JM, *et al.* Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET-scanning. *Radiology* 1993, **188**, 487–490.
9. Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1991, **179**, 765–770.
10. Rodriguez MA, Rehn S, Ahlström H, Sundström C, Glimelius B. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. *J Nucl Med* 1995, **36**, 1790–1796.
11. Beets G, Penninckx F, Schiepers C, *et al.* Clinical value of whole-body positron emission tomography with [^{18}F]fluorodeoxyglucose in recurrent colorectal cancer. *Br J Cancer* 1994, **81**, 1666–1670.
12. Gritters LS. Initial assessment of positron emission tomography using 2-fluorine-18-fluoro-2-deoxy-D-glucose in the imaging of malignant melanoma. *J Nucl Med* 1993, **34**, 1420–1427.
13. Warburg O. On the origin of cancer. *Science* 1956, **123**, 309–314.
14. Som P, Atkins HL, Bardoypadhyay D. A fluorinated glucose analogue 2-fluoro-2-deoxy-D-glucose (F-18): nontoxic tracer for rapid tumor detection. *J Nucl Med* 1980, **21**, 670–675.
15. Engel H, Steinert H, Buck A, Berthold T, Böni H, von Schulthness GK. Whole-body PET: physiological and artifactual fluorodeoxyglucose accumulations. *J Nucl Med* 1996, **37**, 441–446.
16. MacMillan JH, Levine L, Stephens RH. Computed tomography in the evaluation of metastatic adenocarcinoma from an unknown primary site. *Radiology* 1982, **143**, 143–146.
17. Karsell PR, Sheedy PF, O'Connel MJ. Computed tomography in the search of cancer of unknown origin. *JAMA* 1982, **248**, 340–343.
18. Nyström JS, Weiner JM, Heffelfinger-Juttner J, Irwin LE, Bateman JR, Wolf RM. Metastatic and histologic presentation in unknown primary cancer. *Semin Oncol* 1977, **4**, 53–58.
19. Non-small Cell Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *Br Med J* 1995, **311**, 899–909.
20. Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs ipsilateral neck irradiation. *Int J Radiat Oncol Biol Phy* 1997, **37**, 797–802.
21. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variation with body weight and a method for correction. *Radiology* 1993, **189**, 847–850.
22. Lindholm P, Minn H, Leskinen-Kallio S, Bergmanm J, Ruotsalainen U, Joensuu H. Influence of the blood glucose concentration on FDG uptake in cancer—a PET study. *J Nucl Med* 1993, **34**, 1–6.
23. Langen K-J, Braun U, Kops ER, *et al.* The influence of plasma glucose levels on fluorine-18-fluorodeoxyglucose uptake in bronchial carcinomas. *J Nucl Med* 1993, **34**, 355–359.
24. Hamberg LM, Hunter GJ, Alpert NM, Choi NC, Babich JW, Fischmann AJ, *et al.* The dose uptake ratio as an index of glucose metabolism: useful parameter or oversimplification? *J Nucl Med* 1994, **35**, 1308–1312.
25. Strauss LG. Flourine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. *Eur J Nucl Med* 1996, **23**, 1409–1415.
26. Fischman AJ, Alpert NM. FDG-PET in oncology: there's more to it than looking at pictures. *J Nucl Med* 1993, **34**, 6–11.
27. Imran MB, Kubota K, Yamada S, *et al.* Lesion-to-background ratio in nonattenuation-corrected whole-body FDG PET images. *J Nucl Med* 1998, **39**, 1219–1223.