RESEARCH PROTOCOL

Intra-individual patient-based comparison of conventional and digital PET/CT scanners (PETPET study)

PROTOCOL TITLE 'Intra-individual patient-based comparison of conventional and digital PET/CT scanners'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
Conventional PET/CT	**Where the term conventional PET/CT is used, we are referring to te conventional system that is used in this study: the Ingenuity TF PET/CT scanner (Philips Healthcare).**
CT	**Computed Tomography**
ceCT	**Contrast-enhanced CT scan, used for diagnostic purposes.**
CV	**Curriculum Vitae**
Digital PET/CT	**Where the term digital PET/CT is used, we are referring to the digital system that is used in this study: the Vereos PET/CT scanner (Philips Healthcare)**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
FDG	**Fluordeoxyglucose**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MRI	**Magnetic resonance imaging**
NM	**Nuclear Medicine**
PA	**Pathology results**
PET	**Positron Emission Tomography**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organization or**

	performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator.
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TNM	**TNM staging system; tumor (T), nodes (N) and metastasis (M)**
Sv	**The Sievert (Sv) is a derived unit of ionizing radiation, intended to represent the stochastic health risk. For radiation dose assessment, this is defined as the probability of cancer induction and genetic damage.**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

SUMMARY

Rationale: FDG-PET/CT imaging is important for staging, response monitoring and prognosis prediction in patients with cancer. However, the spatial resolution of current PET/CT systems is relatively low, limiting the detection of small lesions and accurate staging. In 2017, a new state-of-the-art digital PET/CT system will be installed at the NM department in Isala. It is expected that this new type of scanner contributes to more accurate staging and possibly more effective patient management. For a period of 6-12 months, both a conventional and a digital PET/CT system will be available in the NM department in Isala. This provides the unique possibility to evaluate the performance of the digital PET/CT system compared with conventional PET/CT. In this study, we will analyze the impact of digital PET/CT on the final diagnostic conclusion of the scan in patients with lung cancer, breast cancer and esophageal cancer.

Objectives: Primary objective: How does the diagnostic outcome of the digital PET/CT study compare to the outcome of conventional PET/CT in patients referred for (re)staging of lung cancer, breast cancer and esophageal cancer?

Secondary objective: What is the image quality (in both quantitative and qualitative terms) of digital PET as compared to conventional PET?

Both the primary and secondary objective are further specified in multiple detailed objectives.

Study design: Single center diagnostic accuracy study using intra-individual comparisons of PET/CT scans

Study population: 225 adults referred for a FDG-PET/CT scan in Isala to evaluate (suspected) lung cancer, breast cancer and esophageal cancer

Main study parameters: Primary: diagnostic outcome of the PET/CT study (number of detected lesions, TNM stage, clinical performance and accidental findings)

Secondary: image quality (rating image quality, diagnostic confidence, normal tissue appearance, lesion contrast and relation with EANM procedure guidelines)

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

- Additional scan time: Immediately after acquisition of the first PET/CT study, an additional PET/CT study will be obtained on the second system. The additional time for the second PET/CT scan will typically be 25 minutes (maximum 40 minutes), in which patients have to lie still on a scanner bed.
- Additional radiation dose: In a standard clinical FDG-PET/CT scan, the average dose is 14 milliSievert (mSv). This consists of the dose from a low-dose CT scan for attenuation-correction and the dose from FDG, depending on patients' body weight. The extra study-related low-dose CT scan will give an additional radiation dose of on average 6 mSv.

1. INTRODUCTION AND RATIONALE

In 2013, more than 100.000 people were diagnosed with cancer in the Netherlands [1]. For an effective treatment, accurate staging of cancer is of great importance. In recent years, Positron Emission Tomography imaging combined with Computed Tomography (PET/CT) (Figure 1A) using the radioactive tracer ^{18}F-fluorodeoxyglucose (FDG) became important for staging, response monitoring and prognosis prediction in patients with cancer [2-4].

With FDG-PET/CT, the glucose consumption of the human body is visualised. Most tumors and inflammations have an increased glucose consumption (thus increased FDG uptake) as compared to healthy tissue. Therefore, FDG-PET/CT is able to characterize malignancies and lesions, find metastases and determine the reaction to treatment by visualizing the degree of glucose (FDG) uptake which than shows up on a PET scan as a 'hotspot'. However, the spatial resolution of current PET/CT systems is relatively low. This results in an underestimation of the true FDG uptake of small lesions, which limits the detection of small lesions and accurate staging [5]. Improvements in PET detector technology may lead to improved image quality, which may translate into a more accurate diagnosis and ultimately may improve patient management.

Recently, a completely new type of PET detectors has been developed. After years of preparatory work, this new detector - called 'digital' detector - is now ready for incorporation into clinical PET/CT scanners. In 2017, one of these new types of PET/CT scanners (Figure 1B) will be installed in the Nuclear Medicine (NM) department in Isala, Zwolle, the Netherlands, as one of the first three systems in the world. As opposed to conventional scanners, this will be a digital system. The development of digital detectors for PET is expected to be a significant improvement in PET technology. PET scanners contain detector material in which a small light flash is produced when a photon strikes. In the old technology this small light flash was amplified using a photomultiplier. This is a glass vacuum tubes that finally yields a small electrical signal. The new digital PET scanner contain a silicon like counting device that allows direct digital photon counting of the flashes produced in the detector crystal, making the old-fashioned photomultiplier technique with its associated issues no longer necessary. This digital detector technology has the potential to improve PET imaging performance by providing better timing, energy and spatial resolution, higher count rate capabilities and linearity, increased contrast, reduced noise and lower required radiation dose. The CT gantry in this system is based on a commercially available CT that has not been modified in this device. This new type of PET scanner could potentially impact many clinical areas, including oncology, neurology and cardiology.

Figure 1: Pictures of a conventional (Fig. 1A) and a digital (Fig. 1B) PET/CT system.

The present study is intended to provide an initial assessment of the digital PET technology as used in a clinical setting. Patient images acquired on the digital PET system will be directly compared to images of the same patient acquired on a commercially released clinical PET/CT system equipped with the conventional photomultiplier tube detectors. For a period of 6-12 months, both a conventional and a digital PET/CT system are available in the NM department in Isala. In this period, extensive comparisons will be made between the conventional and novel digital type of PET/CT system. We will look at technical aspects such as image quality and lesion contrast, as well as clinical aspects such as the final diagnostic outcome of the study.

Furthermore, in the past few years procedure guidelines for FDG-PET tumor imaging were published by the European Association of Nuclear Medicine (EANM) to provide a minimum standard for the acquisition and interpretation of FDG-PET/CT scans [6]. These common standards are useful for quantification, valuable for response monitoring and increasingly used in multi-center trials. For the digital PET/CT system, acquisition- and reconstruction settings to fulfill these procedure guidelines yet need to be determined. Both calibration and validation of various system settings will be done in this study.

In the current study we will focus on three specific patients groups; patients with (suspected) lung cancer, breast cancer and esophageal cancer. There are multiple reasons for choosing these three patients groups for the present study:

1. FDG-PET/CT imaging is frequently used in these patient groups and has importance for diagnosis and disease staging.
2. In many cases within these groups, invasive staging procedures are performed in our hospital after PET/CT acquisition. This provides validation material that can be used to compare the clinical performance of conventional and digital PET/CT.

3. The disease incidence for these three cancer types is fairly high, providing the opportunity to reach a large enough study population within the selected period.
4. In these cancer types, the areas of nodal metastases are the mediastinum, the axillae and the upper abdomen. In this way we will obtain a fairly complete impression of PET staging properties in a large proportion of relevant tissue areas.

With the inclusion of these three patients groups, we will be able to make a comparison of conventional and digital PET/CT for these specified groups. However, we expect that such findings can be extrapolated to obtain an impression of the general clinical impact of digital PET/CT in all patients with cancer. Possibly the data from this study can be used to identify specific clinical areas where the digital technology may outperform conventional PET technology. Such initial data may be used to plan specific, hypothesis-driven follow-up studies to support performance and clinical claims for digital PET in general.

2. OBJECTIVES

2.1 Primary objectives: lesion detection properties

How does the diagnostic outcome of the digital PET/CT study compare to the outcome of conventional PET/CT in patients referred for (re)staging of lung cancer, breast cancer and esophageal cancer? In other words: does digital PET detect more, the same or less abnormalities in patients with cancer.

More in detail:

1.1 What is the difference in the number of lymph node metastases?

1.2 What is the difference in the number of involved lymph node stations?

1.3 What is the difference in the N status?

1.4 What is the difference in the number of distant metastases?

1.5 What is the difference in the number of involved distant metastatic systems (e.g. bone, brain, adrenals, liver, lungs)?

1.6 What is the difference in the M status?

1.7 What is the overall difference in final TNM classification?

1.8 Using a composite reference standard, what is the sensitivity, specificity and accuracy for lymph node staging, distant metastatic and overall staging of digital PET/CT as compared to conventional PET/CT?

1.9 Is there a difference in unrelated accidental findings?

2.2 Secondary objectives: image quality

What is the image quality (in both quantitative and qualitative terms) of digital PET as compared to conventional PET?

2.1 How do experienced readers rate digital PET image quality?

2.2 How does digital PET influence diagnostic confidence for N- and M-staging?

2.3 Are there differences in the appearance of normal tissues between digital and conventional PET?

2.4 What is the lesion detectability for digital PET as compared to conventional PET?

2.5 What is the optimal cut-off value of tumor uptake or lesion contrast to distinguish between benign and malignant lesions for digital PET, and how does this compare to conventional PET?

2.6 What are the optimal settings for digital PET to fulfill EANM procedure guidelines?

2.7 Do conventional and digital PET/CT studies, that both fulfill EANM procedure guidelines, provide comparable final PET/CT results?

Both the set of primary and secondary objective research questions can be studied in a variety of subgroups, based on tumor type, lesion size or other clinical factors.

3. STUDY DESIGN

We will perform a single center diagnostic accuracy study, in which patient-scans obtained using two types of PET/CT scanners (1 clinical study on the conventional system and 1 clinical study on the digital system) will be intra-individually compared.

Patient selection will be performed at the NM department in Isala. Patient eligibility will be based on the information provided by the referring specialist on the requisition for the clinical FDG-PET/CT study.

Patients will be included during the inclusion period of 6-12 months. Patients that meet the inclusion criteria and have signed informed consent will undergo two PET/CT scans on both the conventional and the digital PET system, immediately after each other. The scan order will be randomized per week:

- Week 1: first scan on conventional PET/CT, second scan on digital PET/CT.
- Week 2: first scan on digital PET/CT, second scan on conventional PET/CT. Etc.

For each patient, we start with a separate analysis of conventional and digital PET/CT images. One investigator will evaluate the PET/CT images quantitatively while two NM physicians will give qualitative (visual) judgments. Afterwards, we compare conventional and digital findings for all patients.

PET/CT data will be analyzed based on three subgroups of patients with lung cancer, breast cancer and esophageal cancer respectively. Pathology results and follow-up imaging by PET, CT, echography and MRI will be used as gold standard. When validation results are not available, conventional and digital PET/CT results are just compared with each other. More information on data analysis is described in section 5.2.

4. STUDY POPULATION

4.1 Population (base)

During the time that the study is open, we will select consecutive patients based on the information provided by the referring physician on the requisition for the study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- referred to Isala for a clinically indicated FDG-PET/CT scan
- suspected or proven lung cancer, esophageal cancer or breast cancer, either as a primary diagnosis or follow-up study
- signed informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- age < 18 years
- incapacitated adults
- prisoners
- pregnant patients
- unable to undergo two consecutive PET/CT scans

4.4 Sample size calculation

From the detailed research questions stated in chapter 2, a rough estimate of the number of required subjects will be calculated, although this is difficult because the clinical performance parameters for digital PET are not available yet. The only qualitative impression from preliminary images is that image quality and detection properties are going to be significantly better.

Sample size calculations are performed for primary objectives 1.1 and 1.3. We do not formally calculate estimates for the remaining objectives, but estimate that there will be ample scans to answer these objectives, once the first questions have been answered. Furthermore in general, we expect that around 10% of the patients that are included in this study show a negative PET/CT scan, without the presence of malignant disease. Therefore, we will increase the required number of patients with 10%, to reach the required number of patients with malignancies for this study.

The sample size calculation is performed for the three subgroups of cancer types separately. However, the sample size calculation for patients with lung cancer and patients with breast cancer is identical, due to a roughly comparable disease incidence (and thus a comparable amount of FDG-PET/CT scans acquired) and a comparable expected performance. For esophageal cancer, a separate sample size calculation is provided, due to a lower disease incidence.

Sample size calculation for patients with lung cancer and patients with breast cancer:

Objective 1.1 What is the difference in the number of lymph node metastases?

*For power-calculations we translated this question into: does digital PET detect more, fewer or identical numbers of lymph node metastasis? We would like to be able to detect a **20%** difference, if present. This level is generally considered relevant in obtaining a new type of scanner. Using the two-tailed sign-test, assuming a power of 80% and a p value of 0.05, this requires the inclusion of **49** subjects. After applying the 10%-correction for the inclusion of negative PET/CT scans, the number of required subjects is **54.***

Objective 1.3 What is the difference in the N status?

*For power-calculations we translated this question into: is the N-status on digital PET equal, lower or higher as compared to conventional PET? We would like to be able to detect a **16%** difference, if present. Using the two-tailed sign-test, assuming a power of 80% and a p value of 0.05, this requires the inclusion of **79** subjects. After applying the correction for negative PET/CT scans, the number of required subjects is **87.***

Sample size calculation for patients with esophageal cancer:

The incidence of esophageal cancer is much lower as compared to lung and breast cancer. As a consequence, the number of FDG-PET/CT scans that is acquired for this

patient group is much lower. Therefore, we accept a lower level of power (65%) and a lower significance level ($p < 0.10$) for the sample size calculation for this specific tumor type.

Objective 1.1 What is the difference in the number of lymph node metastases?

*For power-calculations we translated this question into: does digital PET detect more, fewer or identical numbers of lymph node metastasis? We would like to be able to detect a **20%** difference, if present. This level is generally considered relevant in obtaining a new type of scanner. Using the two-tailed sign-test, assuming a power of 65% and a p value of 0.10, this requires the inclusion of **28** subjects. After applying the correction for negative PET/CT scans, the number of required subjects is **31.***

Objective 1.3 What is the difference in the N status?

*For power-calculations we translated this question into: is the N-status on digital PET equal, lower or higher as compared to conventional PET? We would like to be able to detect a **16%** difference, if present. Using the two-tailed sign-test, assuming a power of 65% and a p value of 0.10, this requires the inclusion of **42** subjects. After applying the correction for negative PET/CT scans, the number of required subjects is **46.***

From all above calculations, we aim to include 90 patients with lung cancer, 90 patients with breast cancer and 45 esophageal cancer patients, for a total of 225 patients.

5. METHODS

5.1 Study procedures

5.1.1 Patient selection

During the study period, all referrals for FDG-PET/CT scans in the NM department in Isala will be evaluated by one of the investigators. Based on inclusion and exclusion criteria, the investigator makes an initial selection of patients suitable for this study. Each referral that meets the inclusion criteria will be listed. For these selected patients, we plan a informed consent talk of around 15 minutes with a NM physician, physician assistant or one of the investigators. This talk takes place prior to the first clinical FDG-PET/CT scan. More details on the informed-consent procedure are described in section 8.2 Recruitment and consent.

5.1.2 FDG injection (clinical procedure)

All FDG-PET/CT scans for this study will be acquired on the NM department in Isala (Zwolle). Before acquisition, patients have to be at least 6 hours sober. Before intravenous injection of the radiotracer FDG (GE Healthcare, radiopharmacy, Zwolle), blood glucose levels will be measured to ensure a value below 15 millimol/L. Depending on patients' body weight, 185-500 megabecquerel (MBq) of FDG will be administered (Figure 4).

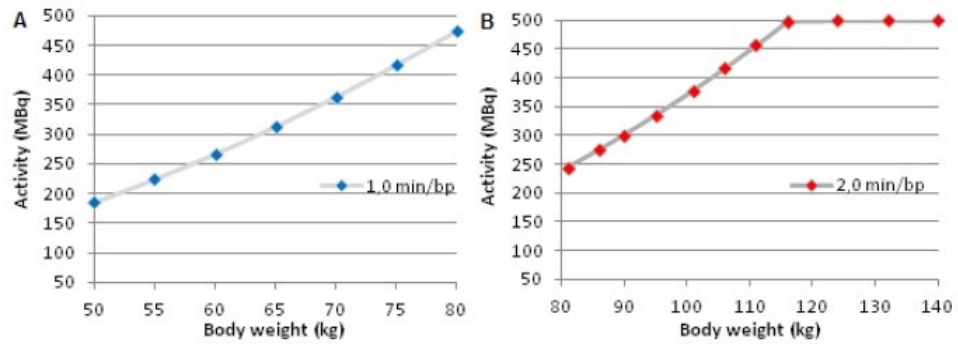


Figure 4: Dose-scan time protocol for the conventional PET/CT system, based on patients' body weight (in kilogram). For patients with a body weight up to 80 kilogram, PET acquisition time is 1 minute per bed position. PET acquisition time is 2 minutes per bed position for patients with a body weight from 81 kilogram. On average 11 bed positions are required to cover the whole-body region.

5.1.3 First PET/CT acquisition

Sixty minutes after FDG tracer injection, a standard clinical whole-body PET/CT scan is performed on the conventional or digital PET/CT scanner. (As mentioned in the study design, the PET scan order is randomized per week). For the first scan, the acquisition times are 1 and 2 minutes per bed position for patients with body weight up to 80 kilogram and from 81 kilogram respectively. To cover the whole-body region, on average 11 bed positions are required. This results in total PET

acquisition times of approximately 11 and 22 minutes for patients with body weight ≤ 80 kg and > 80 kg respectively. Furthermore, attenuation CT acquisition takes around 5 minutes in all patients. Moreover, for many patients an additional diagnostic contrast-enhanced CT scan is acquired on the clinical PET/CT system with a total procedure time of approximately 15 minutes.

5.1.4 Second PET/CT acquisition (study procedure)

Consecutively after the first PET/CT scan, an additional PET/CT scan is acquired on the second PET/CT system. To minimize the decrease in FDG present in the human body when performing the second PET/CT scan, the time between first and second PET/CT scan should be kept as short as possible. However, the amount of FDG present in the human body during the second PET/CT scan will be less as compared to the first PET/CT scan. Therefore, the acquisition time for second PET/CT scanning will equal to first PET/CT scan, plus a compensation for the radioactive decay. Due to differences in PET acquisition times and the acquisition of a diagnostic CT scan, there will be differences in delay time between patients. In general, patients can be divided in four groups for expected delay:

1. Patient bodyweight ≤ 80 kg and no diagnostic ceCT: delay ≈ 21 minutes
2. Patient bodyweight > 80 kg and no diagnostic ceCT: delay ≈ 32 minutes
3. Patient bodyweight ≤ 80 kg and a diagnostic ceCT: delay ≈ 36 minutes
4. Patient bodyweight > 80 kg and a diagnostic ceCT: delay ≈ 47 minutes

FDG has a half-life of 110 minutes. Using the formula for radioactive decay $N(t) = N(0)*0.5^{T/T0.5}$, the percentage of FDG after the delay can be calculated. The correction factor is determined by calculating the inverse of the percentage of FDG, present after the delay. Based on this correction factor, the total acquisition time for the second PET/CT system can be calculated. Table 2 provides an indication of the scan times required for digital PET/CT scanning. As can be seen in this table, patients' bodyweight (≤80 kg or >80kg) is the main predicting factor whether the acquisition time on second PET takes approximately 20 minutes or approximately 35 minutes. Based on this estimation, we expect that the additional time for patients participating in this study will typically be 25 minutes but will not take more than 40 minutes.

Table 2: Indications of total scan time on second PET/CT system, based on expected delays in four groups of patients. The total scan time on second PET/CT includes the time for PET acquisition (with 11 bed positions (bp)) and attenuation CT acquisition.

Patient group	Delay in minutes (≈)	Amount of FDG after delay (%)	Correction factor	Second PET, scan time per bp (s)	Second PET/CT scan time (min)
1	21	88%	1.14	60*1.14 = 68	18
2	32	82%	1.22	120*1.22 = 147	32
3	36	80%	1.25	60*1.25 = 75	19
4	47	74%	1.34	120*1.34 = 161	35

To provide an optimal comparison between conventional and digital PET/CT, we will use a patient-specific protocol for the second PET scan, based on the exact delay for each patient. This delay will be determined once the patient arrives in the room for the second PET/CT scan and will be used to set the final PET scan time per bed position for the second PET scan, for each patient separately.

5.1.5 PET/CT data reconstruction

For both conventional and digital PET/CT, the attenuation correction of PET images is based on CT attenuation maps. For the conventional PET/CT study, images will be reconstructed using standard clinical Isala protocol. This protocol includes two types of reconstructions: one reconstruction method fulfilling EANM guidelines for FDG-PET tumor imaging and one reconstruction method for optimal lesion detection using small 2x2x2 mm^3 voxels [7].

Digital PET/CT images will initially be reconstructed using a protocol advised by the vendor. However, in retrospective we may perform several additional reconstructions on the PET/CT scans obtained during this study. This will be done to determine and evaluate for example optimal settings for image quality, lesion detectability and clinical performance. This will also include the reconstruction fulfilling EANM guidelines for FDG-PET tumor imaging.

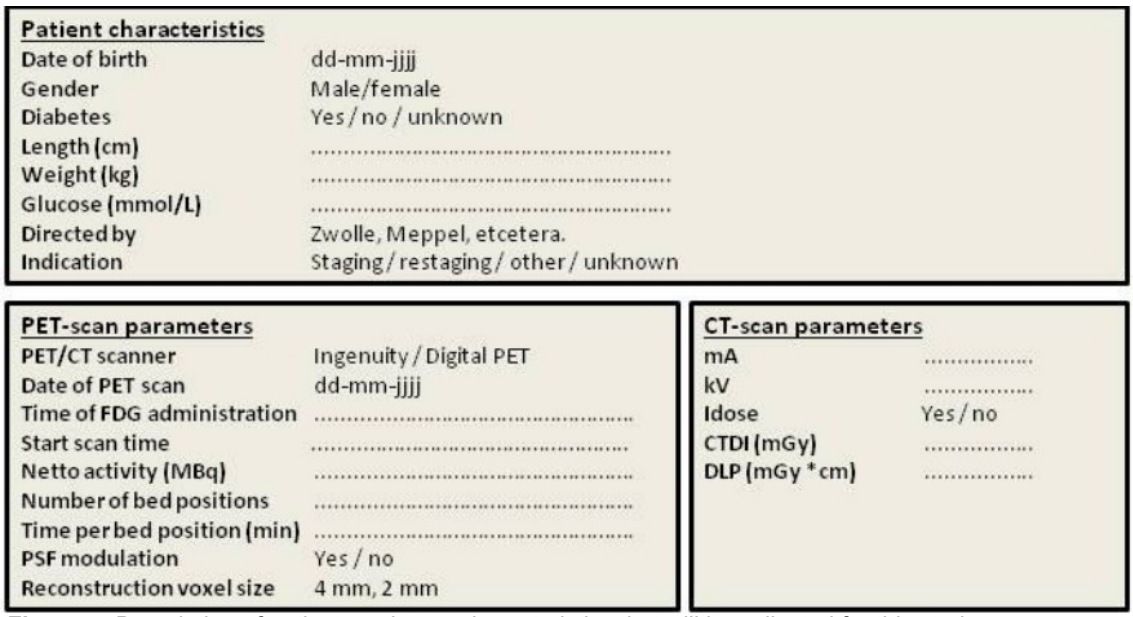
5.1.6 PET/CT diagnoses

Diagnoses will be made from images acquired on both the conventional and digital PET/CT system. The images acquired from the digital PET/CT scan will be included in the patients' medical record. The nuclear medicine physician will mention differences between the analog and digital PET in the PET/CT report, and the referring physician can discuss this with the patient.

5.2 Data collection and analysis

5.2.1 General data collection

For each patient, we will collect several patient- and scan characteristics as presented in Figure 5.



Patient characteristics	
Date of birth	dd-mm-jjjj
Gender	Male/female
Diabetes	Yes / no / unknown
Length (cm)	.....
Weight (kg)	.....
Glucose (mmol/L)	.....
Directed by	Zwolle, Meppel, etcetera.
Indication	Staging / restaging / other / unknown

PET-scan parameters	
PET/CT scanner	Ingenuity / Digital PET
Date of PET scan	dd-mm-jjjj
Time of FDG administration	.....
Start scan time	.....
Netto activity (MBq)	.....
Number of bed positions	.....
Time per bed position (min)	.....
PSF modulation	Yes / no
Reconstruction voxel size	4 mm, 2 mm

CT-scan parameters	
mA	.....
kV	.....
Idose	Yes / no
CTDI (mGy)	.....
DLP (mGy * cm)	.....

Figure 5: Description of patient- and scan characteristics that will be collected for this study.

For each patient, we will start with an analysis of both conventional and digital PET/CT images separately. One investigator will evaluate the PET/CT images quantitatively while two NM physicians will give qualitative (visual) judgments. When both conventional and digital PET/CT images from a patient are evaluated separately, the results will be compared and differences between the image datasets will be identified.

We will focus on PET/CT based TNM staging, which includes evaluation of the primary tumor, regional lymph nodes and distant metastasis. This means that for patients with (suspected) lung cancer, we will focus on the evaluation of primary lung tumor(s), mediastinal and hilair lymph nodes and distant metastases (in particular adrenal glands). For patient with (suspected) breast cancer, we will focus on the analysis of primary breast tumors, regional lymph nodes (axillary, subclaviculair, internal mammary and supraclavicular) and distant metastases. In patients suspicious for esophageal cancer, we will focus on the primary esophageal tumor, regional lymph nodes in the thorax and lower abdomen, and distant metastasis. Furthermore, other (rather unexpected) findings and differences between conventional and digital PET imaging will be studied and documented.

5.2.2 PET/CT evaluation

Quantitative evaluation

The following general measurements will be performed on all PET images:

- Liver noise level
- Lung noise level
- Normal tissue uptake (SUVmean and SUVmax) in both lungs, blood pool, liver, both adrenal glands, spleen, bones and bone marrow.

For all lesions, the following measurements will be performed on PET images:

- SUVmax
- SUVmean (based on 50% SUVmax)
- Volume om mL (based on 50%SUVmax)
- Lesion contrast
- Lesion contrast-to-noise
- Lesion-to-liver ratio
- Lesion-to-aorta ratio

Furthermore, the lesion diameter as measured on the attenuation CT scan will be collected to make stratifications based on lesion diameter.

Qualitative (visual) evaluation

Visual assessment of conventional and digital PET images will be performed by two NM physicians, blinded for patient characteristics and patient history. They perform a general evaluation for:

- PET image quality (4-point scale: poor, fair, good, excellent)
- Liver noise (4-point scale: low, mild, moderate, high)
- Lung noise (4-point scale: low, mild, moderate, high)
- Assessment of any visible artifacts, occurrence of distortion or any other visual impressions

Moreover, each selected lesion will be visually evaluated on both PET datasets using a 4-point scale:

1. No visualization
2. Mild intensity
3. Moderate intensity
4. High intensity

Moreover, the NM physicians will both judge each lesion on a 4-point scale (definitely benign, likely benign, likely malignant, definitely malignant) on both

datasets separately. This is used for performance evaluation in lesion characterization, and to compare the diagnostic confidence.

Finally, the adrenal glands are visually assessed using the following 4-point scale:

1. Uptake below liver uptake
2. Uptake equal to liver
3. Uptake slightly greater than liver uptake
4. Uptake much greater than liver uptake

To reduce the impact of a potential learning effect for reading digital PET images, we will randomize the reading order for both NM physicians.

5.2.3 Validation

For each patient, the results of the PET/CT studies will be compared with available validation results. It is preferred that this regards invasive staging with pathology (PA) evaluation, although it may also include follow-up or information from other imaging modalities such as MRI and contrast-enhanced CT. Validation shall be performed based on findings from both conventional and digital PET/CT.

5.2.4 EANM procedure guidelines

In the present study, we will calibrate and validate the EANM procedure guidelines for FDG-PET tumor imaging on a digital PET/CT system. Calibration of the required acquisition and reconstruction settings will be done by performing a phantom study. Afterwards, the digital PET/CT scans are reconstructed using the predefined acquisition and reconstruction settings.

For each patient, the conventional and digital PET/CT scans that fulfill EANM procedure guidelines will be visually compared by two NM physicians. For both datasets, they will provide a final diagnostic outcome which will be compared. These EANM-fulfilled scans will also be compared quantitatively, but we will be cautious to use those measurements for finite conclusions on EANM-validation due to the time delay between conventional and digital PET/CT.

5.3 Main study parameters

5.3.1 Primary study parameter

Diagnostic outcome of the PET/CT study

In more detail:

- Number of lymph node metastasis
- Involved lymph node stations
- N-status
- Number of distant metastasis
- Involved distant metastatic systems (e.g. bone, brain, adrenals, liver, lungs)
- M-status
- Final TNM classification
- Sensitivity, specificity and accuracy for lymph node staging, distant metastatic and overall staging
- Unrelated accidental findings

5.3.2 Secondary study parameter

PET image quality

In more detail:

- General PET image quality
  - Subjective: whole-body, liver and lung
  - Objective: liver and lung noise
- Diagnostic confidence for N- and M-staging
- Normal tissue appearance
- Lesion detectability (SUVmax, SUVmean (based on 50% SUVmax), lesion volume, lesion contrast, lesion contrast-to-noise ratio, lesion-to-liver ratio, lesion-to-aorta ratio as compared to lesion diameter measured on the attenuation CT)
- Optimal cut-off values of tumor uptake or lesion contrast to distinguish between benign and malignant lesions
- Optimal settings for digital PET to fulfill EANM procedure guidelines
- Comparison of conventional and digital PET fulfilling EANM procedure guidelines, based on:
  - Subjective opinion from NM physicians (lesion-based and patient-based)
  - Quantitative measurements (lesion-based)

5.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

5.5 Replacement of individual subjects after withdrawal

If an included individual subject withdraws from the study, another subject can be included and replaces this subject.

5.6 Follow-up of subjects withdrawn from treatment

There will be no follow up of subjects, withdrawn from this study.

6. SAFETY REPORTING

6.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The occurrence of any adverse events due to the conduct of the study is not foreseen. Risks associated with the digital PET/CT system have been evaluated and are mitigated according to industry safety standards for radiation, mechanical, thermal, and electric hazards. Foreseeable adverse events associated with this investigation linked to the device would be considered very rare and would be the same type of physical events that could occur in any normal PET/CT scan. These would include pinching of skin, minor falls or bumps.

Normal risks of NM scans from the injection of a radiopharmaceutical include allergic reactions, swelling, infections, intravenous injuries, bruising, pain and discomfort. These hazards, if encountered, would likely occur as the result of the scheduled clinical PET/CT scan. Clinical guidelines for the PET and CT scan will be followed according to hospital policy.

The following adverse changes from baseline require reporting as Adverse Events:

- Any adverse change that has either of the following relations to the investigational device or study procedures: 'possibly related' or 'related'
- Any event that is an Unanticipated Adverse Device Effect

An adverse change that does not meet any of the above does not require reporting to the Sponsor (or the METC).

6.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The PI will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the PI has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

6.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7. STATISTICAL ANALYSIS

7.1 Main study parameters

Differences are specified as follows: generally when performing the lesion-based or patient-based comparison between conventional and digital PET, all disagreements in measured scales, numbers of lesions and quantitative data will be regarded as differences. Furthermore, all disagreements in T, N and M stage between conventional and digital PET will be regarded as differences.

7.1.1 Primary objective: diagnostic outcome of the PET/CT studies

For each patient separately, the diagnostic outcome for the conventional and digital PET/CT study will be compared. Measured ordinal differences in for example the N-status or the TNM classification will be assessed based on two methods. The first method is based on the sign test, in which the comparison results in an agreement or a disagreement. The second method is based on the Wilcoxon signed-ranked test, in which the amount of disagreement is also taken into account. Moreover, we will calculate agreement percentages on the diagnostic outcome between both systems. Furthermore, using validation results as a reference, we will determine the sensitivity, specificity and accuracy for both NM physicians based on the following formulas:

$$Sensitivity = N\ PET\ positive\ /\ N\ true\ positive$$

$$Specificty = N\ PET\ negative\ /\ N\ true\ negative$$

$$Accuracy = N\ PET\ positive + N\ PET\ negative\ /\ N\ true\ positive + N\ true\ negative$$

To test whether differences in sensitivity, specificity and accuracy between conventional and digital PET/CT are significant, we will apply the McNemar paired proportion test. A p value of less than 0.05 will be considered to indicate statistical significance.

7.1.2 Secondary objective: PET image quality

General PET image quality

We will perform a population-based comparison between conventional and digital PET for general PET image quality and noise levels in the liver and lung. Differences in scores will be assessed using the sign test and the Wilcoxon signed-rank test. Furthermore, to evaluate the inter-observer variation between the subjective opinions from both NM physicians, we will calculate the kappa and compare the percentage agreement of PET image quality and noise levels in the liver and lung.

Diagnostic confidence

Differences in diagnostic confidence between conventional and digital PET are assessed using the sign test and the Wilcoxon signed-rank test.

Normal tissue appearance

When looking at the normal tissue appearance, we will perform a population-based comparison of average values in normal tissue uptake between conventional and digital PET/CT. Differences will be assessed using the Wilcoxon signed-rank test. It is expected that patient delay may influence normal tissue FDG-uptake. Therefore, we will study the presence of correlations between the amount of time-delay and differences in normal tissue uptake between conventional- and digital scans.

Lesion detectability

For all lesions that are detected on both scans, we will compare all parameters (such as lesion SUVmean, SUVmax and contrast) measured on conventional and digital PET. Differences between conventional and digital PET will be assessed using the Wilcoxon signed-rank test.

Optimal cut-off values

To compare the performance of various quantitative PET evaluation parameters (such as lesion SUVmean, SUVmax and contrast), we will create receiver operating characteristic (ROC) curves and calculate sensitivity, specificity and accuracy values using validation results as a reference. Again, to test whether differences in sensitivity, specificity and accuracy between conventional and digital PET/CT are significant, we will apply the McNemar paired proportion test. A p value of less than 0.05 will be considered to indicate statistical significance. Finally, for each quantitative evaluation parameter, we will determine the optimal cut-off value to distinguish benign from malignant lesions on both conventional and digital PET/CT. This will be based on the value with optimal sensitivity and specificity (highest sum).

EANM procedure guidelines

It is expected that both conventional and digital PET/CT studies, which fulfill EANM procedure guidelines, provide a comparable PET/CT diagnostic outcome. These results will be evaluated for all patients. Differences in diagnostic outcome will be assessed using the sign-test and the Wilcoxon signed-rank test.

Inter-observer agreements

Two NM physicians will evaluate conventional and digital PET/CT images on final diagnostic outcome, general image quality and diagnostic confidence. To evaluate the inter-observer variation between these two operators, we will compare percentage agreements and calculate a kappa.

Both the set of primary and secondary study parameters will be studied in a variety of subgroups, based on tumor type, lesion size and other clinical factors.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (a Dutch act called the 'WMO').

8.2 Recruitment and consent

During the study period, all referrals for FDG-PET/CT scans in the NM department in Isala will be evaluated by one of the investigators. Based on inclusion and exclusion criteria, the investigator makes an initial selection of patients suitable for this study. Because the time period between PET/CT referral and PET/CT acquisition is very short (only a few days), we will approach the patients when they arrive at the NM department for their clinical PET/CT scan.

During a personal talk with a NM physician, physician assistant or one of the investigators, an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study will be provided. Furthermore, the patient receives the study information letter. The patient will be given the opportunity to discuss the participation with family and friends (if they desire) or to further review on their own prior to signing the informed-consent form. After the personal talk, the radioactive tracer FDG is injected and the patient has to wait for 60 minutes (exposure time). After this waiting period, we ask the patient to sign the informed-consent form. Subsequently the first and eventually second PET/CT scan are acquired. The patient will have at least one hour to consider his decision.

The written consent form will be revised if new information becomes available during the study that may be relevant to the subject. Any revision(s) will be submitted to the METC for review and approval in advance of use.

8.3 Benefits and risks assessment, group relatedness

For patients participating in this study, there are two main disadvantages that should be mentioned: the additional scan time and the additional radiation dose. Furthermore, patients may benefit from participation in this study, as the digital PET/CT images may reveal more diagnostic information compared with the conventional PET/CT scan.

8.3.1 Additional scan time

The second PET/CT study will be obtained immediately after the first PET study employing the same FDG injection. Study-participants will therefore remain averagely 30-40 minutes longer in the NM department than non-participants. In this time period, the additional scan will be acquired on the second PET/CT scanner. The additional time in the scanner will typically be 25 minutes (maximum 40 minutes), in which patients have to lie still on a scanner bed.

8.3.2 Additional radiation dose

The extra study-related low-dose CT scan will give an additional radiation dose of on average 6 milliSievert (mSv). In comparison: in a standard clinical FDG-PET/CT scan, the average dose is 14 mSv which constitutes the dose from a low-dose CT scan for attenuation-correction and the dose from FDG, depending on patients' body weight. When the standard clinical PET/CT scan is combined with a diagnostic CT scan using intravenous contrast, the average dose is approximately 22 mSv. Furthermore, a large amount of patients from our study population will be treated with radiotherapy, where patients receive up to 100 times higher doses as compared to the dose that patients receive with diagnostic imaging. Moreover, participating in this study does not influence the ability to acquire other diagnostic imaging scans.

8.4 Justification for the proposed study

Before a novel PET/CT system that is based on a completely new detector technique can enter clinical practice, extensive clinical research is required. The proposed study will provide detailed information on the technical and clinical performance of the novel digital PET/CT system. The extra burden for the patient participating in this study is relative low and furthermore there is a relative low risk for side effects and other issues for patients participating in this study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

The handling of personal data complies with the Dutch Personal Data Protection Act. Research data will be stored in a research database (Research manager). Data is added to the database by two investigators. One investigator has the key to access the source data. This document is protected by an account name and password.

On request, the coded anonymized raw data and processed images, will be provided to Philips for analysis and post-processing. A secure point to point data transfer with an existing capability will be used, or if the data sets are too large for practical transmission, we will use encrypted hard drives.

Each dataset will be coded with an unique study identifier assigned by the principal investigator (PI) or designee. The PI will maintain a document with the name of the patient and their associated study identification number. Additionally, Isala will provide Philips with coded medical record information (i.e., patient medical history), diagnostic reports (as relevant for the study), etc.) when it is determined to aid in the evaluation of the digital PET images. The patients personal health information, such as name, medical record number etc., will not be divulged to Philips. Isala will maintain all research related documents and dataset on secured servers with password protection or in a locked area with limited access.

9.2 Monitoring and Quality Assurance

A study binder will be maintained at the site that will include the protocol, METC documents, Case Report Forms, and other study logs and records. The site study coordinator and investigator will be responsible for keeping the information up-to-date. All records pertaining to the conduct of the clinical study, including case report forms, informed consent forms, source documents, METC correspondence and other study documentation will be retained at the site.

The records will be maintained for a period of at least 15 years, including 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a Pre-market Notification Clearance.

9.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

9.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

9.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the moment that 225 patients are included. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.6 Public disclosure and publication policy

Results provided by this study will be submitted for publication in peer-reviewed scientific journals, but may also be used to support marketing and regulatory claims. Both negative, indifferent and positive results can be considered for publication.

For the remaining arrangements regarding data sharing between the site (Isala) and Philips Healthcare, we refer to the mutually agreed document “Data sharing plan”, version 3

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