An Overview about Positron Emission Tomography (PET)- Computed Tomography (CT) in Evaluating Breast Cancer

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Abstract

The 18 fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan is a valuable, well established tool for diagnostic staging in numerous cancer sites**,** as well as for locally advanced BC to detect distant metastasis. Positron-emission tomography (PET) is a non-invasive imaging method that uses positron-emitting isotopes. It has been used increasingly frequently in clinics, especially in oncology. The most commonly used radiopharmaceutical, FDG tagged with fluorine-18 (18F-FDG) is a glucose analog whose FDG involvement in tissues is in proportion to the use of glucose; it is taken up into cells like glucose but cannot be metabolized. According to the National Comprehensive Cancer Network (NCCN) guidelines, PET/CT is not routine for early diagnosis of breast cancer (BC). Although PET/CT is not routinely recommended for establishing the diagnosis of BC, it may disclose important information about some histo-pathological features of the primary tumor. The uptake of FDG was negatively correlated with hormonal receptor status in patients with large or locally advanced invasive ductal carcinoma. Moreover, the functional nature of PET imaging may provide the possibility of texture analysis in assessing tumor heterogeneity as a new tool for assessment of tumor aggressiveness. The diagnostic accuracy of PET/CT for distant metastasis has been evaluated in multiple studies. The results of a meta-analysis suggested that PET/CT is a valuable alternative when conventional MRI shows indeterminate or benign lesions or is not applicable.

Keywords: Positron Emission Tomography (PET), Computed Tomography (CT), Breast Cancer

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^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan is a valuable, well established tool for diagnostic staging in numerous cancer sites**,** as well as for locally advanced BC to detect distant metastasis. Positron-emission tomography (PET) is a non-invasive imaging method that uses positron-emitting isotopes. It has been used increasingly frequently in clinics, especially in oncology. Even though PET imaging is more sensitive for detection of loco-regional spread and metastatic disease in breast cancer compared to computed tomography (CT) scan alone, its high cost precludes the routine use of PET scan in clinical practice **(1)**
The most commonly used radiopharmaceutical, FDG tagged with fluorine-18 (18F-FDG) is a glucose analog whose FDG involvement in tissues is in proportion to the use of glucose; it is taken up into cells like glucose but cannot be metabolized. The ^{18}F-FDG PET/CT is a diagnostic three-dimensional non-invasive device, routinely employed in neurology, cardiology and oncology which contributes to patient care giving functional informations about glucose metabolism. In particular, staging, restaging, follow-up and response to treatment

of tumors are the most common applications in oncologic field. Many neoplasms show increased glucose metabolism and consequent ^{18}F-FDG uptake ***(1).***

Many studies have pointed out the role of 18F-FDG PET/CT (or 18F-FDG PET) in patients with clinical stage III or II breast cancer. 18F-FDG PET/CT might advantageously replace other staging procedures such as bone scanning and possibly contrast-enhanced CT of the thorax or abdomen–pelvis. Tumor cells are known to have enhanced glycolytic activity and increased uptake of FDG which allow for the visualization of pathologic foci by [18F] FDG-PET/CT. The uptake of FDG might also be influenced by the phenotype, mitotic index and grade of the primary tumor ***(2).***

The lower sensitivity of 18F-FDG imaging than of the sentinel node technique in assessing axillary lymph node involvement is well known and the risk of distant metastasis in early-stage cases is low. These factors, combined with the good but finite specificity of 18F-FDG PET/CT, result in a relative abundance of false-positive findings and a paucity of true positive findings; such findings lead to unwarranted patient anxiety and delay of care with the routine use of 18F-FDG PET/CT for breast cancer detected early***(3).***

PET/CT Scanning Technique:

1- Common clinical indications:

Indications for FDG PET/CT include but are not limited to, the following ***(4).***

Differentiation of benign from malignant lesions.

- Searching for an unknown primary tumor when metastatic disease is discovered as the first manifestation of cancer or when the patient presents with a para-neoplastic syndrome.
- Staging patients with known malignancies.
- Monitoring the effect of therapy on known malignancies.
- Determining whether residual abnormalities detected on physical examination or on other imaging studies following treatment represent tumor or post-treatment fibrosis or necrosis.
- Detecting tumor recurrence, especially in the presence of elevated tumor markers & selection of the region of tumor most likely to yield diagnostic information for biopsy.
- Guiding radiation therapy planning.

Other documents include further indications for FDG PET/ CT ***(4).*** The clinical utility of this valuable technology continues to expand in oncology and therefore an exhaustive list of appropriate indications would not be possible or remain final for long. FDG PET/CT also has an increasingly relevant role in inflammation and infection imaging, cardiology and neurology. In these areas the FDG PET/CT procedure may require specific elements not addressed in these guidelines ***(4).***

2- Procedure/specification of the examination:

The medical record should be reviewed with a special focus on the diagnosis (type of cancer and known sites), oncological history and relevant comorbidity (especially infection/ inflammation and diabetes mellitus). A short interview with the patient and/or family can help clarify some of these issues. Relevant laboratory tests should be considered. The results of prior imaging studies should be available to review, including planar radiography, CT, MRI, bone scanning and FDG PET/ CT. Relevant prior studies should be directly compared with current imaging findings when possible.

The following list shows all aspects that should be considered in the review ***(5).***

- Tumor type (if known) and known tumor sites.
- Oncological history and relevant comorbidity (especially infection/inflammation and diabetes mellitus).
- Neurological or psychiatric clinical presentations, including suspected neurological para-neoplastic syndromes.
- Height and body weight (these must be determined precisely in the case of SUV measurements). Weight must be measured directly prior to each FDG PET/CT examination (also in the case of longitudinal studies) because body weight often changes during the course of disease.

- Serum glucose, date, time.
- Full overview of current and recently used medication, especially (but not limited to) antidiabetic medication, corticosteroids, growth factors and sedatives. In the case of therapy evaluation: type and date of last therapeutic intervention.
- Results of other imaging tests (especially CT, MRI and previous PET/CT), including dates of acquisition, full reports and, if possible, DICOM data of the referred studies for comparison.
- Other examinations performed earlier on the same day as the PET/CT is scheduled. If intravenous contrast agent has been used or specific preparation followed in the 24 – 48 h prior to the FDG PET/CT examination, the situation should be evaluated and noted; if possible such circumstances should be avoided in patient scheduling.
- Allergy to contrast agents. If an FDG PET/CT examination with intravenous CT contrast agent is strictly necessary the referring physician must indicate the premedication protocol to prepare the patient.
- Renal function. Creatinine and/or glomerular filtration should be evaluated, according to national guidelines, if intravenous contrast agent is to be used. (Normal serum creatinine < 1.5mg/dL). If renal function is suboptimal and an FDG PET/CT examination with intra- venous CT contrast agent is necessary, then the referring physician can initiate the protocol for prevention of nephrotoxicity (hydrate the patient and repeat the blood test, and if necessary prescribe medication for prevention of nephrotoxicity).

3- Precautions:

The main purpose of patient preparation to reduce tracer uptake in normal tissue (kidneys, bladder, skeletal muscle, myocardium, brown fat) while maintaining and optimising tracer uptake in the target structures (tumor tissue) and keeping patient radiation exposure levels as low as reasonably possible ***(5).***

- ***Pregnancy (suspected or confirmed):***

For any diagnostic procedure in a female patient known or suspected to be pregnant, a clinical decision is necessary in which the benefits are weighed against the possible harm. The International Commission on Radiological Protection (ICRP) reports that for an adult patient the administration of 259 MBq (7 mCi) of FDG results in an absorbed radiation dose of 4.7 mGy to the nongravid uterus (i.e. 1.8×10^{-2} mGy/MBq) ***(6).*** Direct measurements of FDG uptake in a case study suggested somewhat higher doses than are currently provided in standard models ***(7).***

A pregnancy test may help with the decision, provided the 10 day postovulation blackout is understood. In the event of doubt and in the absence of an emergency, the 10 day rule should be adopted. In Europe, national guidelines may apply ***(5).***

- ***Breastfeeding:***

The ICRP does not recommend interruption of breastfeeding after FDG administration since little FDG is excreted in the milk ***(6).*** However, as the lactating breast accumulates FDG, it is suggested that contact between mother and child be limited for 12 h after injection of FDG to reduce the radiation dose that the infant receives from external exposure to radiation emitted by the mother. It is recommended that the infant be breastfed just before injection, to maximise the time be- tween the injection and the next feed. Breast milk may be expressed and fed to the infant via a bottle for 12 h to help minimise the interruption in close, prolonged contact between the infant and the mother ***(5).***

- ***Diabetes:***

The FDG PET/CT study should preferably be performed in the late morning. Ideally, an attempt should be made to achieve normal glycaemic values prior to the FDG PET/CT study, in consultation with the patient and his/her attending medical doctor ***(5).***

There are three options for scheduling the FDG PET/CT study ***(5).***

1. It can be scheduled for late morning or midday. The patient should eat a normal breakfast by early morning (around 7.00 a.m.) and inject the normal amount of insulin. Thereafter the patient should not

consume any more food or fluids, apart from the prescribed amount of water. FDG should be injected no sooner than 4 h after subcutaneous injection of rapid acting insulin or 6 h after subcutaneous injection of short acting insulin. FDG administration is not recommended on the same day after injection of intermediate-acting and/or long-acting insulin

2. It can be scheduled for early morning. The presence of intermediate-acting insulin administered the evening before should not interfere with the PET/CT study and glycaemia will probably still be under control. If long-acting insulin has been used the evening before, there could be a slight interference with the PET/CT study. Thus, if this is the preferred schedule, intermediate-acting (instead of long-acting) insulin is recommended. The patient should eat a normal breakfast after the PET/CT study and inject the normal amount of insulin.
3. In patients on continuous insulin infusion, if possible the FDG PET/CT study should be scheduled for early in the morning. The insulin pump should be switched off for at least 4 h prior to FDG administration. The patient can have breakfast after the FDG PET/CT study and switch on continuous insulin infusion.

- ***Kidney failure:***

FDG imaging can be performed in patients with kidney failure, although the image quality may be suboptimal and prone to interpretation pitfalls ***(8).***

4- Instructions to patients:

Non-diabetic patients should not consume any food, simple carbohydrates or liquids other than plain (unflavoured) water for at least 4 h prior to the start of the FDG PET/CT study (i.e. with respect to the time of injection of FDG). In practice, this means that patients scheduled to undergo the FDG PET/CT study in the morning should not eat after midnight and preferably should have only a light meal (no alcohol and only a small amount of carbohydrates) during the evening prior to the FDG PET/CT study. Those scheduled for an afternoon FDG PET/CT study may have a light breakfast at least 4 h prior to the time of their PET/CT examination appointment. Medication can be taken as prescribed ***(5).***

- Adequate prehydration is important to ensure a sufficiently low concentration of FDG in the urine (fewer artefacts) and for radiation safety reasons. For example, consumption of 1 L of water during the 2 h prior to injection is suggested. Where necessary, account for the volume of water in oral contrast agent if it is to be given for a diagnostic CT scan ***(5).***
- Coffee or caffeinated beverages are not recommended because even if "sugarless" they may contain traces of simple carbohydrates and have the potential to induce excitant effects; this may also be the case for "sugar-free" beverages ***(5).***
- Parenteral nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the time of FDG injection. In addition, the infusion used to administer intravenous prehydration must not contain glucose ***(5).***
- During the injection of FDG and the subsequent uptake phase, the patient should remain seated or recumbent and silent (this is particularly true for head and neck cancer patients) to minimize FDG uptake in muscles. The patient should be kept warm starting 30 – 60 min before the injection of FDG and continuing throughout the subsequent uptake period and examination to minimise FDG accumulation in brown fat (especially relevant in winter or if the room is air-conditioned) ***(5).***
- Patients must avoid strenuous exercise for at least 6 h before the FDG PET/CT study and preferably for 24 h ***(5).***
- Patients should void immediately prior to the PET/CT examination to reduce bladder activity ***(5).***
- The patient should be able to lie still in the PET/CT system for the duration of the examination (20-45 min). A specific inquiry about claustrophobia at the time the patient is scheduled for the study may decrease the number of nondiagnostic studies and cancellations, and allow premedication planning ***(5).***

- If possible, the patient should put his/her arms above the head; proper support devices (e.g. foam pallets) provided by the manufacturers should be employed whenever feasible ***(5).***
- When a diagnostic contrast-enhanced CT examination with intravenous contrast agent is to be performed, specific indications must be followed ***(5).***

5- Patient preparation:

1. ***Prior to appointment (9).:***

a. Instruct patients to avoid strenuous activity 24 hours prior to FDG injection.

b. Recommend low carbohydrate meals for 24 hours prior to FDG injection and no alcohol the evening prior to examination.

c. Provide fasting instructions (a minimum of 4 hours) with no parenteral nutrition or oral/intravenous fluids containing sugar or dextrose for the same period.

d. Encourage oral hydration with a goal of 1 L (34 oz) in 2 hours prior to appointment.

2. ***Prior to FDG injection (10):***

a. Obtain a focused history that includes:

(Reason for examination, Treatment, Medications, Recent trauma/exercise, Presence of concurrent infection, Presence of diabetes, Specific details and dates should be obtained whenever possible).

b. Consider pre-medications:

i. Anxiolytics can be administered in patients with claustrophobia or anxiety. Oral alprazolam (0.5 mg given 10 to 60 minutes prior to FDG injection) is an option, though patients must be counseled against driving given the medication's sedative and motor-impairing effects.

ii. Oral beta-blockers, such as propranolol 20 mg, can be administered 60 minutes prior to injection to patients with a history of prominent brown fat uptake, but the utility of this intervention is unclear. iii. Intravenous narcotic pain medications, such as fentanyl, can be administered shortly before FDG injection as an alternative means of limiting brown fat uptake of FDG.

c. Serum glucose analysis performed immediately prior to FDG administration (200 mg/dL, then the patient should usually be rescheduled. Prior to rescheduling, a repeat measurement can be performed in about 20 to 30 minutes. If the serum glucose level decreases to 200 mg/dL, then FDG can be administered. If the serum glucose level is decreasing but still >200 mg/dL, then another repeat measurement can be performed in about 20 to 30 minutes or FDG can be administered at the discretion of the interpreting physician. ii. If the serum glucose is >300 mg/dL, then the patient should be rescheduled.

d. Diabetic patient guidelines:

i. PET scan should be scheduled early in the morning (if possible) as this is the time that most diabetic patients have the lowest glucose level. However, some diabetic patients may have lower glucose levels in the afternoon, and for these patients an afternoon appointment is preferable.

ii. Diabetic patients should take their usual insulin or oral medications the day before; after midnight patients should fast (except for water) and take nondiabetic medications.

iii. On the morning of the PET scan, hold all insulin and oral medications if FDG injection is scheduled in the early morning.

iv. If PET scan is scheduled after 10 AM, patient should eat a low-carbohydrate breakfast at least 4 hours before the injection of 1/2 of usual regular (short-acting) insulin or regular dosage of oral medications at least 4 hours before the appointment. Do not use long-acting or mixed (70/30) insulin after midnight.

v. If the patient is on an insulin pump alone, the setting should be maintained until the start of the PET scan. After the PET scan, settings can be adjusted as prescribed.

vi. After completion of the PET scan, patients should be encouraged to eat a meal immediately. It may be advisable for patients to take 1/2 of the usual morning dosage of insulin or regular dosage of oral medications with the post-PET meal to avoid the risk of hypoglycemia.

vii. Technologist should inform the interpreting physician if the patient has hyperglycemia >200 mg/dL or hypoglycemia**.**

3. ***Following injection (uptake period) (11):***

a. Have patient remain seated or recumbent in a quiet room during uptake period (decreases muscle uptake). Additionally, in adult patients with head and neck cancer, oral alprazolam 0.5 mg given immediately after FDG injection reportedly can reduce skeletal muscle uptake that can impede lesion detection and confound scan interpretation.

b. Consider use of heated blankets and a warm waiting room during uptake period (decreases brown fat activity).

c. Patients should void immediately prior to being positioned on the PET/CT table for imaging. In special circumstances, intravenous hydration, diuretic administration, and/or bladder catheterization can be used to reduce radiation burden and artifacts related to accumulated physiologic radiopharmaceutical activity in the ureters and urinary bladder.

d. Consider use of sedation as necessary in younger children or developmentally delayed patients.

Patient positioning:

The arms and hands can be examined positioned above the head by extending the CT scan cranially. Fixation of the arms and patient cooperation are required to avoid motion artifacts. Positioning aids such as foam molds or vacuum-lock bags are used in addition to the standard arm rest to ensure less patient motion and better image coregistration ***(12).***

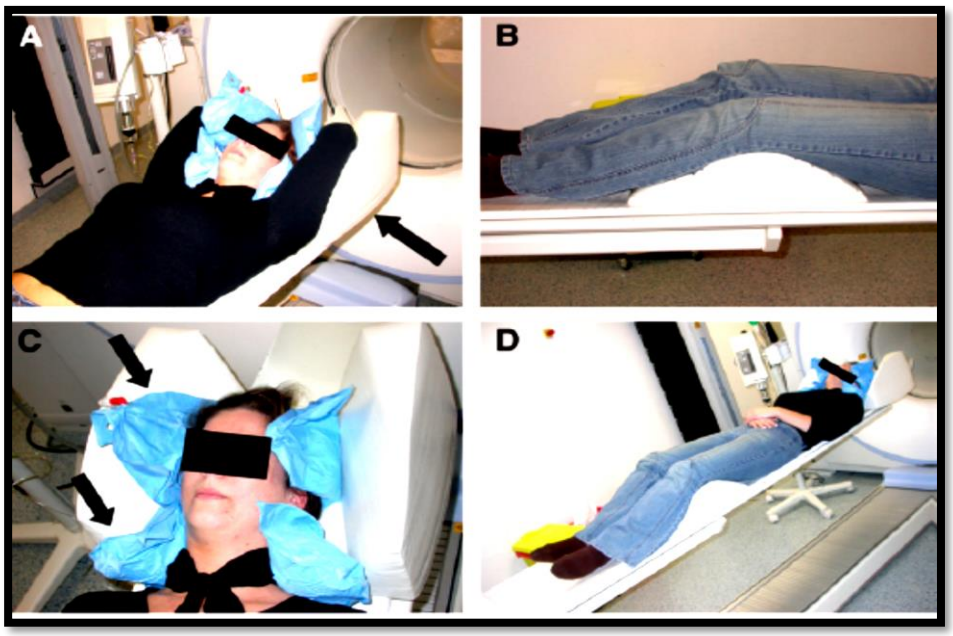

Figure (1): Patient supported with different positioning aids on PET/CT table. **(A)** For whole-body PET/CT, arms are raised above head and supported by foam cushion to avoid truncation artifacts during scanning of thorax and abdomen (arrow). Furthermore, head is placed within foam cushion and may be additionally supported with vacuum-lock bag to prevent head motion (blue vacuum lock bag). **(B)** Legs are supported by another foam mold to inflect patient's knees and to ensure comfortable positioning during scanning. **(C)** For head and neck scanning, vacuum-lock bag is deflated to fix head and neck within foam cushion (arrows). Thus, possible moving artifacts can be avoided. **(D)** Additionally, arms are placed on or beside patient's trunk to avoid truncation artifacts in head and neck area ***(13).***

The examination of the lower limbs requires an additional examination after repositioning of the patient. For scanning of the patient from head to toe, use a divided protocol, starting with a whole-body scan including the arms and the head in the supine, head-first position. After that, the patient is repositioned in the supine, feet-first position. Both scans are performed with intravenous contrast material and a small overlap in the groin ***(13).***

Radiopharmaceutical:

For adults, the administered activity of FDG should be 185 to 740 MBq (5 to 20 mCi). The specific administered activity typically depends upon the local imaging protocol. The local protocol may require a standard activity or the activity may vary as a function of various parameters such as patient size, scanning mode (2-D versus 3-D), percentage of scan bed (slice) overlap, or clinical indication. For variable dosages, other means of determining the administered activity can be based upon a combination of factors, for example, as outlined in European Association of Nuclear Medicine guidelines**,** which use the patient's weight, duration of bed positions in minutes and percent bed position overlap in certain PET/CT systems (some systems do not use bed positions) ***(14)***.

The variable dose calculation's goal is to optimize a personalized dosage with the ALARA principle. Without a dedicated dosage injector with the ability to precisely elute a calculated dosage, a fixed dose with a range may be more practical for adults. To date there are no clear data providing evidence of superiority of parameter-dependent administered activity protocols ***(15).***

Protocol for CT Imaging:

The CT performed as part of a PET/CT examination provides attenuation-correction information and diagnostic information that may be relevant to both PET interpretation and overall patient care. A variety of protocols exist for performing the CT scan in the context of PET/CT scanning. In some cases, low-dose CT scans are designed primarily to provide attenuation correction and anatomic localization. In other cases, the CT portion of the examination is performed with intravenous and/or oral contrast media and optimized CT parameters designed to lower image noise. If a diagnostic CT scan is requested as part of PET/CT, the CT protocol appropriate for the body region(s) requested should be used. Regardless of the CT technique used, a careful review of CT images is necessary for comprehensive interpretation of the PET/CT examination ***(16).***

For a diagnostic CT scan of the abdomen and/or pelvis, intraluminal gastrointestinal contrast media may be administered to improve visualization of the gastrointestinal tract unless medically contraindicated or unnecessary for the clinical indication. This may be positive-contrast media such as diluted barium sulfate or diatrizoic acid or negative-contrast media such as water. Highly concentrated barium collections may result in an attenuation correction artifact that leads to a significant overestimation of the regional FDG concentration and should be avoided; dilute barium sulfate and oral iodinated contrast media cause less overestimation and are less likely to have an adverse impact on PET image quality. When indicated, the CT scan can be performed with intravenous contrast media using appropriate injection techniques. High intravascular concentrations of intravenous contrast media may cause a localized attenuation correction artifact on the PET image but the impact is usually limited ***(17).***

Breathing patterns during CT acquisition should be optimized so that the positions of the diaphragm on the PET emission and the CT transmission images match as closely as possible. If a single-breath-hold technique is used for CT imaging, optimal alignment of the PET and CT images is obtained with respiration suspended in the quiet end-expiratory (end–tidal volume) phase. If respiration is not suspended during CT imaging, the patient should be coached on shallow/quiet breathing. To optimize breathing pattern, gating of the PET and/or CT can be performed in more modern PET/CT scanners ***(9).***

Protocol for PET Emission Imaging:

Emission images are generally obtained 60 minutes following radiopharmaceutical administration. However, this time period may be shorter (no less than 45 minutes) or longer for certain trials or unique clinical situations. Note that consistency of standardized uptake value (SUV) measurements depends on strict observance of the uptake time; therefore, when using a 60-minute interval, an acceptable range of injection to scan time is 55 to 75 minutes ***(18).***

Semi-quantitative estimation of FDG accumulation using the SUV is based on local radioactivity concentration measured on images corrected for attenuation and normalized for the injected activity and body weight, lean body mass, or body surface area. The accuracy of SUV measurements depends on the accuracy of the calibration of the PET device, among other factors. As the SUV is becoming a standard for determining tumor response over time, measures should be taken to minimize the factors that may affect it. These include

using the same scanner configuration on subsequent examinations (including reconstruction algorithms, attenuation maps, etc), maintaining the same interval between injection and scanning, avoiding infiltration of injected activity, and using the same measurement techniques, (VOI volumes, max/peak/mean measurements). Some factors that affect SUV currently remain beyond control, such as variations in serum glucose and patient motion/breathing–related attenuation-correction artifacts ***(18).***

Recording changes in the intensity of FDG uptake with semiquantitative measurements, expressed in absolute values and percent changes, may be appropriate in some clinical scenarios. However, the technical protocol and analysis of images need to be consistent in the 2 data sets ***(9).***

Diagnosis:

According to the National Comprehensive Cancer Network (NCCN) guidelines, PET/CT is not routine for early diagnosis of BC**.** In addition to the high cost, use of PET/CT for establishing the diagnosis of early-stage BC is hampered by its low spatial resolution, which reduces its sensitivity by missing small lesions (< 5 mm). However, PET/CT has a high specificity in diagnosing BC ***(4).***

Although PET/CT is not routinely recommended for establishing the diagnosis of BC, it may disclose important information about some histo-pathological features of the primary tumor**.** Several reports have shown that the extent of FDG uptake by tumor cells is related to tumor grade and subtypes ***(19).***

The uptake of FDG was negatively correlated with hormonal receptor status in patients with large or locally advanced invasive ductal carcinoma**.** With regard to tumor subtypes, triple-negative and HER2-positive BC have higher maximum standardized uptake value (SUVmax) compared to luminal A tumors**.** Moreover, the functional nature of PET imaging may provide the possibility of texture analysis in assessing tumor heterogeneity as a new tool for assessment of tumor aggressiveness ***(20).***

Staging:

Primary staging:

Preoperative staging is critical for a proper treatment plan for any BC patient. Findings from numerous reports indicate that PET/CT may be useful only in the primary staging of patients who are at a considerable risk of metastasis**.** However, prospective studies that have evaluated PET/CT for staging of primary invasive breast cancer are rather scarce, or have been done with a limited number of patients. In a prospective study of 70 BC patients, PET/CT identified the primary tumor in 64 of 70 patients. Additionally, PET/CT identified axillary lymph node involvement in 19 of 70 patients, compared with 24 of 70 that were confirmed during surgery**.** These reports indicate that PET/CT has limited application for primary staging of early-stage BC. PET/CT can be performed for systemic staging of the newly diagnosed stage III and, in some studies, stage IIB breast cancer. Moreover, there is concern about how the tumor type and histology can modify the applicability of primary staging with PET/CT at any stage, an area of further investigation ***(20).***

Lymph node metastasis:

Lymph node metastasis is the single most important prognostic factor for the treatment plan in BC**.** Sentinel node biopsy (SNB) remains the gold standard of lymph node assessment; a positive finding on SNB warrants further investigations with axillary lymph node (ALN) dissection**.** Studies have evaluated the accuracy of PET/CT compared to SNB in diagnosing lymph node metastasis. The results of 25 studies were assessed in a meta-analysis and systematic review to investigate the accuracy of PET/CT in comparison with SNB**.** For example, a positive lymph node on a PET/CT in a woman with a high suspicion of advanced disease may spare SNB and lead to a direct ALN dissection ***(4).*** In general, however, it seems that the sensitivity of PET/CT is limited in comparison with SNB and thus guidelines still consider SNB as the method of choice to diagnose ALN involvement ***(21).***

The combined use of both modalities, which significantly increases sensitivity, is more complementary for assessment of ALN status than using each modality alone**.** PET/CT has a good specificity for diagnosing ALN metastasis, although its sensitivity is limited, especially in early-stage cases**.** Delayed PET/CT scan 90 min after FDG administration was also unable to enhance the diagnostic accuracy for diagnosing ALN metastasis ***(19).*** Additionally, in certain BC subtypes such as ER-positive/HER2-negative and HER2-positive tumors, SUVmax may be considered as an imaging biomarker for predicting ALN metastasis ***(22).***

Internal mammary node metastasis has also been subject to thorough assessments with PET/CT. In a retrospective assessment of 249 patients, PET/CT had a high PPV (87.1 %) in diagnosing internal mammary metastasis among stage III breast cancer patients**.** PET/CT has a higher AUC (0.87) in comparison with US (0.83) for detecting internal mammary node metastasis ***(21).***

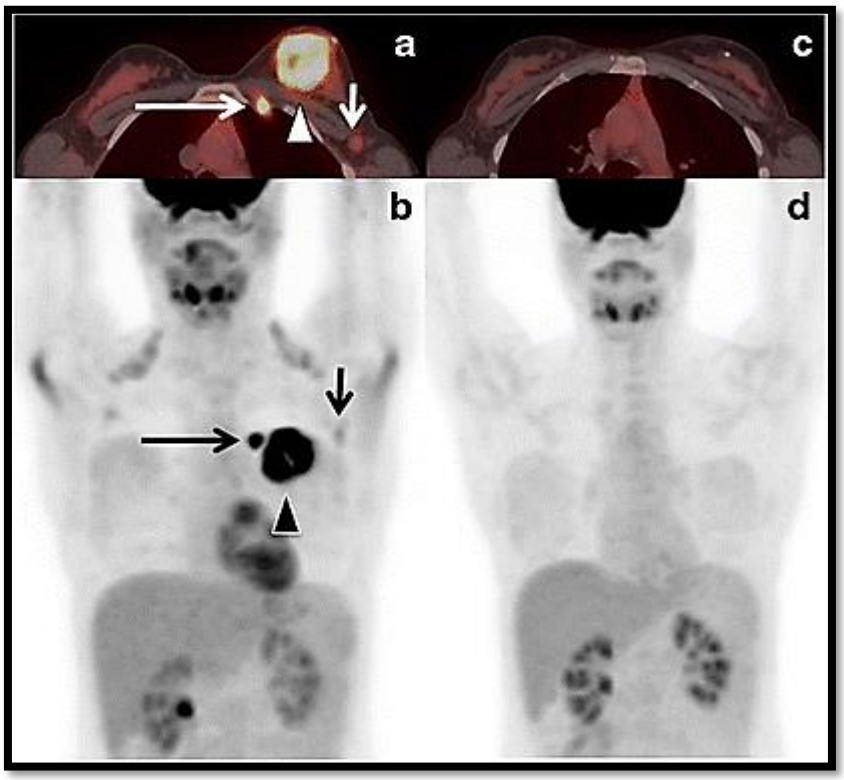

Figure (2): A 38-year-old breast cancer patient with internal mammary nodal metastasis detected by PET/CT that was verified by imaging follow-up. A breast cancer patient with internal mammary nodal metastasis detected by PET/CT that was verified by imaging follow-up. **a**. PET/CT and **b.** PET images showed the primary breast cancer (arrowheads), axillary node (short arrows), and previously unknown left internal mammary node (long arrows). **c.** PET/CT and **d**. PET images following 5 months of neoadjuvant chemotherapy showed resolution of all FDG avid lesions ***(23).***

Distant metastasis:

The most common sites of distant metastasis in BC are bones, lungs, liver and brain, and the conventional imaging studies for detecting distant metastasis include contrast-enhanced CT, bone scintigraphy and MRI**.** The diagnostic accuracy of PET/CT for distant metastasis has been evaluated in multiple studies. The results of a meta-analysis suggested that PET/CT is a valuable alternative when conventional MRI shows indeterminate or benign lesions or is not applicable ***(24).***

Although PET/CT is considered as a good alternative for detection of distant metastasis, the functional nature of this modality gives it advantage for detecting early metastasis to the bone, the most common site of metastasis**.** For example, vertebral bones are among the most common sites of metastasis and may be visualized early as focal areas of increased FDG uptake using PET/CT, while these foci may remain undetected with bone scintigraphy. PET/CT had a higher accuracy than CT for detection of bone metastasis, given that metabolic activity is increased prior to any anatomic changes**.** PET/CT and bone scintigraphy may have a complementary role in case of bone metastasis, since osteoblastic lesions are more accurately detected using bone scintigraphy and osteolytic lesions by PET/CT ***(24).***

PET/CT imaging is able to alter the treatment plan from neoadjuvant or surgical to palliative therapy in stage IIB and III BC especially in younger patients by detecting distant metastasis ***(3).***

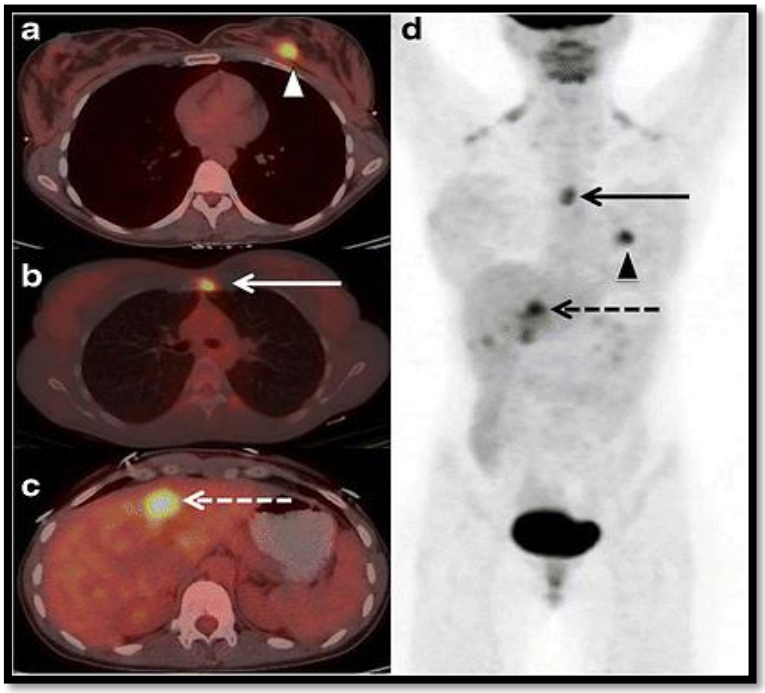

Figure (3):A 29-year-old woman with stage IIA breast cancer was upstaged to stage IV by after doing PET/CT. Axial PET/CT images demonstrated known primary left breast cancer. The arrowhead shows **a.** the primary breast cancer, while the solid arrow is **b**.the previously unknown osseous metastasis and **c** the dashed arrow is the previously unknown liver metastasis. **d.**The PET gives overview of all lesions ***(23).***

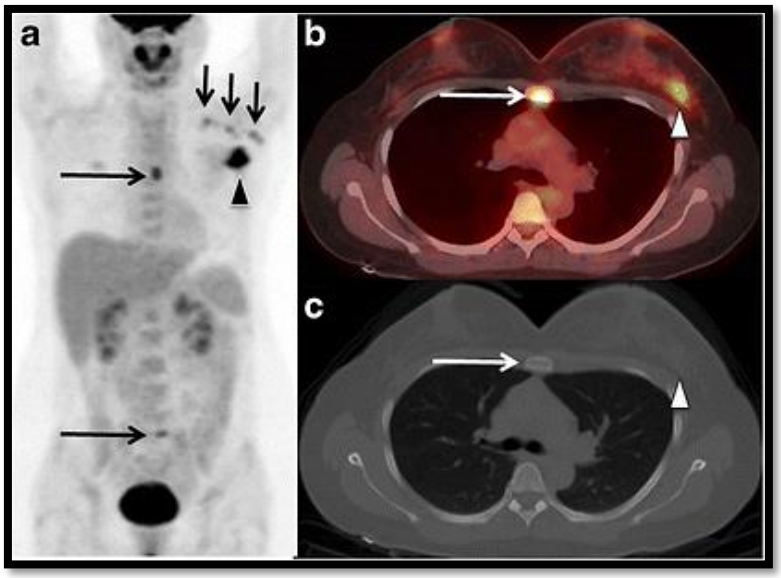

Figure (4): A 32-year-old woman with clinical stage IIB breast cancer was upstaged to stage IV after performing PET/CT. The arrowhead shows **a.** known primary breast cancer, short arrows show known axillary nodal metastases, and long arrows are two foci of FDG uptake in the midline of body. **b.** Axial PET/CT and **c.** axial CT through the chest showed primary breast cancer (arrowhead) and localized one of the midline foci to sternum without osteolytic or osteoslcerotic correlate on CT (long arrows). Biopsy of sternum demonstrated osseous metastasis unknown before PET/CT. The second midline focus was subsequently proven to be sacral metastasis (not shown) ***(23).***

- ***Prognosis:***

An important component of initial evaluation for any BC patient is determination of prognosis, since it plays an important role in designing an individualized treatment plan. To date, a growing body of evidence supports the role of pretreatment PET/CT in risk stratification of advanced-stage BC ***(25).***

Tumor cells with higher metabolic rate avidly take up FDG; thus, PET/CT allows for a more accurate prognostic stratification compared with conventional modalities that only assess the structural features of the primary tumor. In general, FDG uptake correlates with tumor aggressiveness and poorer prognosis, In fact, high pretreatment SUVmax predicts poorer outcomes in certain types of BC including the luminal type and IDC or in patients with bone metastasis ***(26)***.

Higher SUVmax may also indicate a higher chance of disease recurrence especially in patients with hormone receptor-positive BC**.** Moreover, SUVmax was reported to be positively correlated with the tumor size, clinical stage, certain histo-pathological subtypes. A retrospective review of PET/CT scans from 1906 postoperative patients suggested that a cutoff point SUVmax equal to 2.7 is a valuable measure for predicting outcomes such as progression free survival**.** Nevertheless, pretreatment SUVmax may have limited application for tumors that are inherently less FDG avid such as the ILC ***(27).***

PET/CT has advantage over conventional modalities in providing prognostic stratification. In a prospective assessment of 142 patients with newly diagnosed BC and at least grade T2 tumor, patients were evaluated with conventional modalities (mammogram, US, bone scan, abdominal US, and/or CT, X-rays and/or CT of the chest), followed by pretreatment PET/CT. In a retrospective study on 240 patients, the tumor lesion glycolysis 30 % (TLG30%) from pretreatment PET/CT independently correlated with survival outcomes. Also, TLG30% was able to effectively stratify both patients with stage III and IV breast cancer ***(25).***

In another study, whole-body total lesion glycolysis (WTLG) was identified as an independent prognostic factor of survival among patients who had metastasis as the initial presentation. In fact, PET/CT can provide volume-based parameters such as metabolic tumor volume (MTV) and whole-body metabolic tumor volume (WB-MTV) that will enhance its predictive value for disease recurrence and prognosis determination ***(28).***

Advantages and disadvantages of PET/CT:

The main advantage of the PET/CT-guided procedures relies on the possibility of combining functional as well as anatomical imaging in order to precisely identify and target the lesions that could not be otherwise clearly visualized with other common imaging modalities. FDG is still the most widely applied radiotracer both for diagnostic and interventional purposes, lesion-specific radiotracers may be used based on the precise suspected nature of the target disease ***(28).***

Typically, radiotracers have a long-lasting uptake that can persist for several hours within the target lesion. It was reported that a continuous increase in maximum SUV of the target tumors from pre- to post-procedural PET/CT scans. Other commonly used imaging modalities such as US, CT or MRI do not possess such property, only showing a transient contrast-enhancement. This aptitude of the prolonged radiotracer uptake has several different practical advantages:

- Persistent visualization of the target along the course of the procedure**,** hence allowing prolonged interventional sessions.
- The possibility of continuous visualization of the target lesion even in the presence of adverse intraprocedural circumstances which can potentially obscure the target lesion, such as hemorrhage, atelectasis, target displacement ***(29).***
- The ability to precisely target and adequately ablate large tumors, requiring multiple overlapping ablations ***(29).***

On the other hand, assessment of technical success following ablation is more challenging**.** Relative photopenia of the ablation zone may be used to assess technical success following the percutaneous ablation. As such, It was demonstrated that, when compared to contrast-enhanced CT obtained immediately after percutaneous ablation of liver metastasis, PET/CT is able to more accurately predict local recurrence. In particular, they found that tissue radioactivity concentration in the ablation zone normalized to background liver uptake served as a valuable tool when predicting local recurrence at follow-up.

Regarding the dose affecting operators, it should be noted that lead aprons or glasses routinely worn by radiologists during conventional fluoroscopy or CT guided procedures are ineffective against the annihilation energy of PET photons. Therefore, protective lead aprons and glasses are only warranted to protect operators

from the radiation dose generated by CT-fluoroscopy, if this modality is applied to guide the deployment of devices during the procedure. On the other hand, application of some simple precautions can significantly reduce the exposure of operators to the radiation generated by PET. The first essential rule for the operators is to limit the contact with the patients as much as possible.

Another precaution is to perform the procedure according to the half-life (i.e. time needed for the decay of half the total administered dose) of the applied radiotracer. For example, FDG has a 110 min half-life. Therefore, starting the procedure about two hours after administration of the radiotracer allows operators to be exposed only to half of the total dose administered; accordingly, the more the procedure is postponed after radiotracer administration, the less radiation exposure is registered for operators. Minimization of the dose affecting the operator can be further achieved by the "split-dose" technique, which has been described for PET/CT-guided tumor ablations ***(29).***

Basically, the total radiotracer dose to be administered to patients is divided into two different portions: The first portion (30–50% total dose) is administered to achieve lesion targeting, whilst the remainder is administered at the end of the procedure to assess the efficacy of the treatment (i.e. technical success). Such a technique allows the operators to be exposed only to the radiation caused by the first administered portion of the total dose, as whilst assessing the technical success, the operators' presence in the PET/CT suite is not necessary. Moreover, for prolonged ablative procedures, multiple operators may share the same intervention, thus limiting the radiation exposure for each individual operator ***(30).***

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