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Whole body ^{18}F-FDG PET/CT is superior to CT as first line diagnostic imaging in patients referred with serious non-specific symptoms or signs of cancer: a randomized prospective study of 200 patients.

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ABSTRACT

A fast-track pathway has been established in Denmark to investigate patients with serious non-specific symptoms and signs of cancer (NSSC), which are not eligible to enter an organ-specific cancer program. The prevalence of cancer in this cohort is approximately 20%. The optimal screening strategy in patients with NSSC remains unknown.

The aim was to investigate if ^{18}F-FDG-positron emission tomography/computed tomography (PET/CT) was superior to CT as initial imaging modality in patients with NSSC. In a randomized prospective trial the imaging modalities were compared with regard to diagnostic performance.

METHODS

A total of 200 patients were randomized 1:1 to whole body ^{18}F-FDG-PET/CT or CT of the thorax and abdomen as imaging modality. A tentative diagnosis was established after first line imaging. The final referral diagnosis was adjudicated by the physician, when sufficient data was available.

RESULTS

A total of 197 patients were available for analysis as 3 patients withdrew consent prior to scan. Thirty-nine (20%) were diagnosed with cancer, 10 (5%) with an infection, 15 (8%) with an autoimmune disease and 76 (39%) with other diseases. In 57 patients (28%) no specific disease was found.

Compared to CT scans, ^{18}F-FDG-PET/CT had a higher specificity (96 vs. 85%; p=0.028) and a higher accuracy (94 vs. 82%; p=0.017). However, there were no statistically significant differences in sensitivity (83 vs. 70%) or negative predictive values (96 vs. 92%). No difference in days to final referral diagnosis according to randomization group could be shown (7.2 vs. 7.6 days). However, for the subgroups where the imaging modality showed suspicion of malignancy, there was a significant delay to final diagnosis in the CT group compared to the ^{18}F-FDG-PET/CT group (11.6 vs. 5.7 days; p=0.02).

CONCLUSION

We found a higher diagnostic specificity and accuracy of ^{18}F-FDG-PET/CT compared to CT for detecting cancer in patients with NSSC. ^{18}F-FDG-PET/CT should therefore be considered as first line imaging in this group of patients.

Keywords: FDG-PET/CT, molecular imaging, cancer, prospective study, randomized study.

INTRODUCTION

In 2009 fast-tract cancer patient pathways (CPPs) were introduced by the Danish Health and Medicine Authority for patients with NSSC in Denmark. The background for the implementation was that Danish patient experience poorer cancer survival rates than patients from other European countries and were diagnosed with an unfavorable delay (1–4). Since 2012 Diagnostic Outpatient Clinics (DOC) have been established in the Capital Region of Denmark for patients with NSSC as early diagnosis in cancer are of importance for more favourable outcome (5–8). The criteria for referral to DOC is a suspicion from the referring physicians, in more than 95% of the cases the patients general practitioner, that the patient has a NSSC. The referral is typically prompted by one or more of the following observations; increasing health service seeking behaviour, weight loss, tiredness or a group of unspecific symptoms, which do not fit into any of the organ-specific established cancer investigation programs. Cancer prevalence of 16-18% were found in patients investigated at DOC for NSSC in Denmark (9,10).

Patients referred to DOC for NSSC are initially screened for occult malignancy with a physical examination and laboratory evaluation. If malignancy still is suspected, conventional computed tomography (CT) of thorax and abdomen is performed (in >95% of the referred patients above 40 years of age). However, the optimal cancer screening strategy in these patients remains unknown. Integrated positron emission tomography/computed tomography (PET/CT) with the glucose analogue, "2-^{18}F"-fluoro-2-deoxy-D-glucose (FDG) has proven to be of high diagnostic value in staging and restaging of different malignant diseases such as colorectal cancer, lung cancer, breast cancer, head and neck cancer as

well as malignant lymphomas (11–13). The standard whole-body coverage simplifies staging and speeds up decision making on appropriate therapeutic strategies. This promotes ^{18}F-FDG-PET/CT as the imaging modality of choice for work-up in the most common tumor entities as well as some rare malignancies (13). ^{18}F-FDG-PET/CT is more accurate in detecting cancer and provides fewer equivocal findings than ^{18}F-FDG-PET alone, CT alone, or separately acquired ^{18}F-FDG-PET and CT studies in a head-to-head comparison (13). Although these studies have suggested that ^{18}F-FDG-PET/CT might be more sensitive and specific for cancer detection than either modality alone, few of them supports that ^{18}F-FDG-PET/CT should be used for cancer screening (14–19). Accordingly, in a study of 2,911 asymptomatic subjects who underwent both ^{18}F-FDG-PET and other examinations for multiple organs including CT, the detection rate of cancer with ^{18}F-FDG-PET was 1% and sensitivity, specificity, and positive predictive value of ^{18}F-FDG-PET to detect cancer were estimated to be 18%, 95%, and 11%, respectively (20). The detection rate of cancer by ^{18}F-FDG-PET was higher than that of other screening modalities. However, the high false-positive rate makes ^{18}F-FDG-PET screening less useful in the general population with a low prevalence of cancer (21–25). In the so far largest ^{18}F-FDG-PET screening study performed at 233 facilities with inclusion of 155,456 subjects, positive ^{18}F-FDG-PET findings suggesting possible cancer was found in 10.9% of the cases. However, based on further investigations the true positive rate (positive predictive value) was only 32.3% (26). Accordingly, this large-scale study clearly demonstrated that ^{18}F-FDG-PET had a far too high false-positive rate to be applied as screening of the general population.

A study examining the subgroup of patients with a malignancy and an unknown primary tumor found ^{18}F-FDG-PET/CT to be non-superior to conventional CT in the work-up of identifying the primary tumor. Currently, ^{18}F-FDG-PET/CT is not recommended as the primary method for investigation in this group of patients (24). However, as the estimated prevalence of cancer in patients referred to DOC is approximately 10-fold higher than in the above-mentioned studies (9,10), the false-positive rate is expected to be substantially lower and ^{18}F-FDG-PET/CT cannot be ruled out as the best first-line imaging modality in a high cancer prevalence population. Furthermore, the most common non-cancer findings in this population of patients are rheumatoid or infectious diseases where ^{18}F-FDG-PET/CT has shown a better detection rate than routine CT (27).

The aim of this study was therefore, in a randomized prospective trial, to investigate if ^{18}F-FDG-PET/CT was superior to CT as initial imaging modality in NSSC where the prevalence of cancer is approximately 20%. The imaging modalities were compared with regard to diagnostic performance and the time from referral to adjudication of a diagnosis.

METHODS

Participants

Design. A total of 200 consecutive patients were prospectively recruited at their first visit at the DOC, Hvidovre University Hospital between August 14th, 2013 and April 30th, 2014. The criteria for referral to DOC were suspicion from the referring physicians that the patient has a NSSC. The referral was prompted by one or more of the following observations; increasing health service seeking behaviour, weight loss, tiredness or a group of unspecific symptoms, which do not fit into any of the organ-specific established cancer investigation programs. Inclusion criteria were i) age ≥18 years and ii) signed informed consent. Exclusion criteria were i) pregnancy, including risk of pregnancy or lactation ii) alcohol or drug abuse hampering the ability to adhere to the protocol iii) claustrophobia iv) bodyweight above 150 kg, (v) contraindications to CT due to allergy to contrast or impaired renal function defined as P-creatinine level > 0.120 mmol/L or (vi) deemed unfit due to performance status.

The patients were randomized at their first visit to either CT of the thorax and abdomen or ^{18}F-FDG-PET/CT based on a computer-generated list using an 1 to 1 ratio algorithm (GraphPad Software, La Jolla, CA, US). Randomization was performed by a study nurse blinded to patient history and prior to any laboratory testing.

Furthermore patients were screened for disease with a physical examination as well as a laboratory evaluation. The ^{18}F-FDG-PET/CT or CT in combination with results from clinical laboratory test guided the clinicians in diagnostic decisions. Experienced certified radiologists and nuclear medicine physicians evaluated the PET, fused PET/CT, and CT images side by side and a consensus was reached. All the CT of thorax and abdomen were

evaluated by the same experienced certified radiologist. All ^{18}F-FDG-PET/CT or CT scans were furthermore discussed at a multidisciplinary conference with the participation of the following board certified specialist physicians: endocrinologist, gastroenterologist, nuclear medicine physician, radiologist and an infection disease specialist. Oncologists were not part of the multidisciplinary conference team. However if a malignant diagnosis was established or deemed most likely, then patients were referred to oncologists.

A total of 200 patients were randomized. A preliminary tentative diagnosis based on initial imaging, routine laboratory testing was given at the multidisciplinary conference when results of the ^{18}F-FDG-PET/CT or CT scans were available. A final referral diagnose was adjudicated after the patients had finished their full investigational-program for disease at the DOC.

Ethics. All patients received oral and written information and gave written consent before inclusion. The study was approved by the Scientific Ethics Committee of The Capital Region of Denmark (protocol number H-4-2013-063) and complied with the declaration of Helsinki and Danish legislation.

*PET/CT Imaging. F*ollowing at least 6 hours of fasting, 4 MBq/kg of ^{18}F-FDG was injected intravenously (iv) (range 184–444 MBq), followed by a median resting uptake period of 71 min. (intended: 60 min.; range 57–123 min.). Blood glucose levels were tested in all patients prior to injection of **^{18}F**-FDG to ensure blood glucose levels were below 7 mmol/L. This was the case in all patients.

The first 50 of the ^{18}F-FDG-PET/CT scans were performed on a PET/CT scanner (Siemens Biograph 40; Siemens, Erlangen, Germany) at Rigshospitalet. For the remaining

^{18}F-FDG-PET/CT scans a Siemens Biograph mCT 128 4R (Siemens Healthcare, Erlangen, Germany) was used at Hvidovre Hospital. All patients were scanned from vertex to proximal femora. The CT examination was enhanced by iodinated contrast agent given orally (Optiray [Covidien, Hazelwood, MO], 300 mg iodine/mL, 20 mL in 500 mL water 30 minutes before start) and iv (100 mL, 5 mL/s immediately before start). Depending of the weight of the patient PET emission data were acquired for 2½-5 minutes at each of six or seven axial bed positions immediately after acquisition of the diagnostic CT images. Patients were instructed to breathe normally and were immobilized using cushions. PET data were reconstructed using ordinary Poisson ordered-subset-expectation-maximization (3D ordinary poisson OSEM) with resolution modeling (Point-spread function) using 2 iterations and 21 subsets. Time-of-Flight were used for the mCT scans. PET data were corrected for decay, scatter, and random events, and attenuation corrected using the CT data. PET and fused PET/CT images were displayed on Siemens syngo.via workstations for analysis.

CT parameters were tube potential 120 kV, 2 mm slices with a collimation of 1.2 mm × 24, pitch 0.8, CareDose4D on, quality reference mAs 170, and varying tube current for dose reduction. CT data were reconstructed using filtered back projection with a B40f medium kernel, slice increment 1.0 mm, 2-mm slices. CT images were reviewed at a picture archiving and communication system - Impax 5.3 (AGFA Healthcare, München, Germany). Image interpretation was performed according to clinical routine and reported as indicative of malignancy or not.

Experienced radiologists (AKB and EM) and nuclear medicine physicians (AL and JG) in teams of one radiologist and one nuclear medicine physician evaluated the PET, fused

PET/CT, and CT images side by side and a consensus was reached. For malignant findings, interpretation included suggestion of potential primary tumor and the number of metastatic sites. Thus, a PET-negative but obviously malignant-looking tumor seen on the CT part of the PET/CT scan would be defined as a positive lesion and an ^{18}F-FDG PET-positive lesion without clear anatomical CT substrate was classified as negative. A written report on the PET/CT consensus was produced. The effective radiation dose for the ^{18}F-FDG-PET/CT scan was approximately 16 mSv with 8 mSv from the ^{18}F-FDG dose and 8 mSv from the CT scan.

Conventional CT. The diagnostic CT was performed with the use of i.v. contrast enhancement (iomeron, 350 mg/ml; 1,2 ml/kg; flow rate 4 ml/sec). The CT scan was performed with a multidetector CT scanner Philips brilliance (4-64 slides) (Philips Healthcare, Cleveland, OH, US) CT parameters were 120 kV, reference 225 mAs, using 3 mm thickness scan. All patients were scanned from apex of the lungs to the proximal femora. The radiation dose from the CT scan was approximately 8 mSv.

Statistics

Continuous variables were compared between groups using t-test for independent samples whereas Fisher´s exact test was used for categorical variables. $P<0.05$ was considered significant. The sample size was based on ability to demonstrate a difference between the expected PET/CT specificity of 0.95 and the expected CT specificity of 0.85 with a type I error of 5% and a power of 70%. All statistical analyses were performed using SPSS 22 (IBM SPSS statistics for windows, version 22.0 Armonk, NY, IBM Corp).

RESULTS

Patient characteristics

A total of 200 patients were randomized to either ^{18}F-FDG-PET/CT or CT as first line imaging modality. Three patients withdrew consent before being scanned. Accordingly, a total of 95 patients underwent ^{18}F-FDG-PET/CT and 102 patients underwent CT (Fig. 1). Patient characteristics are summarized in Table 1. No significant differences were found regarding gender or age of patients randomized to ^{18}F-FDG-PET/CT versus conventional CT as first imaging modality. The majority of the patients were refereed to DOC from their general practitioner (78%). Referral diagnosis was suspicion of malignant disease (48%), weight loss (34%), suspicion of infection (2%) or other symptoms (16%). No difference in symptoms at referral was found between patients randomized to ^{18}F-FDG-PET/CT versus CT.

After the initial scan and a multi-disciplinary conference, 18 (19%) of the patients randomized to ^{18}F-FDG-PET/CT were found to most likely have a malignant diagnosis compared to 26 (25%) in the group of patients investigated with CT as first diagnostic modality. For ^{18}F-FDG-PET/CT the image findings indicative of malignancy were: lung cancer (5, of which 2 were disseminated), mammary cancer (1 localized and 1 disseminated), 2 sarcomas in pelvic region, head and neck cancer (2) (Fig. 2), pancreatic cancer with carcinomatosis (1), esophageal cancer (1), rectal cancer (1), lymphoma (1), multiple bone metastases (1; most likely prostate cancer) and disseminated cancer with unknown origin (2). For CT only, the findings indicative of malignancy were: lung foci (8), hepato-biliary metastases (7), bone metastases (3), enlarged lymph nodes (2), mammary tumor (1), pancreatic tumor (1), gynaecological cancer (1), colon cancer (1), adrenal tumor (1) and disseminated cancer (1).

Infection was suspected on 5 ^{18}F-FDG-PET/CT scans (3 pneumonia and 2 pharyngitis) and on 3 CT scans (2 pneumonia and 1 diverticulitis). Connective tissue disease was suspected on 3 ^{18}F-FDG-PET/CT scans (2 sarcoidosis and 1 vasculitis) (Fig. 3) but not on any of the CT scans. Normal scans with neither malignant nor benign pathology was reported in 49 (52%) of the ^{18}F-FDG-PET/CT scans whereas this was only the case in 33 (32%) of the CT scans. Further investigations performed at the DOC after the initial scans in the patients suspected of malignant disease are listed in table 2. A total of 26 additional procedures were performed in the ^{18}F-FDG-PET/CT group compared to 41 in the CT group.

The final referral diagnoses established in the 197 patients are listed in table 3. The final referral diagnosis is based on a clinical approach using data obtained from all examinations. A total of 39 patients (20%) were diagnosed with cancer, whereas 10 (5%) were diagnosed with infections: hepatitis C (n=3); pharyngitis (n=2); HIV (n=1), pneumonia (n=1); urinary tract infection (n=1); *Clostridium difficile* gastro-enteritis (n=1) and diverticulitis (n=1). A diagnosis of an auto-immune disease was established in 15 (8%). In 57 (28%) of the cases, patients were discharged from the DOC without any specific disease found. No difference between patients investigated with ^{18}F-FDG-PET/CT or CT was seen.

Diagnostic performance of PET/CT vs. CT for detection of cancer

The results of ^{18}F-FDG-PET/CT and CT are shown diagrammatically in Fig. 4. In brief, of 95 ^{18}F-FDG-PET/CT scans, 15 (16%) were true positive (TP), 74 (78%) were true negative (TN), 3 (3%) false positive (FP) and 3 (3%) false negative (FN) with regard to detection of cancer. For the 102 CT scans 14 (14%) were TP, 70 (69%) TN, 12 (12%) FP and 6 (6%) FN with regard to detection of cancer.

The 3 patients found to be FN with ^{18}F-FDG-PET/CT were, based on further investigation, diagnosed with cancer coli (n=2) and hepatocellular carcinoma (n=1). Regarding CT as first line imaging modality, the 6 FN patients were diagnosed with colon cancer (n=2), gastric cancer (n=1), gallbladder cancer (n=1) and chronic lymphocytic leukemia (n=2). The 3 patients diagnosed as FP with ^{18}F-FDG-PET/CT were after the final workup diagnosed with a benign uterus fibroma, benign angiofibroma and a Warthin tumor. Regarding the 12 patients classified as FP with CT as first line modality patients were diagnosed with: liver cirrhosis (n=4), unspecific reaction in lymph nodes (n=3), lipoma in the liver (n=1), pneumonia (n=1), sarcoidosis (n=1), oesophagus stricture (n=1) or enlarged adrenal glands (n=1).

The diagnostic performance for detection of cancer of ^{18}F-FDG-PET/CT and CT as initial diagnostic imaging modality are summarized in table 4. Compared to CT, ^{18}F-FDG-PET/CT had a higher specificity (96 vs. 85%; p=0.028) and a higher accuracy (94 vs. 82%; p=0.017). However, there were no statistically significant differences in the sensitivity (83 vs. 70%) or negative predictive values (96 vs. 92%). The positive predictive value was borderline significantly higher in the ^{18}F-FDG-PET/CT group compared to the CT group (83 vs. 54%; p=0.057). Overall, the better diagnostic performance in the PET/CT group compared to the CT group was driven by a much lower (3 vs. 12) number of FP cases.

Time to diagnosis

The number of days to adjudication of a final referral diagnosis according to randomization group and results of ^{18}F-FDG-PET/CT or CT are shown diagrammatically in Fig. 4. For the PET/CT and CT groups as a whole, no differences could be shown (7.2 vs. 7.6 days). However, for the subgroups where the initial imaging modality showed suspicion of

malignant disease, there was a significantly longer time to final diagnosis in the CT group compared to the ^{18}F-FDG-PET/CT group (11.6 vs. 5.7 days; p=0.02). The long time to final diagnosis in the CT group was driven by an average of 18 days in the 12 FP patients.

DISCUSSION

The major finding of our study is that ^{18}F-FDG-PET/CT is superior to CT as the initial imaging modality in a population of patients referred to DOC with NSSC where the true prevalence of cancer is 20%. The superiority of ^{18}F-FDG-PET/CT was due to a significantly higher specificity compared to that of CT, for detection of cancer. To the best of our knowledge we are the first to demonstrate this in a randomized, prospective study.

In a previous study of ^{18}F-FDG-PET as primary imaging modality, which was performed in a low prevalence (1%) population, it was clearly demonstrated that ^{18}F-FDG-PET was of limited value due to the high false positive rate (26). However, in the recently established nationwide DOCs in Denmark the prevalence of cancer is much higher and around 16-18% (9,10). Therefore, the false-positive rate will be much lower and ^{18}F-FDG-PET/CT potentially could be of value. In accordance with this, we found in our study a positive predictive value of 83%.

Currently, as standard work-up in DOC, CT has been chosen as the initial imaging modality. However, this leads to relatively many false positive cases that require secondary diagnostic procedures including second line use of ^{18}F-FDG-PET/CT as seen in Table 2. Due to this, we hypothesized that in DOC it might be beneficial to use ^{18}F-FDG-PET/CT instead of CT as the initial imaging modality.

Indeed, our study seems to support this idea since ^{18}F-FDG-PET/CT was superior with respect of diagnostic performance with a higher specificity and accuracy. The positive predictive value was 83% for PET/CT but only 54% for CT. The driver for the poorer performance of CT was, compared to ^{18}F-FDG-PET/CT, a high number of false positive cases. These cases resulted in a long time to final diagnosis in the group initially suspected to

have malignant disease based on CT. In addition, the high number of false positive cases using CT lead to an increased utilisation of secondary diagnostic procedures (Table 2). As we performed a diagnostic CT as part of the ^{18}F-FDG-PET/CT investigation and the scans were evaluated side-by-side by a radiologist and a nuclear medicine physician it is probable that if using low-dose CT the same performance is not to be expected.

It could be argued, that our data is not generalizable and only relates to a Danish setting. However, first the concept of DOCs is now used in several countries in Europe. Moreover, we believe our data are generalizable for any population “enriched” so the *a priori* probability of cancer is around 20%. From a cost-benefit point of view it may be argued that ^{18}F-FDG-PET/CT is more expensive (16). However, the first line use of ^{18}F-FDG-PET/CT instead of CT saved expensive additional procedures as magnetic resonance imaging and ultrasonography as well as secondary ^{18}F-FDG-PET/CT scans. When this increased use of additional procedures is combined with the almost 3 times longer time to final diagnosis of 18 days in the false positive CT group, we believe that total costs may actually decrease using ^{18}F-FDG-PET/CT as first line imaging modality. However, the exact cost structure at the different institutions may influence the point of economical break-even. Regardless of economic factors, there are human costs of being falsely diagnosed with cancer and on average have additional investigation for 18 days until proven not to have cancer.

CONCLUSION

With the results of the present study, implementation of ^{18}F-FDG-PET/CT as the first line imaging modality instead of CT in NSSC patients referred to DOC should be considered. Nevertheless, additional randomized studies are encouraged to confirm our findings.

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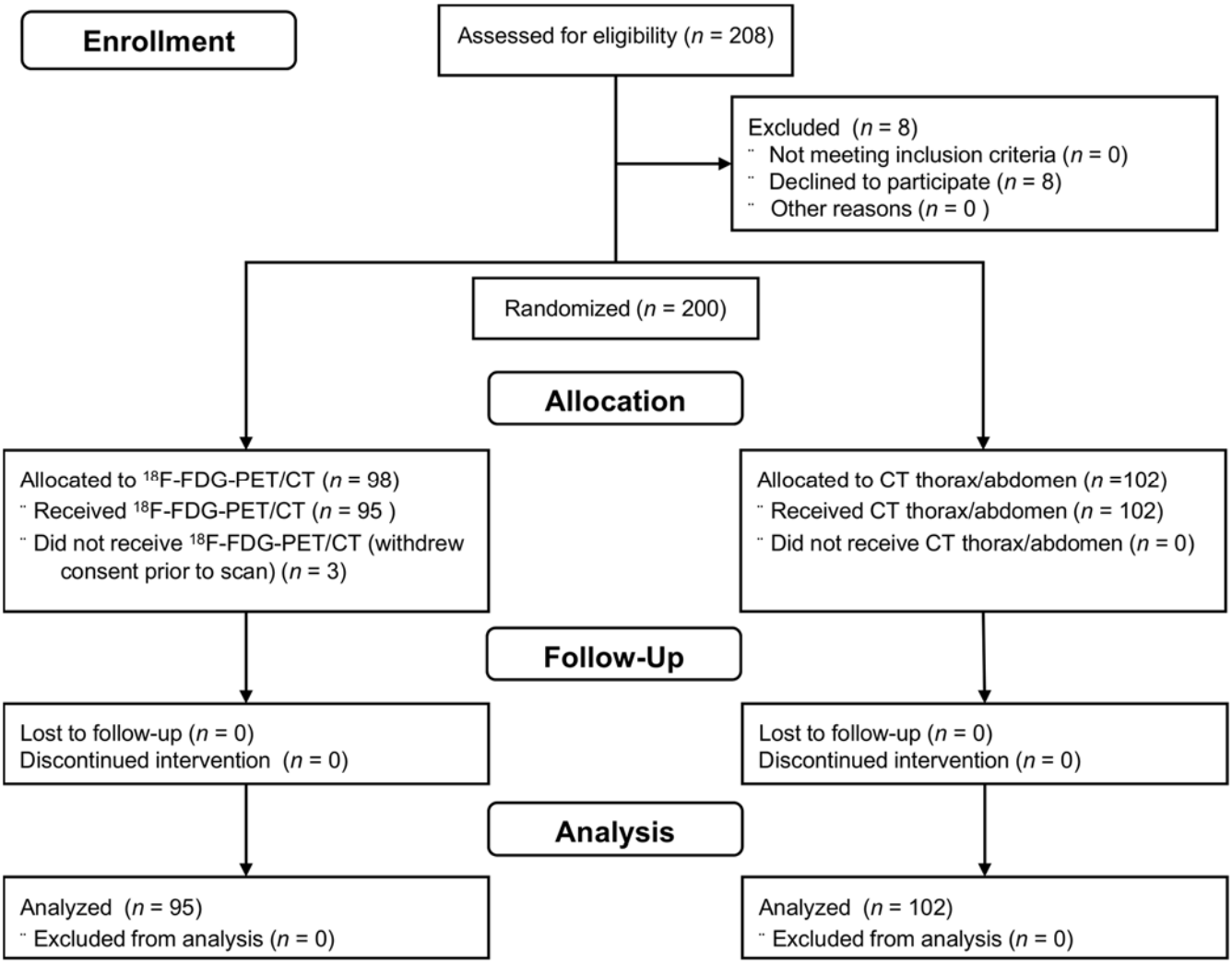
Figure Legends

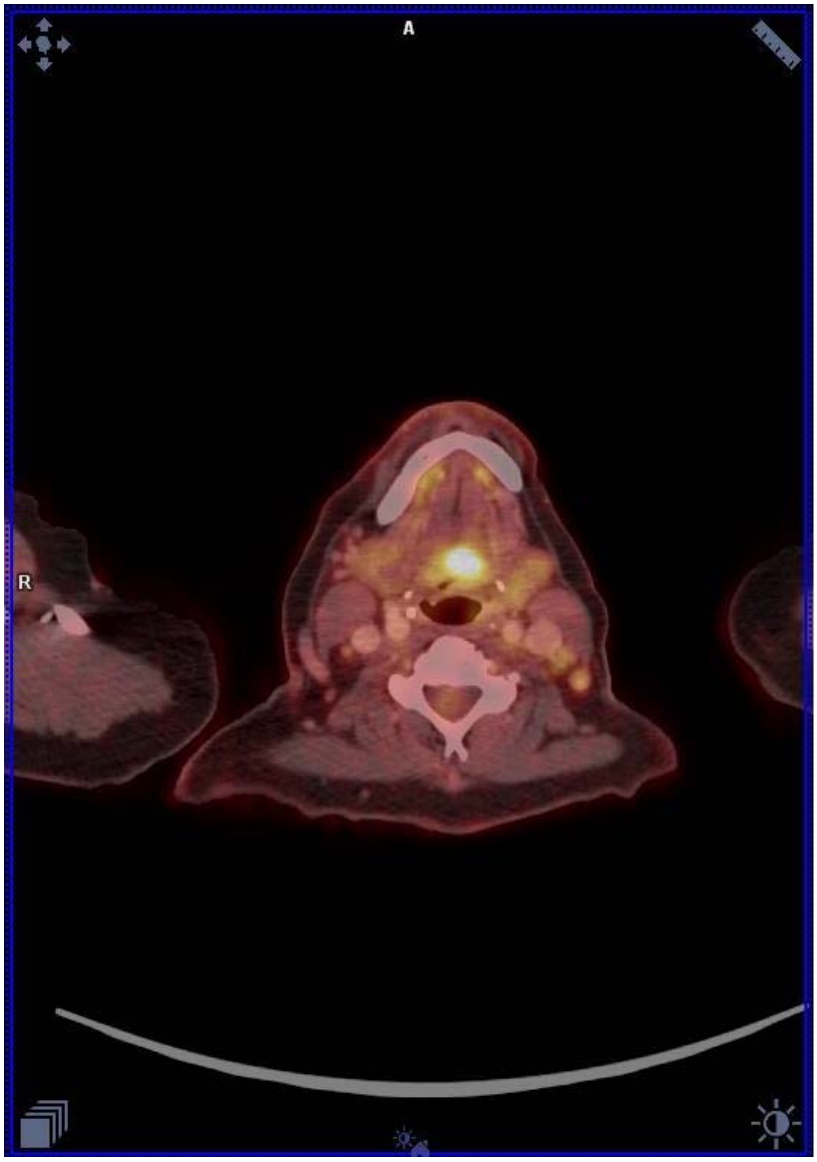
Figure 1.



Flow chart of the study.

Abbreviations: n: number of patients; PET/CT: FDG-positron emission tomography /computed tomography; CT: computed tomography.

Figure 2.



A 59-year-old woman, admitted to DOC due to a weight loss of 5 kg, nausea and diffuse pains in the neck region. A tumor in the oropharynx was visible on FDG-PET/CT. The patient was diagnosed with cancer of the tongue.

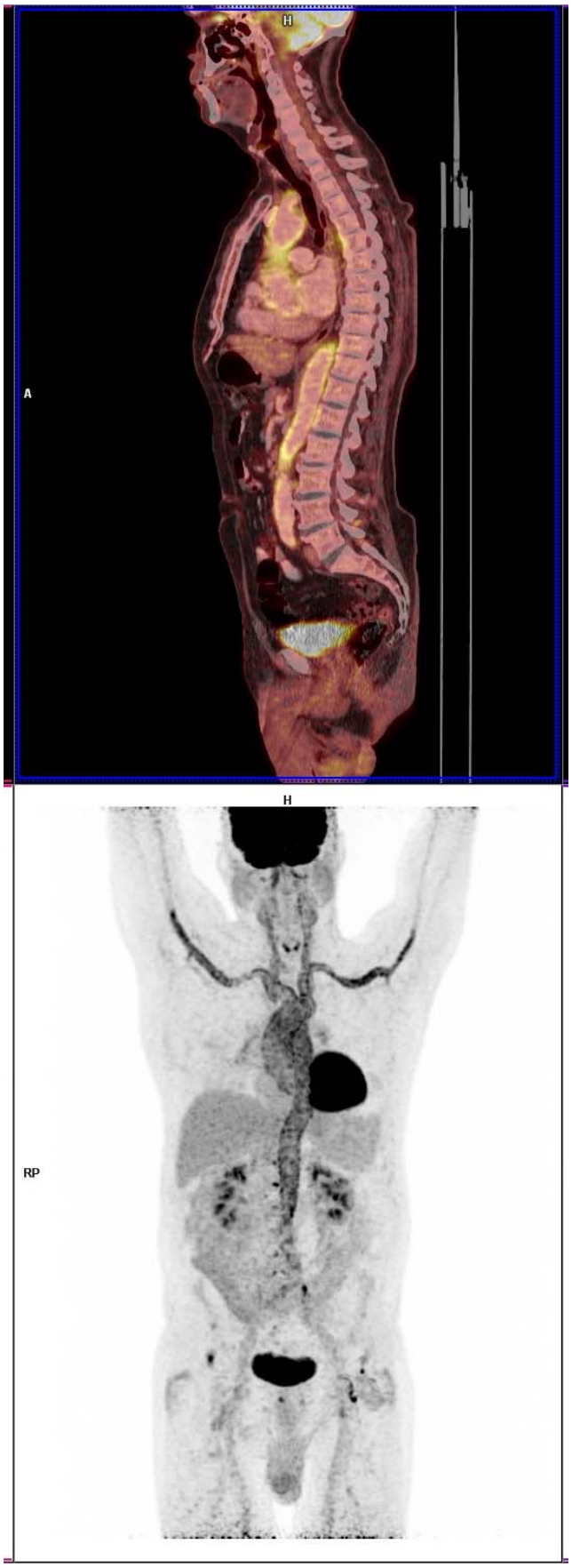
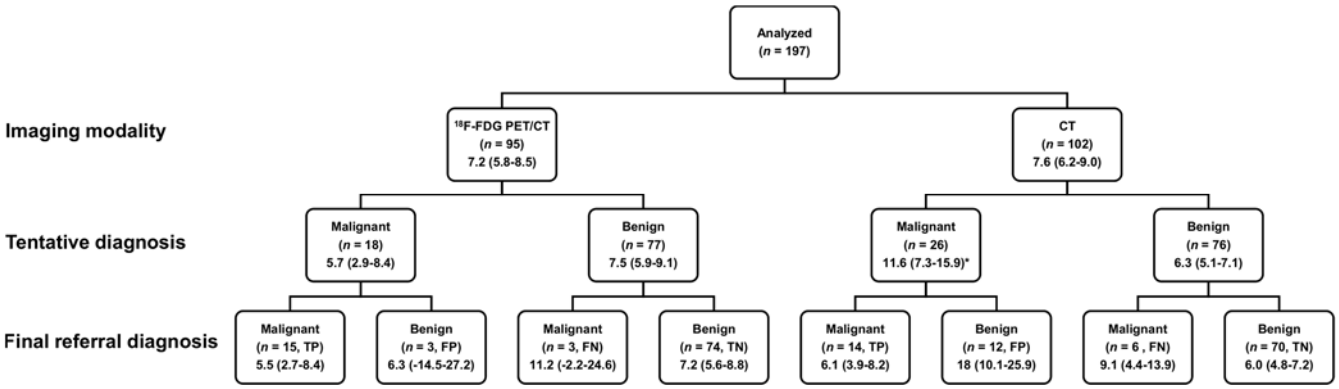


Figure 3.

A 77-year-old male, admitted to DOC due to weight loss of 4 kg, tiredness, anaemia and chest pain. Erythrocyte sedimentation rate elevated to 58 mm. FDG-PET/CT showed increased FDG uptake in the vessel walls and the patient was diagnosed with large vessel vasculitis. Good clinical response to prednisolone.

Figure 4.



Number of days to adjudication of a final referral diagnosis according to randomization group (row 2; imaging modality) and results of FDG-PET/CT or CT (row 3; tentative diagnosis). All numbers are given as mean with 95% CI in parenthesis.

Abbreviations: n: number of patients; FDG-PET/CT: FDG-positron emission tomography/computed tomography; CT: computed tomography; TP: true positive; FP: false positive; FN: false negative; FP: false positive.

Table 1.

Baseline characteristics of the 197 patients included in the study.

	^{18}F-FDG-PET/CT	**CT thorax/abdomen**	***p*-value***
Number	95	102	
Male gender, n (%)	49 (52)	46 (45)	0.39
Age, years (range)	61 (31-90)	64 (26-91)	0.08
Charlston comorbidity score, (Mean±SEM)	0.74 ± 0.10	0.77 ± 0.11	0.80
Referred by:			
General practitioner, n (%)	73 (77)	80 (78)	0.87
Medical specialist practice, n (%)	4 (4)	4 (4)	1.0
Hospital departments, n (%)	18 (19)	18 (18)	0.86
Time to imaging modality after first consultation, days in mean (range)	4.8 (1-15)	4.7 (1-21)	0.59
Clinical laboratory test			
Haemoglobin (mmol/L) (Mean±SEM)	8.3 ± 0.1	8.1 ± 0.1	0.28
White blood cell count (10^9/l) (Mean±SEM)	7.6 ± 0.2	8.3 ± 0.3	0.038
Albumin (g/L) (Mean±SEM)	38 ± 0.9	39 ± 2.4	0.71
ESR (mm/hr) (Mean±SEM)	17.2 ± 2.2	22.7 ± 2.6	0.10
LDH (IU/L) (Mean±SEM)	183 ± 6	188 ± 15	0.80
CRP (mg/L) (Mean±SEM)	11.0 ± 2.1	14.4 ± 2.7	0.31

Abbreviations:

ESR; erythrocyte sedimentation rate, LDH; lactate dehydrogenase, CRP; c-reactive protein;

SEM; Standard error of mean.

* T-test for independent samples or Fisher´s exact test

Tabel 2.

Additional examinations performed at the DOC in patients suspected of malignant diagnose based on first line imaging modality. Numbers in parentheses are cases where the additional examination did not show malignancy. Patients can have more examinations performed.

	^{18}F-FDG-PET/CT	CT thorax/abdomen
Number of patients suspected of malignant disease after first line imaging modality	*n* = 18	*n* = 26
Diagnostic procedures performed after first line imaging modality at the DOC (total): *n* (cases where additional examination did not show malignancy)	26	41
US abdomen	1 (0)	7 (6)
US neck	1 (0)	1 (0)
MRI	3 (1)	1 (1)
Mammography	0	3 (3)
Gastroscopy	3 (0)	2 (2)
Colonoscopy	3 (1)	6 (4)
Bronchoscopy	4 (0)	4 (0)
Gynaecology examination	1 (1)	4 (3)
Tissue biopsy	6 (1)	10 (3)
X-ray	1 (1)	0
FDG-PET-CT	-	3 (1)
Bone marrow aspiration	2 (1)	0
CT urinary tract	1 (1)	0

Abbreviations: *n*, number of patients; ^{18}F-FDG-PET/CT, ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography; CT, computed tomography; US, ultrasound; MRI, magnetic resonance imaging.

Table 3.

Final referral diagnosis in patients included in the study.

	^{18}F-FDG-PET/CT (*n* = 95)	CT thorax/abdomen (*n* = 102)
Final referral diagnosis	***n* (%)**	***n* (%)**
Cancer*	**19 (20)**	**20 (20)**
Lung cancer	4	7
Prostate cancer	2	2
Breast cancer	2	0
B-cell lymphoma	1	1
Colorectal cancer	5	3
Other malignant disease	5	7
Infection†	**5 (5)**	**5 (5)**
Autoimmune disease	**9 (9)**	**6 (6)**
Other diseases	**36 (38)**	**40 (39)**
Gastric ulcer/gastritis	11	5
Liver steatosis/cirrhosis	4	2
COPD	3	4
Cardiovascular disease	3	1
Thyroid disease	3	2
MGUS	4	1
Other	8	25
No disease found	**26 (27)**	**31 (30)**

Abbreviations: *n*, number of patients; COPD: chronic obstructive pulmonary disease; MGUS: monoclonal gammopathy of undetermined significance.

*) Malignant diagnosis was confirmed by tissue biopsies or bone marrow examination in 36 of these 39 patients prior to selection of cancer treatment strategy. The tissues biopsies or bone marrow examinations were obtained either in the DOC work-up prior to referral (n=13) or after referral from DOC.

† Hepatitis C: hepatitis C RNA and antibody positive, pharyngitis: positive throat culture; HIV: antigen/antibody test positive; pneumonia: positive sputum culture; urinary tract infection:

positive urinary culture; Gastro-enteritis: fecal swap PCR positive for *Clostridium difficile* 027; and diverticulitis: clinical picture combined with CT of abdomen.

Table 4.

Comparison of diagnostic performance of ^{18}F-FDG-PET/CT vs. CT thorax/abdomen

	^{18}F-FDG-PET/CT (*n* = 95)	CT (*n* = 102)	P value*
Cancer prevalence	20%	20%	
Sensitivity	83% (57-96%)	70% (46-88%)	0.45
Specificity	96% (89-99%)	85% (76-92%)	0.028
Accuracy	94%(89-99%)	82%(74-89%)	0.017
Positive predictive value	83% (59-96%)	54% (33-74%)	0.057
Negative predictive value	96% (90-99%)	92% (84-97%)	0.33

Abbreviations:

^{18}F-FDG-PET/CT,^{18}F-positron emission tomography/computed tomography; CT, computed tomography

* Fisher's exact test. Numbers in parentheses are 95% confidence intervals calculated using the Wald method.