Public Assessment Report

Scientific discussion

GlucoPET 250 MBq/ml, solution for injection (fludeoxyglucose (18F))

NL/H/4774/001/DC

23 January 2023

This module reflects the scientific discussion for the approval of GlucoPET 250 MBq/ml. The procedure was finalised at 30 September 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Alveolar echinococcosis
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central nervous system
CT	Computed tomography
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EF	Ejection fraction
ERA	Environmental Risk Assessment
FUO	Fever of unknown origin
GLUT1	Facilitative glucose transporter
ICH	International Conference of Harmonisation
ID	Injected dose
LN	Lymph node
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorisation Holder
MRI	Magnetic resonance imaging
MTLE	Mesial temporal lobe epilepsy
PET	Positron emission tomography
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SPECT	Single photon emission computed tomography
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UPT	Unknown primary tumours
U/S	Ultrasound scans

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for GlucoPET 250 MBq/ml, solution for injection, from GE Healthcare B.V.

This medicinal product is for diagnostic use only.

The active substance (fludeoxyglucose (^{18}F)) is indicated for use with positron emission tomography (PET) in adults and pediatric patients. The active substance is abbreviated as ^{18}F-FDG throughout this report.

Oncology
In patients undergoing oncologic diagnostic procedures describing function or diseases where enhanced glucose influx of specific organs or tissues is the diagnostic target. The following indications are sufficiently documented (see also section 4.4 of the SmPC):

Diagnosis:
- Characterisation of solitary pulmonary nodule;
- Detection of cancer of unknown origin, revealed for example by cervical adenopathy, liver or bones metastases;
- Characterisation of a pancreatic mass.

Staging:
- Head and neck cancers including assistance in guiding biopsy;
- Primary lung cancer;
- Locally advanced breast cancer;
- Oesophageal cancer;
- Carcinoma of the pancreas;
- Colorectal cancer particularly in restaging recurrences;
- Malignant lymphoma;
- Malignant melanoma, Breslow >1.5 mm or lymph node metastasis at first diagnosis.

Monitoring of therapeutic response:
- Malignant lymphoma;
- Head and neck cancers.

Detection in case of reasonable suspicion of recurrences:
- Glioma with high grade of malignancy (III or IV);
- Head and neck cancers;
- Thyroid cancer (non-medullary): patients with increased thyroglobulin serum levels and negative radioactive iodine whole body scintigraphy;
- Primary lung cancer;

- Breast cancer;
- Carcinoma of the pancreas;
- Colorectal cancer;
- Ovarian cancer;
- Malignant lymphoma;
- Malignant melanoma.

Cardiology
In the cardiologic indication, the diagnostic target is viable myocardial tissue that takes-up glucose but is hypo-perfused, as it must be assessed beforehand using appropriate blood-flow imaging techniques.
- Evaluation of myocardial viability in patients with severe impaired left ventricular function who are candidates for revascularisation when conventional imaging modalities are not contributive.

Neurology
In the neurologic indication the interictal glucose hypometabolism is the diagnostic target.
- Localisation of epileptogenic foci in the presurgical evaluation of partial temporal epilepsy.

Infectious or inflammatory diseases
In infectious or inflammatory diseases, the diagnostic target is tissue or structures with an abnormal content of activated white blood cells.
In infectious or inflammatory diseases, the following indications are sufficiently documented:

Localisation of abnormal foci guiding the aetiologic diagnosis in case of fever of unknown origin.

Diagnosis of infection in case of:
- Suspected chronic infection of bone and/or adjacent structures: osteomyelitis, spondilitis, diskitis or osteitis including when metallic implants are present;
- Diabetic patient with a foot suspicious of Charcot's neuroarthropathy, osteomyelitis and/or soft tissue infection;
- Painful hip prosthesis;
- Vascular prosthesis;
- Fever in an AIDS patient;
- Detection of septic metastatic sites in case of bacteraemia or endocarditis (see also section 4.4 of the SmPC).

Detection of the extension of inflammation in case of:
- Sarcoidosis;
- Inflammatory bowel disease;
- Vasculitis involving the great vessels.

Therapy follow-up:
Unresectable alveolar echinococcosis, in search for active localisations of the parasite during medical treatment and after treatment discontinuation.

A comprehensive description of the indications and posology is given in the SmPC.

Rationale
Currently, anatomical imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound scans (U/S), play a key role in the diagnosis and treatment of cancer patients. They yield high quality morphological information that clinicians can use in patient management. However, they also present with several important shortcomings. For example, some early malignant changes may not be accompanied by anatomical changes and may therefore not be apparent with these techniques. It is generally recognised that the earlier the stage a cancer is detected at, the better the prognosis. In addition, post treatment changes are usually indistinguishable from recurrence or residual disease. Functional imaging with ^{18}F-FDG tries to overcome these issues. ^{18}F-FDG uptake is not based on size or structural changes but on two key characteristics: the presence of living cells and their metabolic status.

Legal base
The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. For this type of application, MAHs need to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. The MAH also submitted data showing that the bioavailability of GlucoPET is similar to the bioavailability of the product most commonly studied in the scientific literature.

The concerned member state (CMS) involved in this procedure was Norway.

II.   QUALITY ASPECTS

II.1   Introduction

GlucoPET 250 MBq/ml is a clear, colourless or slightly yellow solution.

The product contains as active substance 250 MBq of ^{18}F-FDG at the date and time of calibration per ml.

The solution is packed in in clear glass Ph.Eur. type I vials, sealed with a chlorobutyl rubber type I closure suitable for multiple piercing and an aluminum cap. One single vial contains 1 to 10 ml solution, corresponding to 250 MBq to 2,5 GBq at calibration.

The excipients are disodium citrate sesquihydrate (E-331), sodium citrate dihydrate (E-331), sodium chloride, hydrochloric acid, ethanol 100% and water for injection.

II.2   Drug Substance

The active substance is ^{18}F-FDG, an established active substance described in the European Pharmacopoeia (Ph.Eur.). ^{18}F-FDG is a white powder, freely soluble in water and practically insoluble in acetonitrile, ethanol and diethyl ether.

Manufacturing process
The active substance is formed during the synthetic process carried out by an automated synthesiser and is formulated into the finished product ^{18}F-FDG solution for injection. The active substance is synthesised in three chemical steps and is further purified and pH adjusted during the continuous manufacturing process. The synthetic route and the use of automated computer-assisted synthesizers are common for this type of drug substance and are therefore considered adequately described.

Quality control of drug substance
No specification has been defined for the drug substance as the manufacture of the drug substance and drug product is a continuous process. Critical steps in the manufacturing process are drying, labelling and hydrolysis.

Stability of drug substance
No stability data have been generated for the drug substance as the manufacture of the drug substance and drug product is a continuous process.

II.3   Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been described, the choice of excipients is justified and their functions explained. The main goal was to develop a product that complies with the Ph.Eur. monograph on ^{18}F-FDG injection. A common synthetic route has been chosen. Formulation development was supported by a design of experiments exploring the best combination of the amount of radioactivity, type of buffer, and amount of ethanol, resulting in the currently proposed composition. The manufacturing process includes sterile filtration of the bulk solution followed by aseptic filling of the vials. The choice of the sterilisation method is reasonable in view of the type of product, set up of the automated process, and short half-life.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process of the drug product includes dilution of the drug substance solution to the nominal radioactive concentration, mixing, sterile filtration, and filling into vials. The description of the manufacturing process is considered acceptable. Process validation data on the product has been presented for three manufacturing runs and four double manufacturing runs covering the boundaries of the process.

Control of excipients
Except for disodium citrate sesquihydrate, all excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification largely in accordance with the monograph for ^{18}F-FDG injection in the Ph.Eur. and includes tests for appearance, radionuclidic identity, radiochemical identity, radionuclidic purity, radiochemical purity, chemical purity, residual solvents, ethanol, pH, bacterial endotoxins, radioactivity concentration, radioactive content, and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life specifications are identical except for the test for endotoxins which is only carried out at release. The proposed drug product specification is acceptable. The absence of a test for the Ph.Eur. impurities A, C, and D has been justified. Radiopharmaceuticals are in the scope of the Art. 5(3) Referral on Nitrosamines. A risk evaluation addressing all currently known sources for nitrosamines listed in the EMA Q&A identified no risk.

Satisfactory validation data for the analytical methods have been provided.

The batch analysis results of the process validation batches (three manufacturing runs and four double manufacturing runs) demonstrate compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three manufacturing and four double manufacturing process validation batches in accordance with applicable European guidelines demonstrating the stability of the product for 12 hours. As the vials are multidose vials, an in-use study was carried out with two drug product batches simulating multiple piercing of the stoppers. This in-use study supports the claimed shelf life of 12 hours. On basis of the data submitted, a shelf life was granted of 12 hours if stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4   Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that GlucoPET 250 MBq/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

II.2.1 Primary pharmacodynamics

The key to the use of ^{18}F-FDG is having similar kinetics and biochemical properties as glucose. ^{18}F-FDG is transported across the cell membrane into the cytosol by the same carrier mechanism as glucose. The MAH states that increased facilitative glucose transporter (GLUT1) expression is described in many cancers, including breast, lung, kidney, urinary bladder, stomach, colorectum, endometrium, thyroid, head and neck, liver, ovary, salivary gland, and prostate cancer due to a high metabolic rate and fast growth environment. GLUT1 is a high-affinity glucose transporter, which is restricted to erythrocytes and blood-tissue barriers in most normal tissues. Choi et al (2019) showed that human erythrocytes can be sufficiently labelled with ^{18}F-FDG to acquire whole body images of the vasculature of splenectomised immunodeficient mice using a small animal positron emission tomography (PET)/CT scanner.

According to Wuest et al. (2017), sensitivity and specificity of ^{18}F-FDG imaging is limited in some cancers including breast cancer, mainly due to insufficient expression levels of GLUT1 in up to 50% of all patients. Therefore, the uptake characteristics of several hexose-based PET radiotracers were investigated in murine breast cancer model EMT6. The uptake of ^{18}F-FDG was however the highest, which is for a large part ascribed to metabolic trapping through phosphorylation by hexokinase II. The authors of the publication point to the importance of the GLUT expression levels.

Mochizuki et al. (2001) studied GLUT subtypes in mice with inflammatory lesions and compared the results with those in malignant tumours in relation to ^{14}C-FDG accumulation. The ^{14}C-FDG uptake was significantly higher in the tumour lesion (2.04 ± 0.38 % injected dose (ID)/g) than in the inflammatory lesion (0.72 ± 0.15 %ID/g). The tumour and inflammatory tissues highly expressed GLUT1 and GLUT3. The GLUT1 expression level was significantly higher in the tumour tissue than in the inflammatory tissue. This may partially explain the higher FDG accumulation in the tumour compared to the inflammatory tissue.

Within a given tissue or pathophysiological process, the retention and clearance of ^{18}F-FDG primarily reflects a tripartite dynamic balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities [Smith, 2001]. This study concluded that the rate-limiting step for FDG incorporation is highly complex, is dependent on a variety of factors and that no single step (i.e. glucose transport, phosphorylation or dephosphorylation) is likely to control FDG incorporation in tumours.

Concluding on this: metabolism can be imaged and quantified using ^{18}F-FDG, because it can act as a substrate for glucose in cells. Inside the cell, it is phosphorylated by hexokinase and as such trapped inside the cell. Metabolism can then be quantified by measuring the retained [^{18}F]FDG-6-phosphate by PET. ^{18}F-FDG is thought to accumulate more in tumour tissue than in healthy tissue because of the higher glucose utilisation in tumours and higher expression of glucose transporter GLUT1. Sufficient information was provided to support the primary pharmacodynamics of ^{18}F-FDG.

No studies were provided regarding secondary pharmacodynamics and safety pharmacology and regarding pharmacodynamic drug interactions. Considering the specific action of ^{18}F-FDG and the existing clinical experience this is acceptable. Agents that modify blood glucose levels may affect the sensitivity of the examination. A warning is included in section 4.5 of the SmPC. Other pharmacodynamic interactions are not expected.

III.2   Toxicology

III.2.1   Single dose toxicity
The information in the non-clinical overview was based on a public assessment report from the MHRA. According to the Notice to MAHs (chapter 1, section 5.4 of volume 2A), documents such as EPARs cannot be used to fulfil the requirements for a Well Established Use application, because they do not contain sufficient detail. Nevertheless, the Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95) states that single and repeated dose toxicity investigations are normally not necessary. Considering that toxicity is not expected for this glucose derivative at the recommended use and considering the clinical experience with ^{18}F-FDG, additional single dose studies are not necessary.

III.2.2   Repeat-dose toxicity
Toxicology studies in mice and dogs were described in the publication by Reivich et al (1979). The results were only described very briefly. However, considering that toxicity is not expected for this glucose derivative at the recommended use and considering the clinical experience with ^{18}F-FDG, additional repeated dose studies are not necessary.

III.3   Ecotoxicity/environmental risk assessment (ERA)

Since GlucoPET 250 MBq/ml is intended for generic substitution by well-established use, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.4   Discussion on the non-clinical aspects

The submission is intended for well-established use. As such, the MAH has not provided additional non-clinical studies and further studies are not required. An overview based on literature review is, thus, appropriate. The effects of ^{18}F-FDG are well known, and the literature on pharmacology, pharmacokinetics and toxicology has been adequately reviewed in the MAH's non-clinical overview.

IV.   CLINICAL ASPECTS

IV.1   Pharmacokinetics

GlucoPET 250MB/ml is a solution for injection and, therefore, bioequivalence studies may be waived. Bridging the current test product with the available literature based on quality, as currently provided in the response, is thus considered appropriate. The formulation of GlucoPET is based upon a citrate buffering system, whereas formulations based on phosphate buffer are also available, i.e. Steripet. Long et al. (2013) compared the use of the citrate buffer FASTlab cassettes against the phosphate buffer cassettes using the FASTlab synthesizer and concluded that there were no differences in radiochemical yield and minor differences in other parameters such as radiochemical purity, pH, and residual solvents which would not affect the clinical performance of the products as all values fell within the limits set by the United States Pharmacopeia and Food and Drug Administration. Additionally, the MAH argued that from an intravenous injection perspective, the pH of both tracers are typical for iv administration. Furthermore, the qualities of components of the formulation are insignificant when considering the volume of product injected directly (typically 1-10mL) , which is instantly diluted into the volume of plasma. The RMS considered the presumptions plausible. Nevertheless, in order to confirm the assumption that the formulation buffer would not impact the clinical performance, the MAH performed a literature search. However, although extensive number of published articles which discuss the performance and value of FDG as a PET trace are available, these articles only cite the administered radioactivity as the primary component of the injected product and not the formulation used.

Moreover, the MAH has provided two articles (Carlson et al. 2020 and Cui et al. 2016) in which according the MAH FDG citrate has been used. However, in these articles references to the FDG citrate or DDG citrate FASTlab cassette could not be found.

To conclude, references to the use of the specific formulation for FDG based on citrate in published articles could not be made, due to the fact that specific information on the formulation of the FDG in is not presented. Consequently, bridging of the literature results to the product at issue is not feasible. Nevertheless, considering that GlucoPET is a solution for injection, justification based on quality is considered sufficient. In this respect, considering that Glucopet is generated conform the monograph of the European Pharmacopoeia, it can be concluded that the literature results can be transferred to the products at issue.

IV.2   Pharmacodynamics

GlucoPet is used for diagnostic purpose only and does not exhibit any pharmacologic activity. The mechanism of action of ^{18}F-FDG is described and can be considered sufficient. ^{18}F-FDG has a long standing and well known use in various therapeutic areas.

IV.2.1   Pharmacodynamic interactions with other medicinal products or substances
The MAH has performed a literature review to evaluate the interaction of medicinal products with the FDG scan. In agreement with the information in section 4.5 of the proposed SmPC, it was concluded that the central issue of drug interaction is based upon the medicinal products

modifying the glucose status of the patient. In this respect, the MAH adequately referred to articles which described drugs known to interact with blood glucose levels.

The aim of the fasting procedure is to maintain the blood glucose levels at approximately 80-100mg/dL for the duration of the period post FDG administration as well as during the acquisition period (Dudoignon et al., 2020). Higher and variable blood glucose levels caused by medicinal interactions interfere with the cellular influx of glucose and when scanning with FDG cause the radioactive signal to increase in background tissue such as bone and muscle therefore obscuring the tumour or lesion uptake of interest (Surasi et al., 2014). Ultimately the aim is to produce diagnostic scans where the lesion can be accurately and consistently quantified using methods such as the SUVr measure (Ziai, 2016). Additionally, patient preparation protocols for FDG scanning can be elaborated and consequently many societies are providing guidance for the most optimal dietary and fasting procedures for specific protocols. Once such example is the recent recommendation for the scanning of cardiac sarcoidosis (Christopoulos et al., 2019) as well as consensus for rescheduling the FDG scan if the patient is hyperglycaemic over a certain threshold (Dudoignon et al., 2020).

From the drug interaction perspective any medicinal product that is known to interact with blood glucose levels could affect the quality and interpretability of the FDG examination. Corticosteroids such as dexamethasone increase blood glucose (Bowyer et al., 2017). Other drugs such valproate which is used for the treatment of epilepsy and bipolar disease can increase blood glucose levels by interfering with the cellular glut transporters (Wong et al., 2005) whilst carbamazepine has been shown in case histories to cause hyperglycemia which reverts to normal when the medication is withdrawn (Harika et al., 2019). Hyperglycemia due to phenytoin toxicity was reported as long ago in 1971 (Treasure et al., 1971) whereas a more recent review discusses the issue in paediatric patients (Tosur et al., 2020). The barbiturate phenobartital is known to increase liver metabolising/enzyme activities (Zaccara et al., 2014) and can modulate insulin and blood glucose levels (Sotaniemi et al., 1989) whilst the catecholamines have a marked metabolic effects particularly on utilisation of glucose (Barth et al, 2007). The impact of metformin leading to diffuse bowel signal after an FDG scan is well known(26) and may impact the accuracy of scan interpretation (Steenkamp et al., 2014). There is some suggestion to withhold metformin for several days prior to the FDG scan (Schreuder et al, 2020) however many institutions prefer to keep the patient on the metformin rather than risk the rise in blood glucose which inevitably leads to a variable quality FDG scan (Okamoto et al., 2019).

IV.3   Clinical efficacy

IV.3.1   Introduction

This section provides a literature-based clinical overview addressing the indications and safety profile of ^{18}F-FDG as described in the Guideline and core SmPC and package leaflet EMA/CHMP/448228/2012 published on 19 July 2012. The literature included is extracted from a first clinical expert review conducted in 2005, which contains evidence reviewed by the German Nuclear Medicine Society (Reske & Kotzerke, 2001), the FDA [Federal Register, Vol. 65, No. 48, 12999-13010] and "A Tabulated Summary of the ^{18}F-FDG PET Literature" published by the American Society of Nuclear Medicine (Gambhir et al. 2001). In order to supplement

this section further evidence is extracted from clinical expert review updates from 2013-2016 and UpToDate literature reviews current up to January 2019.

IV.3.2 Dose-response studies

Is it acknowledged that the proposed doses to be used in both adults and children are following the well-established recommendations provided by many scientific societies such as EANM and SNMMI. A weight-based approach is recommended to allow for an adequate image quality and no restrictions are reported for children use based on this approach.

IV.3.3 Main studies

IV.3.3.1 <u>Clinical applications of ^{18}F-FDG in oncology</u>

Currently, anatomical imaging modalities such as CT, MRI and U/S, play a key role in the diagnosis and treatment of cancer patients. They yield high quality morphological information that clinicians can use in patient management. However, they also present with several important shortcomings. Some early malignant changes may not be accompanied by anatomical changes and may therefore not be apparent with these techniques. It is generally recognised that the earlier the stage a cancer is detected at, the better the prognosis. In addition, post treatment changes are usually indistinguishable from recurrence or residual disease. Functional imaging with ^{18}F-FDG tries to overcome these issues. ^{18}F-FDG uptake is not based on size or structural changes but on two key characteristics: the presence of living cells and their metabolic status.

Warburg demonstrated in 1956 that malignant cells had poorer metabolic capabilities as opposed to non-malignant cells (Warburg et al., 1956). Additional research also showed that the activity of the hexokinase (an enzyme that adds phosphorous to sugars such as glucose) was higher in tumour cells than in normal cells, explaining the increased uptake of ^{18}F-FDG (Monakhov et al., 1978). Increased carbohydrate metabolism inside the malignant cell can further be explained by the greater activity of the glycolytic enzymes compared with gluconeogenic enzymes (Weber et al., 1977). According to this relatively increased avidity of neoplastic cells for glucose, ^{18}F-FDG, being an analogue of glucose will accumulate at higher rates in tumour cells as compared with non-neoplastic cells.

^{18}F-FDG PET is more accurate than computed tomography in differentiating benign from malignant lesions as small as 0.7 to 1 cm in diameter (Vansteenkiste et al., 2006). It is estimated that 96 percent of patients with lung cancer will have an abnormal ^{18}F-FDG PET (i.e. sensitivity) and 79 percent of patients without lung cancer will have a normal ^{18}F-FDG PET (i.e. specificity), a diagnostic accuracy of 91 percent (Fischer et al., 2001, Vansteenkiste et al., 2001, Vansteenkiste et al., 2006).

^{18}F-FDG PET correctly excludes cancer in most cases (i.e. good negative predictive value) (Fischer et al. 2001, Vansteenkiste et al. 2001, Vansteenkiste et al. 2004, Vansteenkiste et al. 2006). However, it is not uncommon for an ^{18}F-FDG PET positive nodule to be infectious, inflammatory, or granulomatous in origin (i.e. moderate positive predictive value) (Vansteenkiste et al. 2006).

False-negative results can occur with tumors that have low metabolic activity (eg, adenocarcinoma in situ, carcinoids, and some well-differentiated adenocarcinomas), small

lesions (a critical mass of metabolically active malignant cells is required for detection by PET), and uncontrolled hyperglycemia, which leads to glucose saturation and subsequent delayed uptake of ^{18}F-FDG since glucose competes with deoxy-2-fluoro-D glucose for the transmembrane transport into the cell (Lowe et al. 1998, Vansteenkiste et al. 2006). False positive results can occur in inflammatory conditions and granulomatous diseases (Vansteenkiste et al. 2006).

The average ^{18}F-FDG PET sensitivity and specificity across all oncology applications are estimated at 84% (based on 18,402 patient studies) and 88% (based on 14,264 patient studies), respectively. The average management change across all applications is estimated to be 30% (based on 5,062 patients). These data were obtained combining 419 total articles and abstracts on studies in which ^{18}F-FDG PET was used (Gambhir et al. 2001).

German Interdisciplinary Consensus on the Clinical use of ^{18}F-FDG PET
A questionnaire comprising 24 items was developed for standardised quality assessment according to evidence-based medicine criteria. Out of a total of 533 papers selected, 122 references with 7,092 documented patients fulfilled the criteria for detailed review. Clinical indications (Grade 1a or 1b) were established for differentiating benign from malignant lesions in pulmonary nodules, pancreatic masses and residual masses after chemotherapy in malignant lymphoma (Reske & Kotzerke, 2001).

Staging was improved by ^{18}F-FDG PET in oesophageal cancer, breast cancer, head and neck cancer, lung cancer, malignant lymphoma and malignant melanoma. Effectiveness of radioand/ or chemotherapy could be better controlled in Hodgkin's disease and high-grade non-Hodgkin's lymphoma. Restaging was improved in relapsing thyroid cancer, colorectal cancer, head and neck cancer, lung cancer and malignant melanoma (Reske & Kotzerke, 2001).

FDA Review on the Safety and Effectiveness for Evaluating Glucose Metabolism in Oncology
The FDA's search of the published literature revealed about 150 articles involving clinical trials with ^{18}F-FDG injection in oncology. Of these, the agency identified 16 articles that met the review criteria and had both a study population of greater than 50 and histopathologic confirmation of the type of malignancy. Two of the articles involved adequate and well-controlled trials [Federal Register, Vol. 65, No. 48, 12999-13010].

The review concludes that ^{18}F-FDG can be found to be safe and effective in PET imaging for assessing abnormal glucose metabolism to assist in evaluating malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer.

Summary of the ^{18}F-FDG Literature published by the Society of Nuclear Medicine
A total of 775 references were retrieved from the literature for our review, out of which 473 were included and 302 were excluded for not meeting the standard of evidence required criteria. (Gambir et al. 2001).

Central nervous system
^{18}-FDG has been evaluated in scenarios where structural imaging techniques (CT/MRI) have shortcomings.

Experience in patients shows that ^{18}F-FDG can differentiate between malignant and benign tissues in cases where recurrence or residual brain tumour is suspected on structural images (Bader et al. 1999, Sasaki et al. 1998). 201Tl and labelled aminoacids (IMT or MET) could possibly do the same. However, ^{18}F-FDG may have several advantages in selected patients. This tracer showed positive correlation with histology grade as opposed to [123I]IMT and [11C]MET (Bader et al. 1999, Sasaki et al. 1998). When dealing with low grade tumours, ^{18}F-FDG showed no false positive results while 201Tl had a significant number of them (Sasaki et al. 1998); this would lead to unnecessary treatments. The half-life of 11C is about 20 minutes and consequently this makes the imaging acquisition protocol very demanding. 201Tl has been widely used in nuclear oncology, but also has disadvantages compared with ^{18}F-FDG, namely lower spatial resolution and higher radiation dose to the patient due to a much longer half-life (see Section 2.5.5 "Overview of safety"). Additionally, patients with intracranial neoplasms can have an entire body survey without extra radiation dose by whole body PET scans, in search of a primary source of brain metastases (Kim et al. 1998, Gupta et al. 1999). Finally, ^{18}F-FDG can also provide prognostic information since those patients with residual abnormal uptake after therapy interventions seem to have significantly worse survival rates than those where it is absent (De Witte et al. 2001, Roelcke et al. 1999, Ericson et al. 1996).

Head and neck cancer
^{18}F-FDG avidly accumulates in primary head and neck tumours (Wong et al. 1997). PET scanning of the head and neck area represents a reasonable alternative to panendoscopy but has a significant rate of false positives when the chest is included in the field of view (Keyes et al. 2000). However, ^{18}F-FDG has higher sensitivity and specificity than CT/MRI in detecting LN metastases in primary and recurrent cancer (Table 1).

Table 1. ^{18}F-FDG PET versus CT/ MRI, U/S and neck palpation in lymph node staging in patients with head and neck cancer (N=434).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	82 [67-91]	93 [80-100]	79 [48-94]	93 [82-99]	90 [79-96]
CT/MRI	74 [33-95]	72 [25-97]	60 [20-86]	95 [78-98]	89 [57-93]
U/S	72	70	19	96	70
Palpation	61	97	72	95	93

References: Adams et al. 1998, Kau et al. 1999, McGuirt et al. 1998, Safa et al. 1999, Braams et al. 1995, Benchaou et al. 1996, Wong et al. 1997.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. Values are average; ranges are in "[ ]".

Characterising structural abnormalities after therapy has important implications in clinical management and ^{18}F-FDG has been shown to be able to detect early recurrence and residual disease, reducing the need for multiple random biopsies, a clearly uncomfortable test for the patients (Table 2).

Table 2. ^{18}F-FDG PET versus other modalities in the investigation of recurrent head and neck cancer (N=268).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	91[80-100]	89 [81-96]	70	94	90 [85.7-97]
CT/MRI	61 [22-72]	89 [79-100]	N/R	N/R	65[64.3-66]
U/S	63	65	42	81	64

References: Goerres et al. 2000, Greven et al. 1997, Kao et al. 1998, Lapela et al. 1995a, Lapela et al. 2000, Li et al. 2001, Lowe et al. 1999, Lowe et al. 2000.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. Values are average. Ranges are in "[ ]". N/R: Not reported.

Surveying the entire body with ^{18}F-FDG PET in search of a primary malignancy that debuts as metastatic LN in the head and neck area is also a valid alternative when the primary source has not been found (Braams et al. 1997, Safa et al. 1999). ^{18}F-FDG can also detect early recurrence following failure of therapy in patients with head and neck cancer, allowing for an early change in patient therapy and avoiding the co-morbidities of an anti-cancer regimen with no obvious benefit to patients (Kitagawa et al. 1999, Lowe et al. 1997).

Finally, it is important to mention that the degree of uptake can yield prognostic information since this is the result of the aggressiveness of the tumour (Minn et al. 1997), a clear advantage over structural imaging modalities. Lastly, ^{18}F-FDG can be used not only with hybrid cameras but also as an acceptable alternative to dedicated systems (Pai et al. 1999).

Thyroid Cancer
There is enough evidence that ^{18}F-FDG has several added advantages in the management of patients with differentiated thyroid carcinoma:

- ^{18}F-FDG can differentiate between benign and malignant nodules within the thyroid gland with an accuracy of 73% (Sasaki 1997).
- ^{18}F-FDG PET can yield additional information in the staging and can depict sites of tumour when 131I whole body scintigraphy [WBS] images are negative in those patients with rising tumour markers and no evidence of disease, in 50-95% of the cases depending upon the series (Dietlein et al. 1998, Feine et al. 1996, Grunwald et al. 1996, 1997)
- A mismatching lesion with poor or no 131I concentration but pathological uptake of ^{18}F-FDG correlates with cellular de-differentiation which has poor prognosis (Wang et al. 2000, Feine et al. 1996)
- Finally, there is no indication that thyroid replacement therapy could affect the reliability of ^{18}F-FDG PET scans results and therefore patients do not need to stop hormonal therapy; avoiding the co-morbidities of a hypothyroid state. Therapy withdrawal is necessary for an accurate 131I WBS (administration of recombinant Thyroid Stimulating Hormone [TSH] injections is an expensive alternative) (Wang et al. 1999).

Lung Cancer, including Single Pulmonary Nodule
Differential uptake of ^{18}F-FDG by indeterminate pulmonary lesions (as shown by either simple visual or quantitative analysis) can help in the differentiation of benign from malignant disease (Gupta et al. 1998, Duhaylongsod et al. 1995). The accuracy of this radiopharmaceutical as shown by these series is higher than 90% (n=148). However, sensitivity may decrease if small lesions (<1cm) are evaluated with conventional Single photon emission computed

tomography (SPECT) cameras equipped with high energy collimators instead of dedicated PET scanners (Mastin et al. 1999) and with hybrid cameras (Tatsumi et al. 1999). In the assessment of possible mediastinal involvement from lung cancer, ^{18}F-FDG exhibits higher accuracy than CT (Sasaki et al. 1996, Sazon et al. 1996). Table 3 shows the differences in sensitivity and specificity between ^{18}F-FDG PET and CT in the evaluation of lymph node metastases in patients with lung cancer.

Table 3. ^{18}F-FDG PET and CT in the evaluation of lymph node metastases in patients with lung cancer (N=208).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	84 [67-100]	87 [75-98]	74 [64-91]	93 [89-100]	75 [78-99]
CT	63 [52-72]	84 [79-89]	63 [60-67]	83 [82-83]	51 [67-78]

References: Higashi *et al.* 1998c, Tatsumi *et al.* 1999, Bury *et al.* 1996a, Chin *et al.* 1995, Scott *et al.* 1996, Nettelbladt *et al.* 1998, Magnani *et al.* 1999, Patz *et al.* 1995.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. Values are averages. Ranges are in "[ ]".

^{18}F-FDG can complement information derived from structural imaging, mainly CT in the evaluation of lung malignancy (Albes et al. 1999, Magnani et al. 1999, Vansteenskiste et al. 1998a) (n=123), and possible metastases to the adrenal glands (Erasmus et al. 1997) (n=27). Patients undergoing therapy (surgery, chemo or radiation therapy) for lung cancer can benefit from the functional information obtained from an ^{18}F-FDG scan, since early detection of recurrent/residual disease is not dependent on the therapy induced structural changes (n=199) (Inoue et al. 1995, Frank et al. 1995, Bury et al. 1999, Vansteenskiste et al. 1998b) as well as predicting response to therapy (n=30) (Ichiya et al. 1996).

Some studies have also correlated the degree of ^{18}F-FDG uptake with biological markers of the tumour. There is a significant inverse correlation between the degree of uptake and the degree of cell differentiation (Higashi K et al. 1998b), meaning that the higher the accumulation the less differentiation at the cellular level, which is also correlated with aggressiveness of the tumour (Higashi K et al. 2000) and this can be used to assess patients' survival rates (n=64).

In a large series with 105 patients, ^{18}F-FDG was able to change patient treatment options in 62 cases by accurately either upstaging or downstaging patients and directing delivery of radiation therapy (Kalff et al. 2001), which led to better patient management.

Gupta et al. (1996) found that abnormal ^{18}F-FDG uptake in radiographically indeterminate pulmonary nodules had 83% probability of being malignant, but those lesions without uptake only carried a 4.3% probability (n=63) (Gupta et al. 1996). The experience in 189 patients (Bury et al. 1996b, Lowe et al. 1998, Prauer et al. 1998) shows that ^{18}F-FDG can accurately predict malignancy in cases with indeterminate SPN by structural images, as shown in Table 4.

Table 4. ^{18}F-FDG PET and CT in the evaluation of SPN (N=189).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	95 [90-100]	82 [69-90]	94	100	87
CT	100*	52	74	100	N/R

References: Bury *et al.* 1996b, Lowe *et al.* 1998, Prauer *et al.* 1998.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy.
Values are averages. Ranges are in "[ ]". N/R: Not reported.
* Sensitivity of CT for detecting SPN is considered to be 100 since this is a screening test and all patients were sent to ^{18}F-FDG PET imaging after being found to have SPN by CT.

It should be noted that, when using ^{18}F-FDG in conjunction with conventional SPECT cameras equipped with high energy collimators (specially designed to detect 511 KeV photons), smaller nodules (i.e.: <2 cm) can remain undetected (Worsley et al. 1997) due to the lower spatial resolution and system sensitivity.

Breast Cancer

^{18}F-FDG has been evaluated in the differential diagnosis of breast lesions. The published series indicate that this radiopharmaceutical can differentiate benign from malignant tissue within the breast (n=124) with a sensitivity of 68-94% and a specificity of 84-97% (Avril et al. 1996a, Avril et al. 1997). It can also aid in evaluating the extent of the primary cancer if the entire body is surveyed, having a higher accuracy than physical examination (n=57) (Scheidhauer et al. 1996, Noh et al. 1998), and detecting metastatic LN and other unsuspected sites of disease (n=51) (Avril et al. 1996b). Imaging with ^{18}F-FDG also provides the additional advantage of not being affected by structural changes, i.e. those related with therapeutic or plastic surgery (Noh et al. 1998). In the evaluation of the LN status in the axillae, ^{18}F-FDG has higher accuracy than physical exam (see Table 5), although is not considered a replacement for axillary lymph node dissection (n=167) (Greco et al. 2001).

Table 5. ^{18}F-FDG PET versus physical examination (PE) in the evaluation of axillary LN metastases from breast cancer (N=620).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	89 [79-100]	85 [66-97]	95	96 [95-96]	87 [77-94]
PE	57	90	80	74	76

References: Crippa *et al.* 1998, Utech *et al.* 1996, Adler *et al.* 1997, Crippa *et al.* 1997, Smith *et al.* 1998.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy.
PE: Physical examination.
Values are averages. Ranges are in "[ ]".

Staging primary and recurrent breast cancer benefits from combining structural information from conventional imaging modalities with functional information from ^{18}F-FDG whole-body PET scans. Lesions missed by the former can be depicted by the latter (Bender, 1997; Moon, 1998). This seems not to be the case with bone metastases, while ^{18}F-FDG can detect more osteolitic lesions than conventional bone scans, osteoblastic lesions have lower metabolic rates (Cook, 1998).

Cancer of the digestive system

Gastro-oesophageal cancer

Experience in 8 published trials that fulfilled the selection criteria (total number of 16) shows that oesophageal tumours are capable of concentrating ^{18}F-FDG at a higher rate than surrounding, normal tissues, allowing the differentiation between benign and malignant lesions (n=64) (Fukunaga et al. 1998, McAteer et al. 1999). However, due to the spatial resolution of the PET technique (compared with CT) isolation of disease-free wall and identification of surrounding LN is difficult (n=25) (Rankin et al. 1998). This limitation may be overcome by interpreting anatomical images (i.e.: CT) in combination with functional images (^{18}F-FDG). However, detection of distant LN and metastases by ^{18}F-FDG improves staging in these patients (n=142) (Lerut et al. 2000, Kole et al. 1998, Flamen et al. 2000), and ^{18}F-FDG PET images can provide prognostic information and depict early response to therapy before any structural changes occur (n=81) (Couper et al. 1998, Weber et al. 2001, Brucher et al. 2001). The role of ^{18}F-FDG PET in the preoperative staging of gastric adenocarcinoma is evolving. From the standpoint of locoregional staging, integrated PET/CT imaging can be useful to confirm malignant involvement of CT-detected lymphadenopathy (Yun et al. 2005). However, this usually does not impact the decision to proceed to surgery. Furthermore, a negative PET is not helpful since even large tumors with a diameter of several centimeters can be falsely negative if the tumor cells have a fairly low metabolic activity. Furthermore, most diffuse type gastric cancers (signet ring carcinomas) are not FDG avid (De Potter et al 2002, Kim et al. 2006, Mukai et al. 2006, Chen et al. 2005).

Pancreatic Cancer

The data from 9 out of 26 papers show evidence that: a) that pancreatic cancer can effectively concentrate ^{18}F-FDG at a much higher rate than other benign conditions in the pancreas allowing for non-invasive detection of tumour (Friess et al. 1995, Kato et al. 1995, Keogan et al. 1998) (n=141), and b) this degree of uptake may be mediated by the expression of glucose transporters (GLUT-1) (n=35) (Higashi T et al. 1998). ^{18}F-FDG has a higher diagnostic accuracy than 201Tl SPECT (n=25) (Inokuma et al. 1995a). Diagnostic accuracy is higher than conventional imaging modalities (CIM) as well (see table Table 6 below).

Table 6. ^{18}F-FDG PET versus (CT, U/S) in the differentiation of pancreatic carcinoma from chronic pancreatitis (N=167).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	95 [94-96]	91 [82-100]	96 [94-100]	89 [82-94]	91
U/S	93 [89-97]	55 [45-64]	86 [84-88]	72 [56-88]	83 [78-88]
CT	83 [80-89]	79 [73-89]	87 [80-91]	72 [67-76]	85

References: Inokuma *et al.* 1995b, Stollfuss *et al.* 1995, Imdahl *et al.* 1999.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy.
CIM: conventional imaging modalities.
Values are averages. Ranges are in "[ ]".

Some work (n=19) in monitoring response to therapy also indicates that there is a role for ^{18}F-FDG scanning in this field (Franke et al. 1999).

Colorectal Cancer

^{18}F-FDG PET has high sensitivity for depicting primary Colorectal cancer but remains suboptimal in detecting LN spread (which is also a drawback with CT imaging). However ^{18}F-FDG PET also shows advantages over conventional imaging modalities, i.e. detection of liver metastases, early detection of local recurrence and assessing resectability prior to surgery with curative intent (see Table 7 and Table 8).

Table 7. ^{18}F-FDG PET versus CT in the detection of primary CRC and LN metastases (n=48).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Primary				
FDG-PET	100	43	90	100
CT	37	83	92	21
LN				
FDG-PET	29	96	80	72
CT	29	85	33	81

Reference.: Abdel-Nabi et al. 1998.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value.

Table 8. ^{18}F-FDG PET versus CIM in the detection of liver metastases and local recurrence of CRC (n=349)

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
Liver					
FDG-PET	92 [88-95]	99 [97-100]	99.7 [99-100]	83 [71-97]	94 [92-98]
CT	72 [38-86]	78 [58-97]	82 [75-92]	66 [41-86]	82 [76-93]
CT port	97	7 [5-9]	79 [77-81]	42 [33-50]	78 [76-80
Recurrence					
FDG-PET	89 [79-97]	92 [80-100]	N/R	N/R	95
CT	57 [46-68]	94 [90-98]	N/R	N/R	65

References: Abdel-Nabi et al. 1998, Lai et al. 1996, Delbeke et al. 1997, Vitola et al. 1996, Schiepers et al. 1995, Valk et al. 1999.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. CT port: CT portography. N/R: Not reported.
Values are averages. Ranges are in "[ ]".

^{18}F-FDG can also detect local recurrence when CT/MRI show indeterminate anatomical changes secondary to therapy (n=200) (Keogan, et al. 1997, Ruhlman et al. 1997, Takeuchi et al. 1999, Staib et al. 2000). The addition of ^{18}F-FDG to the diagnostic algorithm in the presurgical evaluation of patients with suspected recurrence has a positive impact in patient management (n=191) (Staib et al. 2000, Topal et al. 2001) and survival (n=43) (Strasberg et al. 2001). Additionally, the use of hand-held gamma probes for detection of ^{18}F-FDG during the surgical procedure seems to be a valuable procedure for intra-operatory staging (n=15) (Desai et al. 2000).

Cancer of the genitourinary tract
Ovarian Cancer
The evidence in 3 selected articles (total of 14) indicates that the addition of ^{18}F-FDG to U/S and MRI in the evaluation of asymptomatic adnexal masses improves the refinement of the differential diagnosis (n=101) (Grab et al. 2000). Furthermore, this holds true also for the staging of known ovarian cancer (n=64) (Schröder et al. 1999, Nakamoto et al. 2001).

Cervical Cancer
Experience drawn from 4 published reports that met the selection criteria (total of 8) shows that ^{18}F-FDG can accumulate in primary cervical cancer and metastatic lymph nodes (n=88) (Sugawara et al. 1999, Rose et al. 1999, Reinhardt et al. 2001), as well as recurrent uterine cancer (n=13) (Umesaki et al. 2000). Interestingly tumour detection rates were slightly higher than those of MRI (n=48) (Reinhardt et al. 2001, Umesaki et al. 2000).

Lymphoma
Evidence from 19 selected articles (total of 55) shows that lymphomas accumulate ^{18}F-FDG at higher rates than non-lymphomatous lesions (n=22) (Lapela et al. 1995b), enabling improved staging (Hoh et al. 1997, Moog et al. 1997, Bangerter et al. 1998, Jerusalem et al. 1999a, Buchman et al. 2000), for which ^{18}F-FDG exhibits higher diagnostic accuracy than CT (n=330). ^{18}F-FDG can also detect additional sites of disease not shown by conventional procedures and identify absence / presence of disease in sites suspected to be involved by structural imaging modalities (n=28) (Jerusalem et al. 2000).

Two studies have compared ^{18}F-FDG with [11C]-Methionine in patients (n=42) with Hodgkin's disease and non-Hodgkin's lymphoma , finding no significant differences in detecting lymphomatous lesions by visual inspection (Rodriguez et al. 1995, Sutinen et al. 2000). Although both tracers appear then to be equally effective, it is worthy to mention that in clinical practice 11C-labelled compounds are more cumbersome to manage than ^{18}F-labelled compounds due to the much shorter half-life of the former compared with the latter.

Areas of abnormal ^{18}F-FDG uptake in the bone marrow have been correlated with suspected and unsuspected foci of lymphoma (n= 184) (Moog et al. 1998, Moog et al. 1999, Carr et al. 1998). Evaluating residual masses with CT or MRI after therapy represents a diagnostic challenge since these anatomical modalities cannot differentiate scar from residual tissue. However viable tumour accumulates ^{18}F-FDG (n=158) (Jerusalem et al. 1999b, de Wit et al. 1997, Maisey et al. 2000, Dimitrakopoulou-Strauss et al. 1995) and this has therapeutic and prognostic implications (n=105) (Jerusalem et al. 2000, Cremerius et al. 2001, Bangerter et al. 1999).

Tumour of Unknown Origin
Surveying the whole-body in search of the source of unknown primary tumours (UPT) with ^{18}F-FDG has the advantage of no additional radiation dose to the patient (as opposed plain radiographs or CT examinations). Four articles (from a total of 13) that fulfilled the selection criteria report equivocal results in an inhomogeneous population of patients with a wide variety of manifestations of UPT. Experience in 39 patients shows a high sensitivity (> 80%) but poorer specificity (<40%) (Lassen et al. 1999, Mukherji et al. 1996) when imaged with ^{18}F-

FDG. The use of ^{18}F-FDG has been shown in selected cases to have utility (n=28) (Bohuslavizki et al. 1999), however the literature is not in full agreement on this issue (Greven et al. 1999).

Musculoskeletal tumours

Evidence was collected from 8 articles that fulfilled the selection criteria from a total of 17. PET scanning with ^{18}F-FDG has high accuracy in depicting primary soft tissue sarcomas, with a mean sensitivity of 95.75% (range, 91-100%), mean specificity of 74.5% (range, 66-82%) and accuracy of 86% (n=204 patients) (Kole et al. 1997, Lucas et al. 1999, Schulte et al. 1999, Schwarzbach et al. 2000). In addition ^{18}F-FDG PET is also sensitive in detecting posttreatment recurrence, with a sensitivity ranging from 93-100% (n=38) (Kole et al. 1997, Schwarzbach et al. 1999). The degree of ^{18}F-FDG uptake is related with the tumour grade (n=70) (Eary et al. 1998) and has implications in patient management during monitoring of therapy (n=20) (Van Ginkel et al. 1996).

Malignant melanoma

In melanomas thicker than 1 mm imaging tests such as chest radiographs, CT or MRI are indicated if clinical and laboratory findings suggest specific organ involvement. The 10-year survival rate is 90% in stage I, 52% in stage II, 33% in stage III and 10% in stage IV (Wagner et al. 2000). Melanoma cells are very avid for ^{18}F-FDG. Experience in 226 patients (from 6 out 21 articles that fulfilled the selection criteria) shows that PET with ^{18}F-FDG has higher diagnostic accuracy in staging than CT, as shown in Table 9.

Table 9. ^{18}F-FDG PET versus CT in the staging of malignant melanoma (N=226).

Method	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
FDG-PET	94.5 [92-100]	80.5 [67-95]	94	57	92.5 [87-98]
CT	70 [55-85]	71 [58-84]	N/R	N/R	77

References: Boni et al. 1995, Steinert, et al. 1995, Holder et al. 1998, Rinne et al. 1998.
Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy.
N/R: Not reported.
Values are averages. Ranges are in "[ ]".

Oncology, miscellaneous

The use of ^{18}F-FDG can help in characterising mediastinal tumours as compared with CT (sensitivity, specificity and accuracy of 90%, 92% and 91% for ^{18}F-FDG PET, and 70%, 83%, and 77% for CT, respectively;(n=22) (Kubota et al. 1996). ^{18}F-FDG has also been shown to accurately distinguish benign from malignant tumours in patients with indeterminate masses in kidneys (n=21) (Goldberg et al. 1997) and adrenal glands (n=20) (Boland et al. 1995).

Conclusion on Oncology

All claimed indications are in accordance with the core SmPC. The studies presented showed that ^{18}F-FDG PET is successfully used in diagnosing, staging and monitoring of cancer. ^{18}F-FDG accumulates at higher rates in tumour cells as compared with non-neoplastic cells. The sensitivity and specificity is estimated to be on average 84 % and 88% respectively, across all oncology applications. The technique can differentiate the malignant lesions from benign, can stage the cancer, detect recurrence and residual disease. Tumours with higher glucose uptake are usually more aggressive and patients with such tumours have poorer prognosis for survival. Therefore, ^{18}F-FDG PET scanning can also be used to assess patient's survival rates.

^{18}F-FDG PET can offer advantages over conventional imaging to detect distant metastasis, treatment-induced changes, differentiate between residual and recurrent disease.

IV.3.3.2 Clinical applications of 18F-FDG in Neurology

Measurement of interictal cerebral glucose metabolism using ^{18}F-FDG PET is a sensitive functional neuroimaging technique in patients with temporal lobe epilepsy. Unilateral temporal lobe hypometabolism on ^{18}F-FDG PET correlates strongly with the temporal lobe of seizure origin and is predictive of seizure freedom following epilepsy surgery, independent of structural MRI findings [LoPinto-Khoury C et al. 2012]. FDG PET can also be clinically useful in patients with extratemporal regions of seizure onset. This includes individuals with focal cortical dysplasia who may have an unremarkable MRI study.

^{18}F-FDG PET images the topographic distribution of glucose uptake in the brain and provides a picture of cerebral metabolism. Ictal scans can be useful but are difficult to obtain except in rare cases such as epilepsia partialis continua. Thus, ^{18}F-FDG PET scans are typically performed in the interictal state, with the goal of detecting focal areas of decreased metabolism (i.e. relative hypometabolism) that are presumed to reflect focal functional disturbances of cerebral activity associated with epileptogenic tissue. ^{18}F-FDG PET is generally performed as part of a presurgical evaluation.

Sensitivity for detecting relative temporal lobe hypometabolism with FDG PET in mesial temporal lobe epilepsy (MTLE) ranges between 80 and 90 percent (Duncan 1997, Valk P et al. 1993, Ryvlin P et al. 1992, Ryvlin P et al. 1998, Gaillard et al. 1995, Swartz B et al. 1992).

Much of the variability in sensitivity reflects the heterogeneity of the epilepsy more than it does the differences in quality or specifications of the PET camera (La Fougère C et al 2009). Some reports suggest that the sensitivity of PET is increased when seizures are more frequent or when performed soon after a seizure has occurred (Henry T et al. 1993).
Only a few patients in the above series included patients with MTLE without hippocampal sclerosis on MRI. However, these and other series have shown that FDG PET can be helpful in lateralising the epileptogenic temporal lobe in "MRI-negative" cases, with a yield that ranges from 45 to almost 90 percent (Gaillard et al. 1995, https://www.uptodate.com/contents/neuroimaging-in-the-evaluation-of-seizures-andepilepsy/ abstract/103, Willmann O et al. 2007, Carne et al. 2004).

The studies identified in the literature has shown that ^{18}F-FDG PET is sensitive for presurgical localisation of epileptogenic foci in patients with medically refractory partial epilepsy. The technique was particularly useful in those cases in which MRI findings were abnormal but no epileptogenic lesion was identified. Overall, the literature data supports the indications in neurology.

IV.3.3.3 Clinical applications of ^{18}F-FDG in cardiology

Ischemia shifts myocyte metabolism preferentially to glucose from fatty acids. Thus, uptake of ^{18}F-FDG by myocytes in an area of dysfunctional myocardium indicates metabolic activity and thus, viability. Regional perfusion can also be assessed with an agent that remains in the vascular space and demonstrates the distribution of blood flow (such as 13N-amonia or 82Rb).

The presence of enhanced 12F-FDG uptake in regions of decreased blood flow, known as a PET mismatch, defines hibernating myocardium by PET imaging, while a concordant reduction in both metabolism and flow, known as PET match, is thought to represent predominantly necrotic myocardium. Regional dysfunction in presence of normal perfusion is indicative of stunning. Myocardial segments with significant reductions in both blood flow and FDG uptake have only a 20 percent chance of functional improvement following revascularisation. In comparison, dysfunctional territories deemed to be hibernating by PET have approximately an 80 to 85 percent chance of functional improvement following revascularisation (Tillisch 1986, Tamaki 1991, Lucignani et al. 1992, Tamaki et al. 1989, Marwick et al 1992, Carrel et al. 1992, Gropler et al. 1992, Tamaki et al. 1995).

The positive and negative predictive values of PET imaging for improvement in asynergy and wall motion score after revascularisation were 76 and 96 percent, respectively. Other studies have shown that the extent of myocardium that demonstrates enhanced FDG uptake in patients with ischemic cardiomyopathy may predict the magnitude of improvement in ejection fraction, exercise tolerance, and heart failure symptoms after surgical revascularisation (Di Carli M et al. 1995, Gerber et al. 2001).

Another analysis reported that scar size on FDG PET was an independent predictor of improvement in ejection fraction after revascularisation. In 70 patients with a mean resting left ventricular ejection fraction (LVEF) of 26 percent, scars were divided into tertiles graded as small, moderate, or large (0 to 16, 16 to 27.5, and 27.5 to 47 percent of total myocardium, respectively) (Beanlands et al. 2002). The change in ejection fraction (EF) after revascularisation was significantly greater for patients with smaller scars (change of 9.0, 3.7, and 1.3 percent, for small, moderate, or large scars respectively). Outcome after coronary artery bypass grafting may be improved by incorporating PET derived viability information, in addition to clinical and angiographic data, into the process of selecting patients with impaired left ventricle (LV) function for revascularisation (Haas F et al. 1997, Lee KS et al. 1994). As an example, one study evaluated the prognostic significance of the presence of viable myocardium, and its interaction with myocardial revascularisation, in patients with LV dysfunction after myocardial infarction (Lee KS et al. 1994). Nonfatal ischemic events occurred in 48 percent of medically-treated FDG (+) patients compared with only 8 percent of FDG (+) revascularised patients and 5 percent of patients with FDG (-) myocardium; however, mortality was similar among FDG (+) and FDG (-) patients. The assessment of viability with metabolic imaging using FDG PET is generally thought to be more sensitive than rest perfusion imaging with SPECT. Clinical experience shows that some myocardial segments that appear severely hypoperfused on SPECT show F-18 FDG uptake, and are thus viable. However, direct comparisons of PET and SPECT in broad groups of patients with a range of LV systolic function are lacking, and therefore, the effect of test choice on patient outcome is unknown. One randomised trial, in which the treating clinicians were blinded to test identity (SPECT or PET), found that the ability to detect myocardial viability with PET or SPECT imaging was the same and that there was no difference in patient outcome when management decisions were based upon the results of either technique (Siebelink H et al. 2001). However, patients in this study had only moderate LV dysfunction (LVEF approximately 30 percent), and there are no comparative data in patients with severe LV systolic dysfunction (Marin-Neto et al. 1998).

IV.3.3.4 Infectious diseases and inflammation

Localisation of Abnormal Foci Guiding the Aetiologic Diagnosis in Case of Fever of Unknown Origin

In a recent review of the literature (Ergul & Cermic, 2011) prospective and retrospective studies in patients with fever of unknown origin (FUO) were reviewed to determine whether the use of FDG – PET was helpful. These studies demonstrated that the contributions to the final diagnosis range from 16% to 69% in patients with FUO by FDG PET or 42% to 89% by PET/CT . (Table 10)

Table 10. Review of Literature on FDG PET or PET/CT in Patients with Fever of Unknown Origin

Author (Year)	Study Design	Patient Number	FDG-PET Technique	PET Helpful (%)	PPV (%)	NPV (%)
Meller *et al.* (2000)	Prospective	18	Coincidence cam	55	92	75
Blockmans *et al.*(2001)	Prospective	58	Full-ring PET	41	-	-
Lorenzen *et al.*(2001)	Retrospective	16	Full-ring PET	69	92	100
Bleeker-Rovers *et al.* (2004)	Retrospective	35	Full-ring PET	37	87	95
Kjaer *et al.* (2004)	Prospective	19	Full-ring PET	16	30	67
Buysschaert *et al.*(2004)	Prospective	74	Full-ring PET	26	—	—
Bleeker-Rowers *et al.* (2007)	Prospective	70	Full-ring PET	33	70	92
Keidar *et al.*(2008)	Prospective	48	PET/CT scan	46	81	100
Balink *et al.*(2009)	Retrospective	68	PET/CT scan	55	93	78
Federici *et al.*(2010)	Retrospective	10	PET/CT scan	50	—	—
Jasper *et al.*(2010)	Retrospective	44	Full-ring PET or PET/CT scan	43	—	—
Ferda *et al.*(2010)	Retrospective	48	PET/CT scan (contrast-enhanced CT)	89	97	75
Keia *et al.*(2010)	Retrospective	12	PET/CT scan	42	71	100
Ergul *et al.*∗	Retrospective	28	PET/CT scan	50	63	100
	Total:	548	-	47	78	88

∗ Unpublished data, PPV: positive predictive value, NPV: negative predictive value

Available data indicate that FDG PET has the potential to play an important role as a second-line procedure in the management of patients with FUO (Ergul & Cermic, 2011, Meller J, 2009). Furthermore, it was concluded that in patients with non-specific symptoms and signs, ^{18}F-FDG PET/CT is very helpful for recognising and excluding diseases, directing further diagnostic decisions, and avoiding unnecessary invasive examinations. It is recommended that ^{18}F-FDG PET/CT should be considered among the first-line diagnostic tools for patients with FUO and IUO. (Kan et al. 2019)

Diagnosis of Infection

A review by Kumar et al. in 2008 considered the use of FDG PET in a variety of infection indications, including those proposed for inclusion in the SmPC (as detailed separately below). The review considers the available literature relevant to each of the indications and supports the use of FDG PET in the diagnosis of these conditions. In addition, an assessment of the value

of FDG PET combined with CT (FDG PET/CT) in critically ill patients suspected of having an infection was performed by Simons et al. (2009). Thirty-five FDG PET/CT scans performed in 33 ICU patients were analysed. Twenty-one FDG PET/CT scans were true positive, three FDG PET/CT scans were considered false positive, and 11 true negatives were found, leading to an overall accuracy of 91%. It was concluded that FDG PET/CT scanning is of additional value in the evaluation of suspected infection in critically ill patients in whom conventional diagnostics did not lead to a diagnosis.

<u>Suspected Chronic Infection of Bone and/or Adjacent Structures: Osteomyelitis, Spondylitis, Diskitis or Osteitis Including when Metallic Implants are Present</u>
A review of a variety of diagnostic imaging techniques for excluding or confirming chronic osteomyelitis (Termaat et al. 2005) demonstrated that FDG PET was the most sensitive technique and had the highest specificity (Table 11).

Table 11. Comparison of Sensitivity and Specificity of Various Imaging Techniques Based on Pooled Clinical Data on Chronic Osteomyelitis

	Sensitivity	Specificity
FDG-PET	96%	91%
Bone Scintigraphy	82%	25%
Leukocyte Scintigraphy	61%	77%
Combined bone and Leukocyte Scintigraphy	78%	84%
MRI	84%	60%

The review of the use of FDG PET in the diagnosis of osteomyelitis noted that FDG PET has been shown to be highly sensitive for detecting chronic osteomyelitis, even in patients who have been treated with antibiotics prior to imaging.

<u>Diabetic Patient with a Foot Suspicious of Charcot's Neuroarthropathy, Osteomyelitis and/or soft Tissue Infection</u>
The review by Kumar et al. 2008 considers that PET/CT fusion imaging would be the study of choice for evaluating complicated diabetic foot. This includes reference to the study by Hopfner et al. (2004) which showed an accurate diagnosis of this condition in 37 patients using FDG PET. It was also concluded that FDG PET can provide an accurate assessment of patients with metal implants, which may otherwise limit evaluation by MRI, and that FDG- PET can correctly distinguish osteomyelitis from Charcot osteoarthropathy, and is valuable in the reliable differentiation of Charcot neuroarthropathy from osteomyelitis both in general and when foot ulcer is present.

The use of FDG PET in soft tissue infection diagnosis allows the identification of inflammatory and cancerous disorders as the underlying cause of FUO in most patients and has been shown to detect infectious and inflammatory disease processes that were undetected when conventional scintigraphic techniques or MRI was used.

<u>Painful Hip Prosthesis</u>
A review of endoprosthesis scans using ^{18}F-FDG PET examinations and multiphase bone scans was performed to evaluate the clinical value of ^{18}F-FDG positron emission tomography (^{18}F-FDG PET) as a diagnostic modality for inflammation and loosening in hip and knee joint

prostheses was performed by Delank et al. (2006). Scans were performed on hip and knee endoprostheses in 27 patients prior to revision surgical procedures planned for prosthetic loosening. Intact prostheses were found at the opposite site in some patients so that additional 9 joints could be examined with the field of view of ^{18}F-FDG PET. Verification and valuation of the PET and scintigraphic image findings were conducted by comparing them with information combined from intraoperative findings, histopathology, and microbiological investigations. The results showed that evidence of loosening was correctly determined in 76.4% of cases using ^{18}F-FDG PET, and in 75% of cases using bone scan.

Reliable differentiation between abrasion-induced and bacterial-caused inflammation was not possible using ^{18}F-FDG PET. The authors concluded that ^{18}F-FDG PET allows reliable prediction of peri-prosthetic septical inflammatory tissue reactions. Because of the high sensitivity of this method, a negative PET result in the setting of a diagnostically unclear situation eliminates the need for revision surgery, but noted that a positive PET result gives no clear differentiation regarding the cause of inflammation.

Other literature references describe and advocate the use of FDG PET in the diagnosis of painful hip and/or knee prostheses (Kumar et al. 2008, De Winter et al. 2002, van Acker et al. 2001). A review by Zhuang et al. 2007 further supports the role of FDG PET in the accurate diagnosis of painful arthroplasty.
In addition, Pianou et al. (2011) describes a case in which a patient with a history of papillary thyroid cancer was referred for an ([18])F-FDG PET/CT scan for evaluation of his metastatic disease. The patient also noted significant pain in his right hip joint which had been subject to prosthesis 30 years previously. The performed, and previous, FDG PET/CT scans showed a relationship between the degree of ([18])F-FDG uptake at the sites of loosening hip arthroplasty to the severity of pain. The authors concluded that in this case the degree of ([18])F-FDG uptake in a loosening hip arthroplasty was related to the severity of pain although inflammation or infection could also play some role, and that further investigation of the relationship between severity of pain and FDG update was needed.

Vascular Prosthesis
The review by Kumar et al. (2008) noted that available literature indicated FDG PET to be a valuable tool for the evaluation of possible infection of vascular grafts. FDG PET is able to detect vascular graft infection even when CT results are negative. It further notes from other literature that whilst both FDG PET and CT are useful in the evaluation of patients with suspected aortic graft infection, employing the characteristic FDG uptake pattern (diffuse and intense) as a diagnostic criterion made the efficacy of FDG PET superior to that of CT. When focal uptake was set as the positive criterion for FDG, the specificity and positive predictive value of PET for the diagnosis of aortic graft infection improved significantly to 95%. It is noted that FDG PET/CT may further enhance accuracy.

The above is further supported in a case study by Treglia et al. (2011) where the use of ^{18}F-FDG PET/CT aided in the detection of the cause of fever of unknown origin in a man presenting with aortic prosthesis inflammation. Kilk et al. (2010) and Tegler (2007) describe specific case studies involving the benefit of FDG PET, and Bruggink et al. (2010) considers the accuracy of FDG PET in diagnosis of such conditions. Spacek et al. (2009) investigated the diagnosis of 'non-acute' vascular prosthesis infection in 96 prostheses and showed PET/CT to give highly

accurate results, considering PET/CT to be an excellent diagnostic modality for suspected vascular prosthesis infection.

Fever in an AIDS Patient
Kumar et al. (2008) noted that FDG PET is able to detect infectious foci even in patients with severe neutropenia and lymphopenia. It was noted that FDG PET was found to be more accurate than CT or MRI in differentiating between malignant central nervous system (CNS) lymphoma and nonmalignant CNS disease processes such as toxoplasmosis, syphilis, and progressive multifocal leukoencephalopathy. Malignant CNS lesions had greater FDG uptake than did nonmalignant lesions in this population. Current data show that PET is especially valuable for differentiating lymphomas from non-malignant CNS lesions affecting the CNS.

In addition Liu (2011) noted that a unique application of FDG PET/CT is the differentiation of cerebral lesions between lymphoma and toxoplasmosis in AIDS patients, which cannot be reliably achieved with either CT or MRI. HIV-associated opportunistic infections may involve different pathogens and multiple tissues, organs or systems. Some preliminary observations revealed a promising role of FDG PET-CT in the diagnosis and identification of these infections such as tuberculosis, fever of unknown origin, pneumocystis pneumonia and candidiasis. However, it should be stressed that FDG PET-CT alone has no role in identifying the pathology of abnormalities. FDG PET-CT, at best, can localise the sites of abnormalities and impact on patient's management in clinical decision making.

Detection of Septic Metastatic Foci in Case of Bacteraemia
The timely detection of metastatic infectious foci in gram-positive bacteremia is crucial, because these foci often require prolonged antibiotic treatment or drainage. The diagnosis of metastatic infectious foci is difficult because localising symptoms are often absent. Vos et al. (2010) investigated whether ^{18}F-FDG PET/CT was able to detect such foci and whether detection influenced clinical outcome. In 115 patients matched with historical controls F-FDG PET/CT was the first to delineate infectious foci in 35 patients (30%). In the remaining 70%, either symptoms on physical examination or other imaging techniques first revealed infectious foci. The sensitivity, specificity, negative predictive value, and positive predictive value of ^{18}F-FDG PET/CT were 100%, 87%, 100%, and 89%, respectively. Relapse rates decreased from 7.4% to 2.6% among study patients (P = 0.09) and from 8.9% to 1.4% in patients with S. aureus (P = 0.04). Overall mortality after 6 months decreased from 32.2% to 19.1% in the ^{18}F-FDG PET/CT group (P = 0.014). Thus, ^{18}F-FDG PET/CT was demonstrated to be a valuable technique that results in lower mortality rates.

Detection of the Extension of Inflammation in case of:
Sarcoidosis
Inflammatory bowel disease
Vasculitis involving the great vessels

Sarcoidosis
A recent review (Treglia G, 2011) of the role of ^{18}FDG PET as a marker of disease activity in patients with sarcoidosis concluded:
(1) positive FDG PET findings should be interpreted with caution in differentiating sarcoidosis from other inflammatory diseases and malignant abnormalities;

(2) FDG PET seems to be a very useful molecular imaging method in assessing disease activity, in staging and identifying occult sites, and in monitoring treatment response in patients with sarcoidosis (Nishiyama Y, 2006);

(3) FDG PET shows a better diagnostic accuracy compared to 67Ga scintigraphy in patients with sarcoidosis, because of a better sensitivity of FDG PET (mainly due to the high quality of FDG PET images with superior contrast and spatial resolution compared to 67Ga scintigraphy) in addition to several practical advantages (less radiation exposure, shorter time between injection and imaging).

Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis are the 2 main subtypes of inflammatory bowel disease (IBD). Although ulcerative colitis affects solely the colon, colonoscopy is associated with an increased risk of perforation. ^{18}F-FDG PET has been evaluated in children and adults with IBD. In a study of 65 children, PET had a good sensitivity of 80% (compared with colonoscopy), and a negative PET scan excluded the presence of inflammation in children with recurrent abdominal pain (Lemberg DA, 2005). In another study of children, the results of PET were compared with histology, and PET reached a sensitivity of 98% and a specificity of 68% (in comparison to endoscopy [90% and 75%, respectively] and ultrasonography [56% and 92%, respectively]). For small- bowel disease, PET was even more reliable (Löffler M, 2006). In a study of adults with IBD, hydro- MRI was clearly inferior to PET, with sensitivities of 40.9% and 85.4%, respectively (Neurath MF, 2002). More studies have demonstrated a good sensitivity for PET in IBD, with a high correlation with disease activity, laboratory parameters, endoscopy, and other parameters (Gotthardt M, 2010).

Vasculitis Involving the Great Vessels

^{18}F-FDG PET is a highly sensitive imaging technique for the detection of inflamed arterial walls. In contrast to ultrasonography, with ^{18}F-FDG PET the thoracic aorta can also be visualised. Other large arteries can be visualised without the limitations associated with ultrasonography (gas in bowels, bones, locations deep within the body), allowing for simple assessment of the abdominal and pelvic arteries (Gotthardt M, 2010).

FDG PET/CT has validity in the evaluation of large-vessel vasculitis, with sensitivity values ranging from 77% to 92% and specificities ranging from 89% to 100%. FDG PET/CT has proven utility in the initial diagnosis of patients suspected of having vasculitis, particularly those who present with non-specific symptoms, in the identification of areas of increased FDG uptake requiring biopsy, and in the evaluation of the extent of disease (Zerizer I, 2010) (Glaudemans AWJM, 2010) (Gotthardt M, 2010).

Therapy Follow-Up

Unresectable alveolar echinococcosis, in search for active localisations of the parasite during medical treatment and after treatment discontinuation.

FDG PET detects metabolic activity in alveolar echinococcosis (AE). The slow changes in metabolic and morphological characteristics require long-term follow-up of patients. A study in 15 patients to evaluate metabolic activity over may years, thus assessing the utility of FDGPET for the evaluation of disease progression and response to treatment. Treatment responses were heterogeneous and varied from progressive disease despite treatment to long-term inactive disease with discontinued treatment. Lack of metabolic activity indicated

suppressed parasite activity and is not equivalent to parasite death. However, metabolic activity may remain suppressed for years, allowing for temporary treatment discontinuation. It was concluded that relapses were reliably detected with PET and restarting benzimidazole treatment prevents parasite expansion (Reuter S, 2008).

In another study in 17 AE patients FDG PET identified increased metabolic activity in the corresponding lesions in 41.2% patients (Ehrhardt AR, 2007). A study in 26 patients with newly diagnosed AE FDG PET was demonstrated to be a sensitive and specific adjunct in the diagnosis of suspected AE and can help in differentiating AE from cystic echinococcosis. The rapid improvement of positive PET scans with benzimidazole therapy in some patients indicated that absent FDG uptake does not necessarily reflect parasite viability (Stumpe KD, 2007). Overall therapeutic follow-up of unresectable alveolar echinococcosis, in which it may be used in the search for active localisations of the parasite during medical treatment and after treatment discontinuation (Zerizer I, 2010) (Glaudemans AWJM, 2010) In conclusion the use of FDG –PET is generally considered useful for the therapeutic follow-up of unresectable alveolar echinococcosis. Data is drawn from small studies but the studies are consistent.

Finally, the MAH has provided new studies (Vaidyanathan et al. 2015, Kung et al. 2019, Kan et al. 2019, Treglia. 2019, Ropers et al. 2020) published between 2016 and 2020 that adequately described the use of 18F-FDG in the diagnosis of infectious and inflammatory diseases. The MAH has presented an overview based on the bibliographic data to support the wide range of proposed indications. ^{18}F-FDG PET is successfully used for many years in the field of (1) oncology for diagnosis, staging, monitoring and detection of tumours; (2) cardiology for identification of viable myocardial tissue; (3) neurology for localisation of epileptogenic foci; (4) infectious and inflammatory diseases for diagnosis and detection of infectious or inflammatory foci. ^{18}F-FDG PET has a well-known and efficient use in the clinical practice in Europe for more than 10 years, and therefore, the well-established use application can be applied. In general, the quality of the overview is considered sufficient and the claimed indications are fully in line with the core SmPC of the product.

IV.4   Clinical safety

No randomised, blinded clinical trials assessing safety of 18F-FDG injection were identified during the literature search. However clinical experience is extensive. A prospective four-year study was performed with 22 collaborating institutions in the USA (Silberstein et al. 1998) using a questionnaire evaluating the number of PET procedures performed and the number of adverse events associated with PET radiopharmaceuticals as well as with non-radioactive pharmaceuticals used for PET. As recorded by Silberstein, there were a total of 33,925 radiopharmaceutical doses. In addition, the total prospective number of administered doses recorded by the participants was 47,876, for a total number of positron emitting radiopharmaceutical administrations of 81,801. No adverse reactions were found from any PET radiopharmaceutical dose. The majority of the studies were performed with 18F-FDG. Another survey study was performed in the EU (MacFarlane et al. 1998) with a total of 26 European PET centres participating. 18F-FDG was by far the most used PET tracer with approximately 200 applications per week and not a single adverse reaction that could be related with any possible toxicological effect of 18F-FDG was reported.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to GlucoPET.

Table 12.   Summary table of safety concerns as approved in RMP

Important identified risks	- None
Important potential risks	- None
Missing information	- None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

This decentralised procedure concerns a well-established use application for GlucoPET. For this authorisation, reference is made to literature. No new clinical studies were conducted. Risk management is adequately addressed. Altogether it is considered that efficacy of ^{18}F-FDG in the treatment of the marketed indications has been established as the majority of studies in subjects showed statistically significant and clinically relevant results. Finally, it is considered that the safety issues that are identified are adequately addressed in the SmPC.

V.   USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Steripet (UK/H/0814/001/MR), which in turn has been bridged to the PIL for MYOVIEW 230 micrograms kit for radiopharmaceutical preparation, lyophilisate for solution for injection, that has been user tested and approved. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI.   OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

GlucoPET 250 MBq/ml, solution for injection has a proven chemical-pharmaceutical quality. GlucoPET has an adequate efficacy and safety profile and is considered widely established.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that well-established use has been demonstrated for GlucoPET, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 September 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4774/001/IE/001	Repeat-use application (NL, BG, CY, EL)	No	5-10-2022	Approved	N/A

LITERATURE REFERENCES

Abdel-Nabi H, Doerr RJ, Lamonica DM, Cronin VR, Galantowicz PJ, Carbone GM, Spaulding MB. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. Radiology. 1998 Mar;206(3):755-60. doi: 10.1148/radiology.206.3.9494497. PMID: 9494497.

Adams S, Baum RP, Stuckensen T, Bitter K, Hör G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med. 1998 Sep;25(9):1255-60. doi: 10.1007/s002590050293. PMID: 9724374.

Adler LP, Faulhaber PF, Schnur KC, Al-Kasi NL, Shenk RR. Axillary lymph node metastases: screening with [F-18]2-deoxy-2-fluoro-D-glucose (FDG) PET. Radiology. 1997 May;203(2):323-7. doi: 10.1148/radiology.203.2.9114082. PMID: 9114082.

Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg. 1994 Sep;220(3):364-72; discussion 372-3. doi: 10.1097/00000658-199409000-00012. PMID: 8092902; PMCID: PMC1234394.

Albes JM, Lietzenmayer R, Schott U, Schülen E, Wehrmann M, Ziemer G. Improvement of non-small-cell lung cancer staging by means of positron emission tomography. Thorac Cardiovasc Surg. 1999 Feb;47(1):42-7. doi: 10.1055/s-2007-1013107. PMID: 10218620.

Avril N, Dose J, Jänicke F, Ziegler S, Römer W, Weber W, Herz M, Nathrath W, Graeff H, Schwaiger M. Assessment of axillary lymph node involvement in breast cancer patients with positron emission tomography using radiolabeled 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. J Natl Cancer Inst. 1996 Sep 4;88(17):1204-9. doi: 10.1093/jnci/88.17.1204. PMID: 8780629.

Avril N, Dose J, Jänicke F, Bense S, Ziegler S, Laubenbacher C, Römer W, Pache H, Herz M, Allgayer B, Nathrath W, Graeff H, Schwaiger M. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. J Clin Oncol. 1996 Jun;14(6):1848-57. doi: 10.1200/JCO.1996.14.6.1848. PMID: 8656253.

Avril N, Bense S, Ziegler SI, Dose J, Weber W, Laubenbacher C, Römer W, Jänicke F, Schwaiger M. Breast imaging with fluorine-18-FDG PET: quantitative image analysis. J Nucl Med. 1997 Aug;38(8):1186-91. PMID: 9255146.

Bader JB, Samnick S, Moringlane JR, Feiden W, Schaefer A, Kremp S, Kirsch CM. Evaluation of l-3-[123I]iodo-alpha-methyltyrosine SPET and [18F]fluorodeoxyglucose PET in the detection and grading of recurrences in patients pretreated for gliomas at follow-up: a comparative study with stereotactic biopsy. Eur J Nucl Med. 1999 Feb;26(2):144-51. doi: 10.1007/s002590050370. PMID: 9933348.

Bangerter M, Moog F, Buchmann I, Kotzerke J, Griesshammer M, Hafner M, Elsner K, Frickhofen N, Reske SN, Bergmann L. Whole-body 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) for accurate staging of Hodgkin's disease. Ann Oncol. 1998 Oct;9(10):1117-22. doi: 10.1023/a:1008486928190. PMID: 9834825.

Bangerter, Markus; Florian Moog, Martin Griesshammer, Klaus Elsner, Jörg Kotzerke, Hermann Heimpel, Lothar Bergmann, Sven Norbert Reske, Norbert Frickhofen, Role of whole body FDG PET imaging in predicting relapse of malignant lymphoma in patients with residual masses after treatment, Radiography, Volume 5, Issue 3, 1999, Pages 155-163, ISSN 1078-8174, https://doi.org/10.1016/S1078-8174(99)90024-X.

Barth, E, et al. Glucose metabolism and catecholamines. Crit Care Med. 2007;35(9 Suppl):S508-18.

Beanlands RS, Ruddy TD, deKemp RA, Iwanochko RM, Coates G, Freeman M, Nahmias C, Hendry P, Burns RJ, Lamy A, Mickleborough L, Kostuk W, Fallen E, Nichol G; PARR Investigators. Positron emission tomography and recovery following revascularization (PARR-1): the importance of scar and the development of a prediction rule for the degree of recovery of left ventricular function. J Am Coll Cardiol. 2002 Nov 20;40(10):1735-43. doi: 10.1016/s0735-1097(02)02489-0. PMID: 12446055.

Benchaou M, Lehmann W, Slosman DO, Becker M, Lemoine R, Rufenacht D, Donath A. The role of FDG PET in the preoperative assessment of N-staging in head and neck cancer. Acta Otolaryngol. 1996 Mar;116(2):332-5. doi: 10.3109/00016489609137852. PMID: 8725543.

Bender H, Kirst J, Palmedo H, Schomburg A, Wagner U, Ruhlmann J, Biersack HJ. Value of 18fluoro-deoxyglucose positron emission tomography in the staging of recurrent breast carcinoma. Anticancer Res. 1997 May-Jun;17(3B):1687-92. PMID: 9179219.

Bohuslavizki KH, Klutmann S, Buchert R et al (1999) Value of F-18-FDG PET in patients with cervical lymph node metastases of unknown origin. Radiol Oncol 33: 207-212

Boland GW, Goldberg MA, Lee MJ, Mayo-Smith WW, Dixon J, McNicholas MM, Mueller PR. Indeterminate adrenal mass in patients with cancer: evaluation at PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology. 1995 Jan;194(1):131-4. doi: 10.1148/radiology.194.1.7997539. PMID: 7997539.

Bowyer, JF, et al. Corticosterone and exogenous glucose alter blood glucose levels, neurotoxicity, and vascular toxicity produced by methamphetamine. J Neurochem. 2017;143(2):198-213.

Braams JW, Pruim J, Kole AC, Nikkels PG, Vaalburg W, Vermey A, Roodenburg JL. Detection of unknown primary head and neck tumors by positron emission tomography. Int J Oral Maxillofac Surg. 1997 Apr;26(2):112-5. doi: 10.1016/s0901-5027(05)80829-x. PMID: 9151165.

Brücher BL, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmerman F, Siewert JR, Schwaiger M. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg. 2001 Mar;233(3):300-9. doi: 10.1097/00000658-200103000-00002. PMID: 11224616; PMCID: PMC1421244.

Bruggink JL, Glaudemans AW, Saleem BR, Meerwaldt R, Alkefaji H, Prins TR, Slart RH, Zeebregts CJ. Accuracy of FDG PET-CT in the diagnostic work-up of vascular prosthetic graft infection. Eur J Vasc Endovasc Surg. 2010 Sep;40(3):348-54. doi: 10.1016/j.ejvs.2010.05.016. Epub 2010 Jun 23. PMID: 20576451.

Buchmann I, Moog F, Schirrmeister H, Reske SN. Positron emission tomography for detection and staging of malignant lymphoma. Recent Results Cancer Res. 2000;156:78-89. doi: 10.1007/978-3-642-57054-4_10. PMID: 10802866.

Bury T, Dowlati A, Paulus P, Corhay JL, Benoit T, Kayembe JM, Limet R, Rigo P, Radermecker M. Evaluation of the solitary pulmonary nodule by positron emission tomography imaging. Eur Respir J. 1996 Mar;9(3):410-4. doi: 10.1183/09031936.96.09030410. PMID: 8729997.

Bury T, Corhay JL, Duysinx B, Daenen F, Ghaye B, Barthelemy N, Rigo P, Bartsch P. Value of FDG PET in detecting residual or recurrent nonsmall cell lung cancer. Eur Respir J. 1999 Dec;14(6):1376-80. doi: 10.1183/09031936.99.14613769. PMID: 10624770.

Carlson, M.L., DiGiacomo, P.S., Fan, A.P. et al. Simultaneous FDG PET/MRI detects hippocampal subfield metabolic differences in AD/MCI. Sci Rep 10, 12064 (2020). https://doi.org/10.1038/s41598-020-69065-0

Carne RP(1), O'Brien TJ, Kilpatrick CJ, MacGregor LR, Hicks RJ, Murphy MA, Bowden SC, Kaye AH, Cook MJ. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain. 2004 Oct;127(Pt 10):2276-85. doi: 10.1093/brain/awh257. Epub 2004 Jul 28.

Carr R, Barrington SF, Madan B, O'Doherty MJ, Saunders CA, van der Walt J, Timothy AR. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood. 1998 May 1;91(9):3340-6. PMID: 9558391.

Carrel T(1), Jenni R, Haubold-Reuter S, von Schulthess G, Pasic M, Turina M. Improvement of severely reduced left ventricular function after surgical revascularization in patients with preoperative myocardial infarction. Eur J Cardiothorac Surg. 1992;6(9):479-84. doi: 10.1016/1010- 7940(92)90244-r.

Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, Noh SH. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. Cancer. 2005 Jun 1;103(11):2383-90. doi: 10.1002/cncr.21074. PMID: 15856477.

Choi JW, Budzevich M, Wang S, Gage K, Estrella V, Gillies RJ. In vivo positron emission tomographic blood pool imaging in an immunodeficient mouse model using 18F-fluorodeoxyglucose labeled human erythrocytes. PLoS One. 2019 Jan 25;14(1):e0211012. doi: 10.1371/journal.pone.0211012. PMID: 30682160; PMCID: PMC6347438.

Christopoulos, G, et al. Suppressing physiologic 18-fluorodeoxyglucose uptake in patients undergoing positron emission tomography for cardiac sarcoidosis: The effect of a structured patient preparation protocol. J Nucl Cardiol. 2019.

Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I. Detection of bone metastases in breast cancer by 18FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions. J Clin Oncol. 1998 Oct;16(10):3375-9. doi: 10.1200/JCO.1998.16.10.3375. PMID: 9779715.

Couper GW, McAteer D, Wallis F, Norton M, Welch A, Nicolson M, Park KG. Detection of response to chemotherapy using positron emission tomography in patients with oesophageal and gastric cancer. Br J Surg. 1998 Oct;85(10):1403-6. doi: 10.1046/j.1365-2168.1998.00963.x. PMID: 9782025.

Cremerius U, Fabry U, Neuerburg J, Zimny M, Bares R, Osieka R, Büll U. Prognostic significance of positron emission tomography using fluorine-18-fluorodeoxyglucose in patients treated for malignant lymphoma. Nuklearmedizin. 2001 Feb;40(1):23-30. PMID: 11373935.

Crippa F, Agresti R, Donne VD, Pascali C, Bogni A, Chiesa C, De Sanctis V, Schiavini M, Decise D, Bombardieri E. The contribution of positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) in the preoperative detection of axillary metastases of breast cancer: the experience of the National Cancer Institute of Milan. Tumori. 1997 Mar-Apr;83(2):542-3. PMID: 9226015.

Crippa F, Agresti R, Seregni E, Greco M, Pascali C, Bogni A, Chiesa C, De Sanctis V, Delledonne V, Salvadori B, Leutner M, Bombardieri E. Prospective evaluation of fluorine-18-FDG PET in presurgical staging of the axilla in breast cancer. J Nucl Med. 1998 Jan;39(1):4-8. PMID: 9443729.

Cui H, Wang X, Lin W, Zhou J, Eberl S, Feng D, Fulham M. Primary lung tumor segmentation from PET-CT volumes with spatial-topological constraint. Int J Comput Assist Radiol Surg. 2016 Jan;11(1):19-29. doi: 10.1007/s11548-015-1231-0. Epub 2015 Jul 2. PMID: 26133651.

De Potter T(1), Flamen P, Van Cutsem E, Penninckx F, Filez L, Bormans G, Maes A, Mortelmans L. Whole-body PET with FDG for the diagnosis of recurrent gastric cancer. Eur J Nucl Med Mol Imaging. 2002 Apr;29(4):525-9. doi: 10.1007/s00259-001-0743-8. Epub 2002 Feb 23.

De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. Eur J Clin Microbiol Infect Dis. 2002 Apr;21(4):247-57. doi: 10.1007/s10096-002-0708-2. Epub 2002 Apr 20. PMID: 12072934.

Delank KS, Schmidt M, Michael JW, Dietlein M, Schicha H, Eysel P. The implications of 18F-FDG PET for the diagnosis of endoprosthetic loosening and infection in hip and knee arthroplasty: results from a prospective, blinded study. BMC Musculoskelet Disord. 2006 Mar 3;7:20. doi: 10.1186/1471-2474-7-20. PMID: 16512924; PMCID: PMC1409773.

Delbeke D, Vitola JV, Sandler MP, Arildsen RC, Powers TA, Wright JK Jr, Chapman WC, Pinson CW. Staging recurrent metastatic colorectal carcinoma with PET. J Nucl Med. 1997 Aug;38(8):1196-201. PMID: 9255148.

Desai DC, Arnold M, Saha S, Hinkle G, Soble D, Fry J, DePalatis LR, Mantil J, Satter M, Martin EW. Correlative Whole-Body FDG PET and Intraoperative Gamma Detection of FDG Distribution in Colorectal Cancer. Clin Positron Imaging. 2000 Sep;3(5):189-196. doi: 10.1016/s1095-0397(00)00052-2. PMID: 11348847.

de Wit M, Bumann D, Beyer W, Herbst K, Clausen M, Hossfeld DK. Whole-body positron emission tomography (PET) for diagnosis of residual mass in patients with lymphoma. Ann Oncol. 1997;8 Suppl 1:57-60. PMID: 9187431.

De Witte O, Lefranc F, Levivier M, Salmon I, Brotchi J, Goldman S. FDG PET as a prognostic factor in high-grade astrocytoma. J Neurooncol. 2000 Sep;49(2):157-63. doi: 10.1023/a:1026518002800. PMID: 11206011.

Di Carli MF, Asgarzadie F, Schelbert HR, Brunken RC, Laks H, Phelps ME, Maddahi J. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. Circulation. 1995 Dec 15;92(12):3436-44. doi: 10.1161/01.cir.92.12.3436. PMID: 8521565.

Dimitrakopoulou-Strauss A, Strauss LG, Goldschmidt H, Lorenz WJ, Maier-Borst W, van Kaick G. Evaluation of tumour metabolism and multidrug resistance in patients with treated malignant lymphomas. Eur J Nucl Med. 1995 May;22(5):434-42. doi: 10.1007/BF00839058. PMID: 7641752.

Dudoignon, D, Pattison, DA, Legallois, D, Hicks, RJ, Aide, N. The utility of pharmacological and radiological interventions to optimize diagnostic information from PET/CT. Cancer Imaging. 2020;20(1):68.

Duhaylongsod FG, Lowe VJ, Patz EF Jr, Vaughn AL, Coleman RE, Wolfe WG. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). J Thorac Cardiovasc Surg. 1995 Jul;110(1):130-9; discussion 139-40. doi: 10.1016/S0022-5223(05)80018-2. PMID: 7609536.

Duncan JS(1). Imaging and epilepsy. Brain. 1997 Feb;120 (Pt 2):339-77. doi:10.1093/brain/120.2.339.

Eary JF, Conrad EU, Bruckner JD, Folpe A, Hunt KJ, Mankoff DA, Howlett AT. Quantitative [F-18]fluorodeoxyglucose positron emission tomography in pretreatment and grading of sarcoma. Clin Cancer Res. 1998 May;4(5):1215-20. PMID: 9607579.

Ehrhardt AR, Reuter S, Buck AK, Haenle MM, Mason RA, Gabelmann A, Kern P, Kratzer W. Assessment of disease activity in alveolar echinococcosis: a comparison of contrast enhanced ultrasound, three-phase helical CT and [(18)F] fluorodeoxyglucose positron emission tomography. Abdom Imaging. 2007 Nov;32(6):730-6. doi: 10.1007/s00261-006-9173-1. Epub 2007 Feb 7. PMID: 17285403.

Erasmus JJ, Patz EF Jr, McAdams HP, Murray JG, Herndon J, Coleman RE, Goodman PC. Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. AJR Am J Roentgenol. 1997 May;168(5):1357-60. doi: 10.2214/ajr.168.5.9129444. PMID: 9129444.

Ergül N, Cermik TF. FDG PET or PET/CT in Fever of Unknown Origin: The Diagnostic Role of Underlying Primary Disease. Int J Mol Imaging. 2011;2011:318051. doi: 10.1155/2011/318051. Epub 2011 Mar 3. PMID: 21490728; PMCID: PMC3065735.

Ericson K, Kihlström L, Mogard J, Karlsson B, Lindquist C, Widén L, Collins VP, Stone-Elander S. Positron emission tomography using 18F-fluorodeoxyglucose in patients with stereotactically irradiated brain metastases. Stereotact Funct Neurosurg. 1996;66 Suppl 1:214-24. doi: 10.1159/000099813. PMID: 9032864.

Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med. 1996 Sep;37(9):1468-72. PMID: 8790195.

Fischer BM, Mortensen J, Højgaard L. Positron emission tomography in the diagnosis and staging of lung cancer: a systematic, quantitative review. Lancet Oncol. 2001 Nov;2(11):659-66. doi: 10.1016/S1470-2045(01)00555-1. PMID: 11902536.

Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De Leyn P, Van Raemdonck D, Coosemans W, Ectors N, Haustermans K, Mortelmans L. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol. 2000 Sep 15;18(18):3202-10. doi: 10.1200/JCO.2000.18.18.3202. PMID: 10986052.

Frank A, Lefkowitz D, Jaeger S, Gobar L, Sunderland J, Gupta N, Scott W, Mailliard J, Lynch H, Bishop J, et al. Decision logic for retreatment of asymptomatic lung cancer recurrence based on positron emission tomography findings. Int J Radiat Oncol Biol Phys. 1995 Jul 30;32(5):1495-512. doi: 10.1016/0360-3016(94)00622-R. PMID: 7635795.

Franke C, Klapdor R, Meyerhoff K, Schauman M. 18-FDG positron emission tomography of the pancreas: diagnostic benefit in the follow-up of pancreatic carcinoma. Anticancer Res. 1999 Jul-Aug;19(4A):2437-42. PMID: 10470172.

Friess H, Langhans J, Ebert M, Beger HG, Stollfuss J, Reske SN, Büchler MW. Diagnosis of pancreatic cancer by 2[18F]-fluoro-2-deoxy-D-glucose positron emission tomography. Gut. 1995 May;36(5):771-7. doi: 10.1136/gut.36.5.771. Erratum in: Gut 1995 Sep;37(3):448. PMID: 7797130; PMCID: PMC1382685.

Fukunaga T, Okazumi S, Koide Y, Isono K, Imazeki K. Evaluation of esophageal cancers using fluorine-18-fluorodeoxyglucose PET. J Nucl Med. 1998 Jun;39(6):1002-7. PMID: 9627333.

Gaillard WD(1), Bhatia S, Bookheimer SY, Fazilat S, Sato S, Theodore WH. FDG PET and volumetric MRI in the evaluation of patients with partial epilepsy. Neurology. 1995 Jan;45(1):123-6. doi: 10.1212/wnl.45.1.123.

Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med. 2001 May;42(5 Suppl):1S-93S. PMID: 11483694.

Gerber BL, Vanoverschelde JL, Bol A, Michel C, Labar D, Wijns W, Melin JA. Myocardial blood flow, glucose uptake, and recruitment of inotropic reserve in chronic left ventricular ischemic dysfunction. Implications for the pathophysiology of chronic myocardial hibernation. Circulation. 1996 Aug 15;94(4):651-9. doi: 10.1161/01.cir.94.4.651. PMID: 8772684.

Glaudemans AW, Signore A. FDG PET/CT in infections: the imaging method of choice? Eur J Nucl Med Mol Imaging. 2010 Oct;37(10):1986-91. doi: 10.1007/s00259-010-1587-x. PMID: 20700737; PMCID: PMC2933007.

Goerres GW, Haenggeli CA, Allaoua M, Albrecht SR, Dulguerov P, Becker M, Allal AS, Lehmann W, Slosman DO. Direct comparison of F-18-FDG PET and ultrasound in the follow-up of patients with squamous cell cancer of the head and neck. Nuklearmedizin. 2000 Dec;39(8):246-50. PMID: 11189902.

Goldberg MA, Mayo-Smith WW, Papanicolaou N, Fischman AJ, Lee MJ. FDG PET characterization of renal masses: preliminary experience. Clin Radiol. 1997 Jul;52(7):510-5. doi: 10.1016/s0009-9260(97)80327-3. PMID: 9240703.

Gotthardt M, Bleeker-Rovers CP, Boerman OC, Oyen WJ. Imaging of inflammation by PET, conventional scintigraphy, and other imaging techniques. J Nucl Med. 2010 Dec;51(12):1937-49. doi: 10.2967/jnumed.110.076232. Epub 2010 Nov 15. PMID: 21078798.

Grab D, Flock F, Stöhr I, Nüssle K, Rieber A, Fenchel S, Brambs HJ, Reske SN, Kreienberg R. Classification of asymptomatic adnexal masses by ultrasound, magnetic resonance imaging, and positron emission tomography. Gynecol Oncol. 2000 Jun;77(3):454-9. doi: 10.1006/gyno.2000.5768. PMID: 10831359.

Greco M, Crippa F, Agresti R, Seregni E, Gerali A, Giovanazzi R, Micheli A, Asero S, Ferraris C, Gennaro M, Bombardieri E, Cascinelli N. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose-positron emission tomography: clinical evaluation and alternative management. J Natl Cancer Inst. 2001 Apr 18;93(8):630-5. doi: 10.1093/jnci/93.8.630. PMID: 11309439.

Greven KM, Williams DW 3rd, Keyes JW Jr, McGuirt WF, Watson NE Jr, Case LD. Can positron emission tomography distinguish tumor recurrence from irradiation sequelae in patients treated for larynx cancer? Cancer J Sci Am. 1997 Nov-Dec;3(6):353-7. PMID: 9403048.

Greven KM, Keyes JW Jr, Williams DW 3rd, McGuirt WF, Joyce WT 3rd. Occult primary tumors of the head and neck: lack of benefit from positron emission tomography imaging with 2-[F-18]fluoro-2-deoxy-D-glucose. Cancer. 1999 Jul 1;86(1):114-8. doi: 10.1002/(sici)1097-0142(19990701)86:1<114::aid-cncr16>3.0.co;2-e. PMID: 10391570.

Gropler RJ(1), Geltman EM, Sampathkumaran K, Pérez JE, Moerlein SM, Sobel BE, Bergmann SR, Siegel BA. Functional recovery after coronary revascularization for chronic coronary artery disease is dependent on maintenance of oxidative metabolism. J Am Coll Cardiol. 1992 Sep;20(3):569-77.

Grünwald F, Schomburg A, Bender H, Klemm E, Menzel C, Bultmann T, Palmedo H, Ruhlmann J, Kozak B, Biersack HJ. Fluorine-18 fluorodeoxyglucose positron emission tomography in the follow-up of

differentiated thyroid cancer. Eur J Nucl Med. 1996 Mar;23(3):312-9. doi: 10.1007/BF00837630. PMID: 8599963.

Grünwald F, Menzel C, Bender H, Palmedo H, Willkomm P, Ruhlmann J, Franckson T, Biersack HJ. Comparison of 18FDG PET with 131iodine and 99mTc-sestamibi scintigraphy in differentiated thyroid cancer. Thyroid. 1997 Jun;7(3):327-35. doi: 10.1089/thy.1997.7.327. PMID: 9226199.

Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med. 1996 Jun;37(6):943-8. PMID: 8683316.

Gupta N, Gill H, Graeber G, Bishop H, Hurst J, Stephens T. Dynamic positron emission tomography with F-18 fluorodeoxyglucose imaging in differentiation of benign from malignant lung/mediastinal lesions. Chest. 1998 Oct;114(4):1105-11. doi: 10.1378/chest.114.4.1105. PMID: 9792584.

Gupta NC, Nicholson P, Bloomfield SM. FDG PET in the staging work-up of patients with suspected intracranial metastatic tumors. Ann Surg. 1999 Aug;230(2):202-6. doi: 10.1097/00000658-199908000-00010. PMID: 10450734; PMCID: PMC1420862.

Haas F(1), Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, Schwaiger M. Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease. J Am Coll Cardiol. 1997 Dec;30(7):1693-700.

Harika, V, Parveen, S, Venkatasubbaiah, M, Varma, KVS, Devasree, S. Carbamazepine-induced hyperglycemia: A rare case report. Indian J Pharmacol. 2019;51(5):352-3.

Henry TR(1), Engel J Jr, Mazziotta JC. Clinical evaluation of interictal fluorine-18-fluorodeoxyglucose PET in partial epilepsy. J Nucl Med. 1993 Nov;34(11):1892-8.

Higashi K, Ueda Y, Seki H, Yuasa K, Oguchi M, Noguchi T, Taniguchi M, Tonami H, Okimura T, Yamamoto I. Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. J Nucl Med. 1998 Jun;39(6):1016-20. PMID: 9627336.

Higashi T, Tamaki N, Torizuka T, Nakamoto Y, Sakahara H, Kimura T, Honda T, Inokuma T, Katsushima S, Ohshio G, Imamura M, Konishi J. FDG uptake, GLUT-1 glucose transporter and cellularity in human pancreatic tumors. J Nucl Med. 1998 Oct;39(10):1727-35. PMID: 9776278.

Higashi K, Ueda Y, Ayabe K, Sakurai A, Seki H, Nambu Y, Oguchi M, Shikata H, Taki S, Tonami H, Katsuda S, Yamamoto I. FDG PET in the evaluation of the aggressiveness of pulmonary adenocarcinoma: correlation with histopathological features. Nucl Med Commun. 2000 Aug;21(8):707-14. doi: 10.1097/00006231-200008000-00002. PMID: 11039452.

Hoh CK, Glaspy J, Rosen P, Dahlbom M, Lee SJ, Kunkel L, Hawkin RA, Maddahi J, Phelps ME. Whole-body FDG PET imaging for staging of Hodgkin's disease and lymphoma. J Nucl Med. 1997 Mar;38(3):343-8. PMID: 9074514.

Holder WD Jr, White RL Jr, Zuger JH, Easton EJ Jr, Greene FL. Effectiveness of positron emission tomography for the detection of melanoma metastases. Ann Surg. 1998 May;227(5):764-9; discussion 769-71. doi: 10.1097/00000658-199805000-00017. PMID: 9605668; PMCID: PMC1191363.

Höpfner S, Krolak C, Kessler S, Tiling R, Brinkbäumer K, Hahn K, Dresel S. Preoperative imaging of Charcot neuroarthropathy in diabetic patients: comparison of ring PET, hybrid PET, and magnetic resonance imaging. Foot Ankle Int. 2004 Dec;25(12):890-5. doi: 10.1177/107110070402501208. PMID: 15680102.

Ichiya Y, Kuwabara Y, Sasaki M, Yoshida T, Omagari J, Akashi Y, Kawashima A, Fukumura T, Masuda K. A clinical evaluation of FDG PET to assess the response in radiation therapy for bronchogenic carcinoma. Ann Nucl Med. 1996 May;10(2):193-200. doi: 10.1007/BF03165392. PMID: 8800448.

Imdahl A, Nitzsche E, Krautmann F, Högerle S, Boos S, Einert A, Sontheimer J, Farthmann EH. Evaluation of positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose for the differentiation of chronic pancreatitis and pancreatic cancer. Br J Surg. 1999 Feb;86(2):194-9. doi: 10.1046/j.1365-2168.1999.01016.x. PMID: 10100786.

Inokuma T, Tamaki N, Torizuka T, Fujita T, Magata Y, Yonekura Y, Ohshio G, Imamura M, Konishi J. Value of fluorine-18-fluorodeoxyglucose and thallium-201 in the detection of pancreatic cancer. J Nucl Med. 1995 Feb;36(2):229-35. PMID: 7830119.

Inoue T, Kim EE, Komaki R, Wong FC, Bassa P, Wong WH, Yang DJ, Endo K, Podoloff DA. Detecting recurrent or residual lung cancer with FDG PET. J Nucl Med. 1995 May;36(5):788-93. PMID: 7738649.

Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, Fillet G. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood. 1999 Jul 15;94(2):429-33. PMID: 10397709.

Jerusalem G, Warland V, Najjar F, Paulus P, Fassotte MF, Fillet G, Rigo P. Whole-body 18F-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. Nucl Med Commun. 1999 Jan;20(1):13-20. doi: 10.1097/00006231-199901000-00004. PMID: 9949408.

Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, Fillet G. Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. Haematologica. 2000 Jun;85(6):613-8. PMID: 10870118.

Kalff V, Hicks RJ, MacManus MP, Binns DS, McKenzie AF, Ware RE, Hogg A, Ball DL. Clinical impact of (18)F fluorodeoxyglucose positron emission tomography in patients with non-small-cell lung cancer: a prospective study. J Clin Oncol. 2001 Jan 1;19(1):111-8. doi: 10.1200/JCO.2001.19.1.111. PMID: 11134203.

Kan Y, Wang W, Liu J, Yang J, Wang Z. Contribution of 18F-FDG PET/CT in a case-mix of fever of unknown origin and inflammation of unknown origin: a meta-analysis. Acta Radiol. 2019 Jun;60(6):716-725. doi: 10.1177/0284185118799512. Epub 2018 Sep 11. PMID: 30205705.

Kao CH, ChangLai SP, Chieng PU, Yen RF, Yen TC. Detection of recurrent or persistent nasopharyngeal carcinomas after radiotherapy with 18-fluoro-2-deoxyglucose positron emission tomography and comparison with computed tomography. J Clin Oncol. 1998 Nov;16(11):3550-5. doi: 10.1200/JCO.1998.16.11.3550. PMID: 9817274.

Kato T, Fukatsu H, Ito K, Tadokoro M, Ota T, Ikeda M, Isomura T, Ito S, Nishino M, Ishigaki T. Fluorodeoxyglucose positron emission tomography in pancreatic cancer: an unsolved problem. Eur J Nucl Med. 1995 Jan;22(1):32-9. doi: 10.1007/BF00997245. PMID: 7698152.

Kau RJ, Alexiou C, Laubenbacher C, Werner M, Schwaiger M, Arnold W. Lymph node detection of head and neck squamous cell carcinomas by positron emission tomography with fluorodeoxyglucose F 18 in a routine clinical setting. Arch Otolaryngol Head Neck Surg. 1999 Dec;125(12):1322-8. doi: 10.1001/archotol.125.12.1322. PMID: 10604409.

Keogan, M., Lowe, V., Baker, M. et al. Local recurrence of rectal cancer:evaluation with F-18 fluorodeoxyglucose PET imaging. Abdom Imaging 22, 332–337 (1997). https://doi.org/10.1007/s002619900202

Keogan MT, Tyler D, Clark L, Branch MS, McDermott VG, DeLong DM, Coleman RE. Diagnosis of pancreatic carcinoma: role of FDG PET. AJR Am J Roentgenol. 1998 Dec;171(6):1565-70. doi: 10.2214/ajr.171.6.9843289. PMID: 9843289.

Keyes JW Jr, Chen MY, Watson NE Jr, Greven KM, McGuirt WF, Williams DW 3rd. FDG PET evaluation of head and neck cancer: value of imaging the thorax. Head Neck. 2000 Mar;22(2):105-10. doi: 10.1002/(sici)1097-0347(200003)22:2<105::aid-hed1>3.0.co;2-n. PMID: 10679897.

Kilk, K., Hyhlik-Dürr, A., Afshar-Oromieh, A. et al. Chronischer zentraler Gefäßprotheseninfekt. Chirurg 81, 653–656 (2010). https://doi.org/10.1007/s00104-010-1886-6

Kim DG, Kim CY, Paek SH, Lee DS, Chung JK, Jung HW, Cho BK. Whole-body 18F-FDG PET in the management of metastatic brain tumours. Acta Neurochir (Wien). 1998;140(7):665-73; discussion 673-4. doi: 10.1007/s007010050161. PMID: 9781280.

Kitagawa Y, Sadato N, Azuma H, Ogasawara T, Yoshida M, Ishii Y, Yonekura Y. FDG PET to evaluate combined intra-arterial chemotherapy and radiotherapy of head and neck neoplasms. J Nucl Med. 1999 Jul;40(7):1132-7. PMID: 10405132.

Kole AC, Plukker JT, Nieweg OE, Vaalburg W. Positron emission tomography for staging of oesophageal and gastroesophageal malignancy. Br J Cancer. 1998 Aug;78(4):521-7. doi: 10.1038/bjc.1998.526. PMID: 9716038; PMCID: PMC2063088.

Kubota K, Yamada S, Kondo T, Yamada K, Fukuda H, Fujiwara T, Ito M, Ido T. PET imaging of primary mediastinal tumours. Br J Cancer. 1996 Apr;73(7):882-6. doi: 10.1038/bjc.1996.157. PMID: 8611400; PMCID: PMC2074273.

Kumar R, Basu S, Torigian D, Anand V, Zhuang H, Alavi A. Role of modern imaging techniques for diagnosis of infection in the era of 18F-fluorodeoxyglucose positron emission tomography. Clin Microbiol Rev. 2008 Jan;21(1):209-24. doi: 10.1128/CMR.00025-07. PMID: 18202443; PMCID: PMC2223836.

Kung BT, Seraj SM, Zadeh MZ, Rojulpote C, Kothekar E, Ayubcha C, Ng KS, Ng KK, Au-Yong TK, Werner TJ, Zhuang H, Hunt SJ, Hess S, Alavi A. An update on the role of ^{18}F-FDG PET/CT in major infectious and inflammatory diseases. Am J Nucl Med Mol Imaging. 2019 Dec 15;9(6):255-273. PMID: 31976156; PMCID: PMC6971480.

la Fougère C, Rominger A, Förster S, Geisler J, Bartenstein P. PET and SPECT in epilepsy: a critical review. Epilepsy Behav. 2009 May;15(1):50-5. doi: 10.1016/j.yebeh.2009.02.025. Epub 2009 Feb 21. PMID: 19236949.

Lai DT, Fulham M, Stephen MS, Chu KM, Solomon M, Thompson JF, Sheldon DM, Storey DW. The role of whole-body positron emission tomography with [18F]fluorodeoxyglucose in identifying operable colorectal cancer metastases to the liver. Arch Surg. 1996 Jul;131(7):703-7. doi: 10.1001/archsurg.1996.01430190025007. PMID: 8678767.

M Lapela, R Grénman, T Kurki, H Joensuu, S Leskinen, P Lindholm, M Haaparanta, U Ruotsalainen, H Minn. Head and neck cancer: detection of recurrence with PET and 2-[F-18]fluoro-2-deoxy-D-glucose. radiology 1995; 197:205-211.

Lapela M(1), Leskinen S, Minn HR, Lindholm P, Klemi PJ, Söderström KO, Bergman J, Haaparanta M, Ruotsalainen U, Solin O, Joensuu H. Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorine-18-fluorodeoxyglucose. Blood. 1995 Nov 1;86(9):3522-7.

Lapela M, Eigtved A, Jyrkkiö S, Grénman R, Kurki T, Lindholm P, Nuutinen J, Sutinen E, Solin O, Bjornskov I, Bretlau P, Friberg L, Holm S, Jensen M, Sand Hansen H, Minn H. Experience in qualitative and quantitative FDG PET in follow-up of patients with suspected recurrence from head and neck cancer. Eur J Cancer. 2000 May;36(7):858-67. doi: 10.1016/s0959-8049(00)00037-x. PMID: 10785590.

Lee KS, Marwick TH, Cook SA, Go RT, Fix JS, James KB, Sapp SK, MacIntyre WJ, Thomas JD. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and revascularization. Circulation. 1994 Dec;90(6):2687-94.

Lemberg DA, Issenman RM, Cawdron R, Green T, Mernagh J, Skehan SJ, Nahmias C, Jacobson K. Positron emission tomography in the investigation of pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2005 Aug;11(8):733-8. doi: 10.1097/01.mib.0000172810.49619.cb. PMID: 16043988.

Lerut T, Flamen P, Ectors N, Van Cutsem E, Peeters M, Hiele M, De Wever W, Coosemans W, Decker G, De Leyn P, Deneffe G, Van Raemdonck D, Mortelmans L. Histopathologic validation of lymph node staging with FDG PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. Ann Surg. 2000 Dec;232(6):743-52. doi: 10.1097/00000658-200012000-00003. PMID: 11088069; PMCID: PMC1421267.

Liu IJ, Zafar MB, Lai YH, Segall GM, Terris MK. Fluorodeoxyglucose positron emission tomography studies in diagnosis and staging of clinically organ-confined prostate cancer. Urology. 2001 Jan;57(1):108-11. doi: 10.1016/s0090-4295(00)00896-7. PMID: 11164153.

Liu Y. Demonstrations of AIDS-associated malignancies and infections at FDG PET-CT. Ann Nucl Med. 2011 Oct;25(8):536-46. doi: 10.1007/s12149-011-0506-y. Epub 2011 Jun 15. PMID: 21674240.

Löffler M, Weckesser M, Franzius C, Schober O, Zimmer KP. High diagnostic value of 18F-FDG PET in pediatric patients with chronic inflammatory bowel disease. Ann N Y Acad Sci. 2006 Aug;1072:379-85. doi: 10.1196/annals.1326.014. PMID: 17057218.

Long JZ, Jacobson MS, Hung JC. Comparison of FASTlab 18F-FDG production using phosphate and citrate buffer cassettes. J Nucl Med Technol. 2013 Mar;41(1):32-4. doi: 10.2967/jnmt.112.112649. Epub 2013 Jan 14. PMID: 23318199.

LoPinto-Khoury C, Sperling MR, Skidmore C, Nei M, Evans J, Sharan A, Mintzer S. Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. Epilepsia. 2012 Feb;53(2):342-8. doi: 10.1111/j.1528-1167.2011.03359.x. Epub 2011 Dec 22. PMID: 22192050.

Lowe VJ, Dunphy FR, Varvares M, Kim H, Wittry M, Dunphy CH, Dunleavy T, McDonough E, Minster J, Fletcher JW, Boyd JH. Evaluation of chemotherapy response in patients with advanced head and neck cancer using [F-18]fluorodeoxyglucose positron emission tomography. Head Neck. 1997 Dec;19(8):666-74. doi: 10.1002/(sici)1097-0347(199712)19:8<666::aid-hed4>3.0.co;2-3. PMID: 9406745.

Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, Karis J, Hubner K, Delbeke D, Heiberg EV, Patz EF, Coleman RE. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol. 1998 Mar;16(3):1075-84. doi: 10.1200/JCO.1998.16.3.1075. PMID: 9508193.

Lowe VJ, Kim H, Boyd JH, Eisenbeis JF, Dunphy FR, Fletcher JW. Primary and recurrent early stage laryngeal cancer: preliminary results of 2-[fluorine 18]fluoro-2-deoxy-D-glucose PET imaging. Radiology. 1999 Sep;212(3):799-802. doi: 10.1148/radiology.212.3.r99se26799. PMID: 10478249.

Lucas JD, O'Doherty MJ, Cronin BF, Marsden PK, Lodge MA, McKee PH, Smith MA. Prospective evaluation of soft tissue masses and sarcomas using fluorodeoxyglucose positron emission tomography. Br J Surg. 1999 Apr;86(4):550-6. doi: 10.1046/j.1365-2168.1999.01090.x. PMID: 10215835.

Lucignani G, Tassi L, Fazio F, Galli L, Grana C, Del Sole A, Hoffman D, Francione S, Minicucci F, Kahane P, Messa C, Munari C. Double-blind stereo-EEG and FDG PET study in severe partial epilepsies: are the electric and metabolic findings related? Eur J Nucl Med. 1996 Nov;23(11):1498-507. doi: 10.1007/BF01254475. PMID: 8854849.

D J Macfarlane , V Sondak , T Johnson , R L Wahl. Prospective evaluation of 2-[18F]-2-deoxy-D-glucose positron emission tomography in staging of regional lymph nodes in patients with cutaneous malignant melanoma. doi/10.1200/JCO.1998.16.5.1770

Magnani P, Carretta A, Rizzo G, Fazio F, Vanzulli A, Lucignani G, Zannini P, Messa C, Landoni C, Gilardi MC, Del Maschio A. FDG/PET and spiral CT image fusion for medistinal lymph node assessment of non-small cell lung cancer patients. J Cardiovasc Surg (Torino). 1999 Oct;40(5):741-8. PMID: 10597015.

Maisey NR, Hill ME, Webb A, Cunningham D, Flux GD, Padhani A, Ott RJ, Norman A, Bishop L. Are 18fluorodeoxyglucose positron emission tomography and magnetic resonance imaging useful in the prediction of relapse in lymphoma residual masses? Eur J Cancer. 2000 Jan;36(2):200-6. doi: 10.1016/s0959-8049(99)00249-x. PMID: 10741278.

Marin-Neto JA(1), Dilsizian V, Arrighi JA, Perrone-Filardi P, Bacharach SL, Bonow RO. Thallium scintigraphy compared with 18F-fluorodeoxyglucose positron emission tomography for assessing myocardial viability in patients with moderate versus severe left ventricular dysfunction. Am J Cardiol. 1998 Nov 1;82(9):1001-7.

Marwick TH(1), MacIntyre WJ, Lafont A, Nemec JJ, Salcedo EE. Metabolic responses of hibernating and infarcted myocardium to revascularization. A follow-up study of regional perfusion, function, and metabolism. Circulation. 1992 Apr;85(4):1347-53.

Mastin ST, Drane WE, Harman EM, Fenton JJ, Quesenberry L. FDG SPECT in patients with lung masses. Chest. 1999 Apr;115(4):1012-7. doi: 10.1378/chest.115.4.1012. PMID: 10208202.

McAteer D, Wallis F, Couper G, Norton M, Welch A, Bruce D, Park K, Nicolson M, Gilbert FJ, Sharp P. Evaluation of 18F-FDG positron emission tomography in gastric and oesophageal carcinoma. Br J Radiol. 1999 Jun;72(858):525-9. doi: 10.1259/bjr.72.858.10560332. PMID: 10560332.

McGuirt WF, Greven K, Williams D 3rd, Keyes JW Jr, Watson N, Cappellari JO, Geisinger KR. PET scanning in head and neck oncology: a review. Head Neck. 1998 May;20(3):208-15. doi: 10.1002/(sici)1097-0347(199805)20:3<208::aid-hed5>3.0.co;2-4. PMID: 9570626.

Meller J, Sahlmann CO, Gürocak O, Liersch T, Meller B. FDG PET in patients with fever of unknown origin: the importance of diagnosing large vessel vasculitis. Q J Nucl Med Mol Imaging. 2009 Feb;53(1):51-63. PMID: 19182728.

Minn H, Lapela M, Klemi PJ, Grénman R, Leskinen S, Lindholm P, Bergman J, Eronen E, Haaparanta M, Joensuu H. Prediction of survival with fluorine-18-fluoro-deoxyglucose and PET in head and neck cancer. J Nucl Med. 1997 Dec;38(12):1907-11. PMID: 9430467.

Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, Hosokawa M, Kohanawa M, Tamaki N. FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. J Nucl Med. 2001 Oct;42(10):1551-5. PMID: 11585872.

Monakhov, N. K., Neistadt, E. L., Shavlovskii, M. M., Shvartsman, A. L., & Neifakh, S. A. (1978). Physicochemical properties and isoenzyme composition of hexokinase from normal and malignant human tissues. Journal of the National Cancer Institute, 61(1), 27-34.

Moog F, Bangerter M, Diederichs CG, Guhlmann A, Kotzerke J, Merkle E, Kolokythas O, Herrmann F, Reske SN. Lymphoma: role of whole-body 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) PET in nodal staging. Radiology. 1997 Jun;203(3):795-800. doi: 10.1148/radiology.203.3.9169707. PMID: 9169707.

Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen N, Reske SN. 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J Clin Oncol. 1998 Feb;16(2):603-9. doi: 10.1200/JCO.1998.16.2.603. PMID: 9469348.

Moog F, Kotzerke J, Reske SN. FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. J Nucl Med. 1999 Sep;40(9):1407-13. PMID: 10492357.

Moon DH, Maddahi J, Silverman DH, Glaspy JA, Phelps ME, Hoh CK. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med. 1998 Mar;39(3):431-5. PMID: 9529287.

Mukai K, Ishida Y, Okajima K, Isozaki H, Morimoto T, Nishiyama S. Usefulness of preoperative FDG PET for detection of gastric cancer. Gastric Cancer. 2006;9(3):192-6. doi: 10.1007/s10120-006-0374-7. PMID: 16952037.

Nakamoto Y, Saga T, Ishimori T, Mamede M, Togashi K, Higuchi T, Mandai M, Fujii S, Sakahara H, Konishi J. Clinical value of positron emission tomography with FDG for recurrent ovarian cancer. AJR Am J Roentgenol. 2001 Jun;176(6):1449-54. doi: 10.2214/ajr.176.6.1761449. PMID: 11373212.

Nettelbladt OS, Sundin AE, Valind SO, Gustafsson GR, Lamberg K, Långström B, Björnsson EH. Combined fluorine-18-FDG and carbon-11-methionine PET for diagnosis of tumors in lung and mediastinum. J Nucl Med. 1998 Apr;39(4):640-7. PMID: 9544671.

Neurath MF, Vehling D, Schunk K, Holtmann M, Brockmann H, Helisch A, Orth T, Schreckenberger M, Galle PR, Bartenstein P. Noninvasive assessment of Crohn's disease activity: a comparison of 18F-fluorodeoxyglucose positron emission tomography, hydromagnetic resonance imaging, and granulocyte scintigraphy with labeled antibodies. Am J Gastroenterol. 2002 Aug;97(8):1978-85. doi: 10.1111/j.1572-0241.2002.05836.x. PMID: 12190164.

Nishiyama Y, Yamamoto Y, Fukunaga K, Takinami H, Iwado Y, Satoh K, Ohkawa M. Comparative evaluation of 18F-FDG PET and 67Ga scintigraphy in patients with sarcoidosis. J Nucl Med. 2006 Oct;47(10):1571-6. PMID: 17015889.

Noh, DY., Yun, IJ., Kim, JS. et al. Diagnostic Value of Positron Emission Tomography for Detecting Breast Cancer. World J. Surg. 22, 223–228 (1998). https://doi.org/10.1007/s002689900374

Okamoto, S, et al. Effect of drugs containing glucose on FDG-PET image quality. Ann Nucl Med. 2019;33(11):828-34.

Pai M, Park CH, Suh JH, Koh JH. Fluorine-18 fluorodeoxyglucose imaging using dual-head coincidence positron emission tomography without attenuation correction in patients with head and neck cancer. Clin Nucl Med. 1999 Jul;24(7):495-500. doi: 10.1097/00003072-199907000-00004. PMID: 10402001.

Pianou NK, Pneumaticos SG, Vlachos L, Chatziioannou SN. Can pain influence the severity of findings of an (18)F-FDG PET/CT scan in loosening hip arthroplasty? Hell J Nucl Med. 2011 Sep-Dec;14(3):318-9. PMID: 22087460.

Präuer HW, Weber WA, Römer W, Treumann T, Ziegler SI, Schwaiger M. Controlled prospective study of positron emission tomography using the glucose analogue [18f]fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg. 1998 Nov;85(11):1506-11. doi: 10.1046/j.1365-2168.1998.00915.x. PMID: 9823912.

Rankin SC, Taylor H, Cook GJ, Mason R. Computed tomography and positron emission tomography in the pre-operative staging of oesophageal carcinoma. Clin Radiol. 1998 Sep;53(9):659-65. doi: 10.1016/s0009-9260(98)80292-4. PMID: 9766719.

Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, Ihling C, Högerle S, Mix M, Moser E, Krause TM. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. Radiology. 2001 Mar;218(3):776-82. doi: 10.1148/radiology.218.3.r01mr19776. PMID: 11230656.

Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, Casella V, Fowler J, Hoffman E, Alavi A, Som P, Sokoloff L. The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ Res. 1979 Jan;44(1):127-37. doi: 10.1161/01.res.44.1.127. PMID: 363301.

Reske, S. N., & Kotzerke, J. (2001). FDG-PET for clinical use. European journal of nuclear medicine, 28(11), 1707-1723.

Reuter S, Grüner B, Buck AK, Blumstein N, Kern P, Reske SN. Long-term follow-up of metabolic activity in human alveolar echinococcosis using FDG PET. Nuklearmedizin. 2008;47(4):147-52. PMID: 18690373.

Rinne D, Baum RP, Hör G, Kaufmann R. Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. Cancer. 1998 May 1;82(9):1664-71. doi: 10.1002/(sici)1097-0142(19980501)82:9<1664::aid-cncr11>3.0.co;2-2. PMID: 9576286.

Rodriguez M, Rehn S, Ahlström H, Sundström C, Glimelius B. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. J Nucl Med. 1995 Oct;36(10):1790-6. PMID: 7562044.

Roelcke U, von Ammon K, Hausmann O, Kaech DL, Vanloffeld W, Landolt H, Rem JA, Gratzl O, Radü EW, Leenders KL. Operated low grade astrocytomas: a long term PET study on the effect of radiotherapy. J Neurol Neurosurg Psychiatry. 1999 May;66(5):644-7. doi: 10.1136/jnnp.66.5.644. PMID: 10209179; PMCID: PMC1736349.

Ropers FG, van Mosseveld RMP, Bleeker-Rovers CP, van Velden FHP, van Assema DME, Adam JA, Lam MGEH, Tolboom N, Dekkers OM, de Geus-Oei LF, Frings V. Evaluation of FDG PET/CT Use in Children with Suspected Infection or Inflammation. Diagnostics (Basel). 2020 Sep 18;10(9):715. doi: 10.3390/diagnostics10090715. PMID: 32961994; PMCID: PMC7554864.

Rose PG, Adler LP, Rodriguez M, Faulhaber PF, Abdul-Karim FW, Miraldi F. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. J Clin Oncol. 1999 Jan;17(1):41-5. doi: 10.1200/JCO.1999.17.1.41. PMID: 10458216.

Ruhlmann J, Schomburg A, Bender H, Oehr P, Robertz-Vaupel GM, Vaupel H, Wolter H, Kozak B, Biersack HJ. Fluorodeoxyglucose whole-body positron emission tomography in colorectal cancer patients studied in routine daily practice. Dis Colon Rectum. 1997 Oct;40(10):1195-204. doi: 10.1007/BF02055166. PMID: 9336115.

Ryvlin P(1), Philippon B, Cinotti L, Froment JC, Le Bars D, Mauguière F. Functional neuroimaging strategy in temporal lobe epilepsy: a comparative study of 18FDG PET and 99mTc-HMPAO-SPECT. Ann Neurol. 1992 Jun;31(6):650-6.

Ryvlin P(1), Bouvard S, Le Bars D, De Lamérie G, Grégoire MC, Kahane P, Froment JC, Mauguière F. Clinical utility of flumazenil-PET versus [18F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. Brain. 1998 Nov;121 (Pt 11):2067-81.

Safa AA, Tran LM, Rege S, Brown CV, Mandelkern MA, Wang MB, Sadeghi A, Juillard G. The role of positron emission tomography in occult primary head and neck cancers. Cancer J Sci Am. 1999 Jul-Aug;5(4):214-8. PMID: 10439166.

Sasaki M, Ichiya Y, Kuwabara Y, Akashi Y, Yoshida T, Fukumura T, Murayama S, Ishida T, Sugio K, Masuda K. The usefulness of FDG positron emission tomography for the detection of mediastinal lymph node metastases in patients with non-small cell lung cancer: a comparative study with X-ray computed tomography. Eur J Nucl Med. 1996 Jul;23(7):741-7. doi: 10.1007/BF00843701. PMID: 8662111.

Sasaki M, Ichiya Y, Kuwabara Y, Akashi Y, Yoshida T, Fukumura T, Masuda K. An evaluation of FDG PET in the detection and differentiation of thyroid tumours. Nucl Med Commun. 1997 Oct;18(10):957-63. doi: 10.1097/00006231-199710000-00011. PMID: 9392798.

Sasaki M, Kuwabara Y, Yoshida T, Nakagawa M, Fukumura T, Mihara F, Morioka T, Fukui M, Masuda K. A comparative study of thallium-201 SPET, carbon-11 methionine PET and fluorine-18 fluorodeoxyglucose PET for the differentiation of astrocytic tumours. Eur J Nucl Med. 1998 Sep;25(9):1261-9. doi: 10.1007/s002590050294. PMID: 9724375.

Sazon DA, Santiago SM, Soo Hoo GW, Khonsary A, Brown C, Mandelkern M, Blahd W, Williams AJ. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. Am J Respir Crit Care Med. 1996 Jan;153(1):417-21. doi: 10.1164/ajrccm.153.1.8542152. PMID: 8542152.

Scheidhauer K, Scharl A, Pietrzyk U, Wagner R, Göhring UJ, Schomäcker K, Schicha H. Qualitative 18F-FDG positron emission tomography in primary breast cancer: clinical relevance and practicability. Eur J Nucl Med. 1996 Jun;23(6):618-23. doi: 10.1007/BF00834522. PMID: 8662094.

Schiepers C, Penninckx F, De Vadder N, Merckx E, Mortelmans L, Bormans G, Marchal G, Filez L, Aerts R. Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. Eur J Surg Oncol. 1995 Oct;21(5):517-22. doi: 10.1016/s0748-7983(95)97046-0. PMID: 7589597.

Schreuder N, Klarenbeek H, Vendel BN, Jager PL, Kosterink JGW, van Puijenbroek EP. Discontinuation of metformin to prevent metformin-induced high colonic FDG uptake: is 48 h sufficient? Ann Nucl Med. 2020 Nov;34(11):833-839. doi: 10.1007/s12149-020-01509-z. Epub 2020 Aug 19. PMID: 32815120; PMCID: PMC7584522.

Schulte M, Brecht-Krauss D, Heymer B, Guhlmann A, Hartwig E, Sarkar MR, Diederichs CG, Schultheiss M, Kotzerke J, Reske SN. Fluorodeoxyglucose positron emission tomography of soft tissue tumours: is a non-invasive determination of biological activity possible? Eur J Nucl Med. 1999 Jun;26(6):599-605. doi: 10.1007/s002590050427. PMID: 10369945.

Schwarzbach M, Willeke F, Dimitrakopoulou-Strauss A, Strauss LG, Zhang YM, Mechtersheimer G, Hinz U, Lehnert T, Herfarth C. Functional imaging and detection of local recurrence in soft tissue sarcomas by positron emission tomography. Anticancer Res. 1999 Mar-Apr;19(2B):1343-9. PMID: 10365104.

Schwarzbach MH, Dimitrakopoulou-Strauss A, Willeke F, Hinz U, Strauss LG, Zhang YM, Mechtersheimer G, Attigah N, Lehnert T, Herfarth C. Clinical value of [18-F]] fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. Ann Surg. 2000 Mar;231(3):380-6. doi: 10.1097/00000658-200003000-00011. PMID: 10714631; PMCID: PMC1421009.

Siebelink HM, Blanksma PK, Crijns HJ, Bax JJ, van Boven AJ, Kingma T, Piers DA, Pruim J, Jager PL, Vaalburg W, van der Wall EE. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomography-guided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardium. J Am Coll Cardiol. 2001 Jan;37(1):81-8. doi: 10.1016/s0735-1097(00)01087-1. PMID: 11153777.

Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med. 1998 Dec;39(12):2190-2. PMID: 9867168.

Sotaniemi, EA, Karvonen, I. Glucose tolerance and insulin response to glucose load before and after enzyme inducing therapy in subjects with glucose intolerance and patients with NIDDM having hyperinsulinemia or relative insulin deficiency. Diabetes Res. 1989;11(3):131-9.

Smith IC, Ogston KN, Whitford P, Smith FW, Sharp P, Norton M, Miller ID, Ah-See AK, Heys SD, Jibril JA, Eremin O. Staging of the axilla in breast cancer: accurate in vivo assessment using positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. Ann Surg. 1998 Aug;228(2):220-7. doi: 10.1097/00000658-199808000-00012. PMID: 9712568; PMCID: PMC1191464.

Spacek M, Belohlavek O, Votrubova J, Sebesta P, Stadler P. Diagnostics of "non-acute" vascular prosthesis infection using 18F-FDG PET/CT: our experience with 96 prostheses. Eur J Nucl Med Mol Imaging. 2009 May;36(5):850-8. doi: 10.1007/s00259-008-1002-z. Epub 2008 Dec 24. PMID: 19107480.

Staib L, Schirrmeister H, Reske SN, Beger HG. Is (18)F-fluorodeoxyglucose positron emission tomography in recurrent colorectal cancer a contribution to surgical decision making? Am J Surg. 2000 Jul;180(1):1-5. doi: 10.1016/s0002-9610(00)00406-2. PMID: 11036130.

Steenkamp, DW, McDonnell, ME, Meibom, S. Metformin may be associated with false-negative cancer detection in the gastrointestinal tract on PET/CT. Endocr Pract. 2014;20(10):1079-83.

Stollfuss JC, Glatting G, Friess H, Kocher F, Berger HG, Reske SN. 2-(fluorine-18)-fluoro-2-deoxy-D-glucose PET in detection of pancreatic cancer: value of quantitative image interpretation. Radiology. 1995 May;195(2):339-44. doi: 10.1148/radiology.195.2.7724750. PMID: 7724750.

Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. Ann

Surg. 2001 Mar;233(3):293-9. doi: 10.1097/00000658-200103000-00001. PMID: 11224615; PMCID: PMC1421243.

Stumpe KD, Renner-Schneiter EC, Kuenzle AK, Grimm F, Kadry Z, Clavien PA, Deplazes P, von Schulthess GK, Muellhaupt B, Ammann RW, Renner EL. F-18-fluorodeoxyglucose (FDG) positron-emission tomography of Echinococcus multilocularis liver lesions: prospective evaluation of its value for diagnosis and follow-up during benzimidazole therapy. Infection. 2007 Feb;35(1):11-8. doi: 10.1007/s15010-007-6133-9. PMID: 17297583.

Sugawara Y, Eisbruch A, Kosuda S, Recker BE, Kison PV, Wahl RL. Evaluation of FDG PET in patients with cervical cancer. J Nucl Med. 1999 Jul;40(7):1125-31. PMID: 10405131.

Surasi, DS, Bhambhvani, P, Baldwin, JA, Almodovar, SE, O'Malley, JP. 18F-FDG PET and PET/CT patient preparation: a review of the literature. Journal of nuclear medicine technology. 2014;42(1):5-13.

Sutinen E, Jyrkkiö S, Varpula M, Lindholm P, Grönroos T, Lehikoinen P, Teräs M, Minn H. Nodal staging of lymphoma with whole-body PET: comparison of. J Nucl Med. 2000 Dec;41(12):1980-8. PMID: 11138682.

Swartz BE(1), Tomiyasu U, Delgado-Escueta AV, Mandelkern M, Khonsari A. Neuroimaging in temporal lobe epilepsy: test sensitivity and relationships to pathology and postoperative outcome. Epilepsia. 1992 Jul-Aug;33(4):624-34. doi: 10.1111/j.1528-1157.1992.tb02338.x.

Takeuchi O, Saito N, Koda K, Sarashina H, Nakajima N. Clinical assessment of positron emission tomography for the diagnosis of local recurrence in colorectal cancer. Br J Surg. 1999 Jul;86(7):932-7. doi: 10.1046/j.1365-2168.1999.01178.x. PMID: 10417568.

Tamaki N(1), Yonekura Y, Yamashita K, Saji H, Magata Y, Senda M, Konishi Y, Hirata K, Ban T, Konishi J. Positron emission tomography using fluorine-18 deoxyglucose in evaluation of coronary artery bypass grafting. Am J Cardiol. 1989 Oct 15;64(14):860-5. doi: 10.1016/0002-9149(89)90832-1.

Tamaki N, Ohtani H, Yamashita K, Magata Y, Yonekura Y, Nohara R, Kambara H, Kawai C, Hirata K, Ban T, et al. Metabolic activity in the areas of new fill-in after thallium-201 reinjection: comparison with positron emission tomography using fluorine-18-deoxyglucose. J Nucl Med. 1991 Apr;32(4):673-8. PMID: 2013806.

Tamaki N, Kawamoto M, Tadamura E, Magata Y, Yonekura Y, Nohara R, Sasayama S, Nishimura K, Ban T, Konishi J. Prediction of reversible ischemia after revascularization. Perfusion and metabolic studies with positron emission tomography. Circulation. 1995 Mar 15;91(6):1697-705. doi: 10.1161/01.cir.91.6.1697. PMID: 7882476.

Mitsuaki Tatsumi, Kenji Yutani, Yoshiyuki Watanabe, Shinichiro Miyoshi, Noriyuki Tomiyama, Takeshi Johkoh, Hideo Kusuoka, Hironobu Nakamura, Tsunehiko Nishimura. Feasibility of Fluorodeoxyglucose Dual-Head Gamma Camera Coincidence Imaging in the Evaluation of Lung Cancer: Comparison with FDG PET. Journal of Nuclear Medicine Apr 1999, 40 (4) 566-573.

Tegler G, Sörensen J, Björck M, Savitcheva I, Wanhainen A. Detection of aortic graft infection by 18-fluorodeoxyglucose positron emission tomography combined with computed tomography. J Vasc Surg. 2007 Apr;45(4):828-30. doi: 10.1016/j.jvs.2006.12.018. PMID: 17398393.

Termaat MF, Raijmakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg Am. 2005 Nov;87(11):2464-71. doi: 10.2106/JBJS.D.02691. PMID: 16264122.

Tillisch J, Brunken R, Marshall R, Schwaiger M, Mandelkern M, Phelps M, Schelbert H. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med. 1986 Apr 3;314(14):884-8. doi: 10.1056/NEJM198604033141405.

Topal B, Flamen P, Aerts R, D'Hoore A, Filez L, Van Cutsem E, Mortelmans L, Penninckx F. Clinical value of whole-body emission tomography in potentially curable colorectal liver metastases. Eur J Surg Oncol. 2001 Mar;27(2):175-9. doi: 10.1053/ejso.2000.1075. PMID: 11345944.

Tosur, M, Viau-Colindres, J, Astudillo, M, Redondo, MJ, Lyons, SK. Medication-induced hyperglycemia: pediatric perspective. BMJ Open Diabetes Res Care. 2020;8(1).

Treasure, T, Toseland, PA. Hyperglycaemia due to phenytoin toxicity. Arch Dis Child. 1971; 46(248): 563-4.

Treglia G, Taralli S, Giordano A. Emerging role of whole-body 18F-fluorodeoxyglucose positron emission tomography as a marker of disease activity in patients with sarcoidosis: a systematic review. Sarcoidosis Vasc Diffuse Lung Dis. 2011 Oct;28(2):87-94. PMID: 22117499.

Treglia G, Maggi F, Bonomo L, Giordano A. Usefulness of fluorine-18 fluorodeoxyglucose PET/computed tomography in diagnosis of aortitis and treatment response evaluation in a patient with aortic prosthesis. J Cardiovasc Med (Hagerstown). 2011 Nov;12(11):814-6. doi: 10.2459/JCM.0b013e32834ba0fd. PMID: 21934523.

Treglia G. Diagnostic Performance of ^{18}F-FDG PET/CT in Infectious and Inflammatory Diseases according to Published Meta-Analyses. Contrast Media Mol Imaging. 2019 Jul 25;2019:3018349. doi: 10.1155/2019/3018349. PMID: 31427907; PMCID: PMC6683817.

Umesaki N, Tanaka T, Miyama M, Kawabe J, Okamura T, Koyama K, Ochi H, Ogita S. The role of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET) in the diagnosis of recurrence and lymph node metastasis of cervical cancer. Oncol Rep. 2000 Nov-Dec;7(6):1261-4. doi: 10.3892/or.7.6.1261. PMID: 11032926.

Utech CI, Young CS, Winter PF. Prospective evaluation of fluorine-18 fluorodeoxyclucose positron emission tomography in breast cancer for staging of the axilla related to surgery and immunocytochemistry. Eur J Nucl Med. 1996 Dec;23(12):1588-93. doi: 10.1007/BF01249621. PMID: 8929312.

Vaidyanathan S, Patel CN, Scarsbrook AF, Chowdhury FU. FDG PET/CT in infection and inflammation--current and emerging clinical applications. Clin Radiol. 2015 Jul;70(7):787-800. doi: 10.1016/j.crad.2015.03.010. Epub 2015 Apr 25. PMID: 25917543.

Valk PE(1), Laxer KD, Barbaro NM, Knezevic S, Dillon WP, Budinger TF. High-resolution (2.6-mm) PET in partial complex epilepsy associated with mesial temporal sclerosis. Radiology. 1993 Jan;186(1):55-8. doi: 10.1148/radiology.186.1.8416586.

Van Acker F, Nuyts J, Maes A, Vanquickenborne B, Stuyck J, Bellemans J, Vleugels S, Bormans G, Mortelmans L. FDG PET, 99mtc-HMPAO white blood cell SPET and bone scintigraphy in the evaluation of painful total knee arthroplasties. Eur J Nucl Med. 2001 Oct;28(10):1496-504. doi: 10.1007/s002590100603. PMID: 11685492.

van Ginkel RJ, Hoekstra HJ, Pruim J, Nieweg OE, Molenaar WM, Paans AM, Willemsen AT, Vaalburg W, Koops HS. FDG PET to evaluate response to hyperthermic isolated limb perfusion for locally advanced soft-tissue sarcoma. J Nucl Med. 1996 Jun;37(6):984-90. PMID: 8683328.

Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verbeken EK. Potential use of FDG PET scan after induction chemotherapy in surgically staged IIIa-N2 non-small-cell lung cancer: a prospective pilot study. The Leuven Lung Cancer Group. Ann Oncol. 1998 Nov;9(11):1193-8. doi: 10.1023/a:1008437915860. PMID: 9862049.

Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Bogaert J, Maes A, Deneffe GJ, Nackaerts KL, Verschakelen JA, Lerut TE, Mortelmans LA, Demedts MG. Lymph node staging in non-small-cell lung cancer with FDG PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol. 1998 Jun;16(6):2142-9. doi: 10.1200/JCO.1998.16.6.2142. PMID: 9626214.

Vitola JV, Delbeke D, Sandler MP, Campbell MG, Powers TA, Wright JK, Chapman WC, Pinson CW. Positron emission tomography to stage suspected metastatic colorectal carcinoma to the liver. Am J Surg. 1996 Jan;171(1):21-6. doi: 10.1016/S0002-9610(99)80067-1. PMID: 8554144.

Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PF, van Dijk AP, Cuijpers ML, Adang EM, Wanten GJ, Kullberg BJ, Oyen WJ. 18F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. J Nucl Med. 2010 Aug;51(8):1234-40. doi: 10.2967/jnumed.109.072371. Epub 2010 Jul 21. PMID: 20660384.

Wagner JD, Schauwecker D, Davidson D, Coleman JJ 3rd, Saxman S, Hutchins G, Love C, Hayes JT. Prospective study of fluorodeoxyglucose-positron emission tomography imaging of lymph node basins in melanoma patients undergoing sentinel node biopsy. J Clin Oncol. 1999 May;17(5):1508-15. doi: 10.1200/JCO.1999.17.5.1508. PMID: 10334538.

Wang W, Macapinlac H, Larson SM, Yeh SD, Akhurst T, Finn RD, Rosai J, Robbins RJ. [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (131)I whole body scans and elevated serum thyroglobulin levels. J Clin Endocrinol Metab. 1999 Jul;84(7):2291-302. doi: 10.1210/jcem.84.7.5827. PMID: 10404792.

Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, Yeung H, Macapinlac H, Rosai J, Robbins RJ. Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab. 2000 Mar;85(3):1107-13. doi: 10.1210/jcem.85.3.6458. PMID: 10720047.

Warburg, O. (1956). On the origin of cancer cells. Science, 123(3191), 309-314.

Weber, G. (1977). Enzymology of Cancer Cells: (Second of Two Parts). New England Journal of Medicine, 296(10), 541-551.

Weber W, Bartenstein P, Gross MW, Kinzel D, Daschner H, Feldmann HJ, Reidel G, Ziegler SI, Lumenta C, Molls M, Schwaiger M. Fluorine-18-FDG PET and iodine-123-IMT SPECT in the evaluation of brain tumors. J Nucl Med. 1997 May;38(5):802-8. PMID: 9170450.

Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschläger G, Busch R, Siewert JR, Schwaiger M, Fink U. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol. 2001 Jun 15;19(12):3058-65. doi: 10.1200/JCO.2001.19.12.3058. PMID: 11408502.

Willmann O, Wennberg R, May T, Woermann FG, Pohlmann-Eden B. The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy A meta-analysis. Seizure. 2007 Sep;16(6):509-20. doi: 10.1016/j.seizure.2007.04.001. Epub 2007 May 25. PMID: 17532231.

Wong WL, Chevretton EB, McGurk M, Hussain K, Davis J, Beaney R, Baddeley H, Tierney P, Maisey M. A prospective study of PET-FDG imaging for the assessment of head and neck squamous cell carcinoma. Clin Otolaryngol Allied Sci. 1997 Jun;22(3):209-14. doi: 10.1046/j.1365-2273.1997.00852.x. PMID: 9222623.

Wong, HY, et al. Sodium valproate inhibits glucose transport and exacerbates Glut1-deficiency in vitro. J Cell Biochem. 2005;96(4):775-85.

Worsley DF, Celler A, Adam MJ, Kwong JS, Müller NL, Coupland DB, Champion P, Finley RJ, Evans KG, Lyster DM. Pulmonary nodules: differential diagnosis using 18F-fluorodeoxyglucose single-photon emission computed tomography. AJR Am J Roentgenol. 1997 Mar;168(3):771-4. doi: 10.2214/ajr.168.3.9057532. PMID: 9057532.

Wuest M, Hamann I, Bouvet V, Glubrecht D, Marshall A, Trayner B, Soueidan OM, Krys D, Wagner M, Cheeseman C, West F, Wuest F. Molecular Imaging of GLUT1 and GLUT5 in Breast Cancer: A Multitracer Positron Emission Tomography Imaging Study in Mice. Mol Pharmacol. 2018 Feb;93(2):79-89. doi: 10.1124/mol.117.110007. Epub 2017 Nov 15. PMID: 29142019.

Yun M, Lim JS, Noh SH, Hyung WJ, Cheong JH, Bong JK, Cho A, Lee JD. Lymph node staging of gastric cancer using (18)F-FDG PET: a comparison study with CT. J Nucl Med. 2005 Oct;46(10):1582-8. PMID: 16204706.

Zaccara, G, Perucca, E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord. 2014;16(4):409-31.

Zerizer I, Tan K, Khan S, Barwick T, Marzola MC, Rubello D, Al-Nahhas A. Role of FDG PET and PET/CT in the diagnosis and management of vasculitis. Eur J Radiol. 2010 Mar;73(3):504-9. doi: 10.1016/j.ejrad.2010.01.021. Epub 2010 Feb 20. PMID: 20172676.

Zhuang H, Yang H, Alavi A. Critical role of 18F-labeled fluorodeoxyglucose PET in the management of patients with arthroplasty. Radiol Clin North Am. 2007 Jul;45(4):711-8, vii. doi: 10.1016/j.rcl.2007.05.010. PMID: 17706535.

Ziai, P. Role of Optimal Quantification of FDG PET Imaging in the Clinical Practice of Radiology. Radiographics. 2016;36(2):481-96.