Normal Physiologic and Benign Foci with F-18 FDG Avidity on PET/CT in Patients with Breast Cancer

Soon-Ah Park · Kwang-Man Lee · UnJong Choi ·
Hun Soo Kim · Hye-Won Kim · Jeong Hoon Song

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Abstract

Purpose The aim of this study was to evaluate the physiologic and benign F-18 fluorodeoxyglucose (FDG) avid foci in patients with breast cancer.

Methods On 309 F-18 FDG PET/CT scans of 241 women with breast cancer, the hypermetabolic lesions compared with the surrounding normal region were evaluated retrospectively. Available reports of other relevant radiological imaging, medical records, and follow-up PET/CT were reviewed for explanations of the abnormal uptake.

Results Among the 70 physiologic foci, muscular uptake of the lower neck following the surgical and/or radiation

therapy of ipsilateral breast (29%), hypermetabolic ovaries (16%) and uterine (10%) uptake during the ovulatory and menstrual phases during the normal menstrual cycle were identified, and also hypermetabolic brown fat in cold-induced thermogenesis (7%), non-specific bowel uptake (35%) were observed. Among the 147 benign lesions, sequelae of the chest wall and breasts following surgical and/or radiation therapy, were often observed (27%). Hypermetabolic thyroid glands were noted as adenomas and chronic thyroiditis (18%). Reactive hyperplasia of cervical or mediastinal lymph nodes (32%), degenerative osteoarthritis and healed fractures (15%), hypermetabolic benign lung lesions (6%) were observed.

Conclusion Altered physiologic and benign F-18 FDG uptake in the lower cervical muscle and chest wall following ipsilateral breast surgery or radiotherapy were common, and also normal physiologic uptake in ovary and uterus, brown fat, thyroid were considered as predominant findings in women patients with breast cancer. Knowledge of these findings might aid in the interpretation of FDG PET/CT in patients with breast cancer.

Keywords Breast · Carcinoma · F-18 fluorodeoxyglucose · FDG · Physiologic · Benign

S.-A. Park

Department of Nuclear Medicine, Wonkwang University College of Medicine and Institute of Wonkwang Medical Science, Iksan, Republic of Korea

K.-M. Lee (✉) · U. Choi

Department of Surgery, Wonkwang University College of Medicine and Institute of Wonkwang Medical Science, 344-2 Shinyong-Dong, Iksan, Jeollabuk-do 570-749, Republic of Korea
e-mail: leekm@wonkwang.ac.kr

H. S. Kim

Department of Pathology, Wonkwang University College of Medicine and Institute of Wonkwang Medical Science, Iksan, Republic of Korea

H.-W. Kim

Department of Radiology, Wonkwang University College of Medicine and Institute of Wonkwang Medical Science, Iksan, Republic of Korea

J. H. Song

Department of Plastic and Reconstructive Surgery, Wonkwang University College of Medicine and Institute of Wonkwang Medical Science, Iksan, Republic of Korea

Introduction

Breast cancer is a well publicized cancer and the second most common cause of mortality in women. Early diagnosis and close follow-up of these patients are important for appropriate patient management. Functional imaging methods such as the positron emission tomography/computed tomography (PET/CT) have gained widespread clinical acceptance and have been used extensively

in the evaluation and clinical management of patients with breast cancer for the initial diagnosis, preoperative staging, monitoring the response to therapy, and restaging of recurrence [1–7].

The radiotracer most widely used in clinical practice for PET is the glucose analogue, 2-[F-18]fluoro-2-deoxy-D-glucose (F-18 FDG), based on the increased glucose metabolism of malignant cells. Increased FDG accumulation in neoplastic tissues is a function of increased expression and activity of glucose transporter proteins and of the glucose phosphorylating enzyme hexokinase. The results are due to increased anaerobic metabolism of cancer cells and the metabolic trapping of FDG within the tumor cells, due to the absence of metabolic pathways for the breakdown of FDG [8]. However, FDG is not specific to neoplastic processes. FDG also accumulates at sites of physiological tracer biodistribution such as the brain, muscles, salivary glands, myocardium, gastrointestinal tract, urinary tract or as a result of benign, inflammatory, or granulomatous processes [9, 10]. To effectively and accurately interpret PET, complete knowledge of the physiological and altered physiological FDG uptake, as well as an awareness of benign uptake, is essential to avoid false-positive interpretations in patients with malignancy. PET/CT is rapidly evolving and playing an increased role in the field of oncology, and the PET/CT has been useful for breast cancer. The PET/CT has been shown to improve not only the sensitivity of PET interpretation but also its specificity; this combined approach provides anatomical information as part of the CT component.

The aim of the present study was to evaluate increased FDG uptake on PET/CT at normal physiologic sites and various benign lesions that could be confused with malignant lesions that lead to false-positive findings in patients with breast cancer.

Materials and Methods

Patient Population

Three hundred and nine consecutive FDG PET/CT studies of 241 women (aged 23–82 years; mean 49.3 ± 10 years), who were assessed for known or suspected breast malignancies and follow-up evaluation following treatment, were retrospectively evaluated. Seventy-six women that had clinical or imaging suspicion of a breast malignancy had FDG PET/CT for staging; 233 scans were obtained from follow-up of the 165 patients. The mean time interval between the last treatment and the FDG PET/CT study was 21.2 months. Prior treatment included surgery, chemotherapy, and radiotherapy; surgery was followed by radiotherapy in 26 patients; surgery and chemotherapy was given to

73 patients; surgery, radiotherapy and chemotherapy was performed in nine patients; surgery alone, such as breast conserving surgery or mastectomy, was performed in 52 patients, and chemotherapy was given to only five patients (Table 1). All patients with FDG-avid foci localized by PET/CT, regardless of the intensity of the uptake and the presence or absence of findings on the CT component, were identified and reviewed. All patients provided informed consent for the PET/CT study and for assessment of their clinical records for follow-up.

The primary breast tumors included ductal carcinoma in situ ($n=31$), invasive ductal carcinoma ($n=196$), invasive lobular carcinoma ($n=9$), mixed invasive ductal and invasive lobular carcinoma ($n=1$) and invasive mucinous carcinoma ($n=4$).

Imaging Protocol

All patients fasted for at least 6 h before the PET/CT scan and only glucose-free water was allowed. An intravenous injection of 5.18 MBq of FDG/kg of body weight was administered and the patients rested for 60 min before the imaging. PET/CT data, using a PET/CT system (Biograph, Siemens, Germany), was obtained with patients in the supine position. Emission images were acquired after CT scanning, and an emission scan was performed in nine bed positions at 2.5 min per step. Attenuation correction was performed based on the CT data, and the data were resized from a 512×512 matrix to a 128×128 matrix to match the PET emission data for image fusion. The PET data were reconstructed iteratively using the ordered subset expectation maximization software provided by the manufacturer. PET, CT and PET/CT images of the whole body were displayed in the axial, coronal, and sagittal planes and were reviewed on a dedicated workstation. PET data were also displayed on a rotating maximum intensity projection (MIP).

Interpretation and Analysis of PET/CT Images

The presence of abnormal FDG uptake was interpreted on the MIP, axial, coronal and sagittal images. Foci with a

Table 1 Treatment type of breast malignancy

Treatment	Number of patients
Surgery and radiotherapy	26
Surgery and chemotherapy	73
Surgery, radiotherapy and chemotherapy	9
Surgery only	52
Chemotherapy only	5

higher FDG uptake than the surrounding or contralateral normal tissues were considered abnormal uptake. Visual inspection was most frequently relied on when interpreting the PET/CT results; however, the maximum standardized uptake value (maxSUV) was also used for a semiquantitative assessment of the radiotracer uptake in a given tissue. The maxSUV of a given tissue was calculated with the following formula: [the maximum ROI activity (MBq/g)]/[injected dose (MBq)/body weight (g)]. Regions of interest (ROIs) were overlaid over FDG-avid lesions. The maxSUV was measured uniformly by an experienced nuclear medicine physician.

The final diagnosis of the physiological and benign lesions was based on the presence of associated morphological findings on the CT component of the PET/CT or radiographic and other clinical information available in the patient's medical record. Changes in the FDG uptake on the follow-up PET/CT, available pathology findings and laboratory tests were also reviewed to explain the abnormal uptake.

Results

Normal or Altered Physiologic Uptake

There were several sites of normal physiologic accumulation of FDG in muscle, bowel, brown fat tissue, ovaries, uterus, distal esophagus, lactating breasts and non-specific axillary lymph nodes. Among the 70 physiologic foci, the ipsilateral muscular uptake of the lower neck and shoulder muscles were observed in the patients that had modified radical mastectomy or breast conserving surgery (29%). The FDG uptake was mild unilaterally in the muscles of the lower neck with a mean maxSUV of 2.2 during the post therapy follow-up period (Fig. 1). Hypermetabolic ovaries (16%) and the uterus (10%) during the ovulatory and menstrual phases of the normal menstrual cycle were observed. The functional follicle of the ovaries was a unilateral, focal, and discoid finding with moderate-to-high uptake at the ovulatory phase of the normal menstrual cycle (Fig. 2). The mean maxSUV measured in the ovaries and

Fig. 1a–c Contraction-induced muscular FDG uptake. MIP image (**a**), coronal scan (**b**) and axial scan (**c**) demonstrating that intense unilateral uptake in the right anterior neck (*arrows*) corresponds to the tense sternocleidomastoid muscle in a 49-year-old woman who underwent breast conserving surgery and radiation therapy due to the right breast malignancy

Fig. 2a–d Increased physiologic distribution of FDG combined with malignant mass of right breast and ipsilateral metastatic axillary lymphadenopathy. **a** On MIP PET image there are multiple areas of increased FDG uptake in the bilateral supraclavicular regions, right axillary area, right breast, gastrointestinal tract, uterus and left ovary of a 42-year-old woman with right breast malignancy. **b** Coronal and **c** axial PET/CT images demonstrate that the symmetrical uptake in the brown adipose tissue of bilateral supraclavicular regions, non-specific uptake in the gastrointestinal tract, uterus and left ovary correspond to the physiologic uptake (*arrows*). **d** An additional asymmetric uptake in the right axillary region on axial PET/CT image demonstrate enlarged lymph nodes on CT component which are consistent with metastatic axillary lymphadenopathy (*circle*)

uterus was 5.0 and 3.3, respectively. Hypermetabolic brown fat in cold-induced thermogenesis (7%) showed moderate to high FDG uptake in the brown adipose tissues of the supraclavicular region, mid axillary line, and paraspinal regions of the posterior mediastinum with a mean maxSUV of 4.1 (Fig. 2). The patients with hypermetabolic brown fat, ovaries, and uterus were younger than the other patients showing hypermetabolic physiologic uptake. Non-specific uptake of bowel (33%), distal esophagus (3%), lactating breasts (1%), and axillary lymph node owing to the extravasation of intravenous injection of FDG (1%) were observed. The quantitative analysis showed that the maxSUV of the gastrointestinal tract was higher, with a mean maxSUV of 6.3 and a wide range from 2.6 to 12.4,

than the aforementioned sites. The PET scan showed diffuse or focal hypermetabolic foci in the stomach, the small bowel and the colon. The corresponding CT scan and PET/CT fusion imaging did not show wall thickening or nodular lesions in the gastrointestinal tract. The physiologic FDG avid foci and the characteristics of the enrolled patients are shown in Table 2.

Non-physiological Benign Lesions

Among the 147 benign lesions, increased FDG uptake in the chest wall and breasts following surgical intervention and/or radiation therapy were the most common (27%). Increased FDG uptake in surgical scars, granulation tissue,

Table 2 Normal physiologic sites with increased FDG uptake

FDG avid sites		Value, <i>n</i> (%)	Mean maxSUV	Range of maxSUV	Clinical characteristics	
					Age	Causes
1	Bowel	23 (33%)	6.3±3.9	2.6–12.4	52.0±9.1	Non-specific
2	Muscle (lower neck and shoulder)	20 (29%)	2.1±0.4	1.7–2.6	52.9±8.6	Active contraction in tense patients following surgical intervention
3	Brown fat	5 (7%)	4.1±1.0	3.1–5.6	43.4±5.1	Cold-induced thermogenesis
4	Ovary	11 (16%)	5.0±2.1	2.7–7.4	43.2±6.3	Late follicular phase during the normal menstrual cycle
5	Uterus	7 (10%)	3.3±0.5	2.9–3.6	47.0±9.3	Secretory phase during the normal menstrual cycle
6	Distal esophagus	2 (3%)	3.5±0.4	3.7–6.3	42.0±8.5	Non-specific
7	Breast	1 (1%)	2.0		29.0	Lactating breast
8	Axillary lymph node	1 (1%)	2.1		56.0	Accidental tracer extravasation into tissue

postoperative inflammation and radiation-induced fibrosis were found in 27% of studies (39/147). The average time from surgery and/or radiotherapy was 21.2 months (Fig. 3). The FDG uptake was diffuse and mild (mean maxSUV 1.8); correlative imaging with contrast enhanced CT or US showed fibrosis, fat necrosis, seroma and skin thickening with edematous soft tissue in patients who underwent radiotherapy. The foci of increased FDG uptake following surgery and/or radiotherapy decreased in incidence and intensity over time on follow-up FDG PET/CT. Among the 39 lesions, increased FDG uptake was seen in 15 surgical scars, five granulation tissues, four postoperative inflam-

mations, four fat necroses, two seromas, and nine lesions after radiotherapy. Hypermetabolic lesions of the thyroid gland were noted as nodular lesions and/or chronic thyroiditis (18%). Mild to moderate FDG uptake was observed in the benign nodular lesions of the thyroid and/or thyroiditis with a mean maxSUV of 3.8 (range 2.2–6.8) (Fig. 3). Reactive hyperplasia of lymph nodes associated with pulmonary tuberculosis or inflammation were observed in mediastinal (16%), cervical (10%) and axillary lymph nodes (6%). Multiple areas of benign lymphadenopathy associated with inactive pulmonary tuberculosis or inflammation showed mild to moderate FDG uptake with a mean maxSUV of 2.5

Fig. 3a–c Mildly increased FDG uptake in surgically induced loco-regional scar tissue and thyroid adenoma. **a** MIP PET image showing mildly increased FDG uptake in the right breast and thyroid bed. **b, c** Axial PET/CT images demonstrate surgically induced loco-regional

scar tissue (*long arrows*) and thyroid adenoma (*short arrows*) in a 57-year-old woman who underwent breast-conserving surgery and right thyroid lobectomy. Thyroid adenoma was confirmed by histopathologic examination

(range 1.7–3.4) in the mediastinal lymph nodes, 2.6 (range 2.4–2.9) in the cervical lymph nodes and 1.3 (range 0.7–1.8) in the axillary lymph nodes. Active arthritis in the shoulder, sternoclavicular and facet joints of the spine (8%) and bony fractures were detected (9%). Benign pulmonary lesions were also observed in early acute radiation pneumonitis or later pulmonary fibrosis following radiotherapy, inflammatory nodule, subsegmental atelectasis and inactive pulmonary tuberculosis (6%). Mild FDG uptake with a mean maxSUV of less than 2.8 was observed in the shoulder, facet joints of the spine, old fractures and pulmonary lesions.. The mean maxSUV of the FDG avid foci and the characteristics of the enrolled patients are shown in Table 3.

Discussion

Normal physiologic uptake in the muscles, ovary, uterus, brown adipose tissue and gastrointestinal tract has been reported by several groups of investigators [11–18]. Among these physiologic foci, as shown in this study, altered physiologic uptake in the lower neck muscles following ipsilateral breast surgical and/or radiation therapy, functional ovary and uterus during normal menstruation cycle, brown adipose tissue associated with cold-induced thermogenesis could be predominant findings on FDG PET/CT in women patient with breast cancer.

Physiologic FDG uptake in the neck muscles may cause a diagnostic dilemma in the interpretation of PET scans. Frequently, muscle uptake can be distinguished from malignant nodal uptake by identifying the characteristic patterns of linear symmetric uptake. However, muscles often demonstrate more focal uptake patterns. The combined PET/CT most frequently shows FDG uptake local-

ized to the myotendinous junction. These focal areas of FDG uptake can be difficult to distinguish from abnormal lymph nodes. On PET/CT scans, intense asymmetric FDG uptake can also be seen in the sternocleidomastoid muscle and can mimic an enlarged lymph node. Often, inspection of coronal or sagittal reconstructed images will facilitate characterization of muscle uptake by demonstrating the linearity on one or more images.

The endometrium and inflammatory changes in the ovaries during the normal menstrual cycle can also show normal accumulation of FDG in premenopausal women [14]. The menstrual cycle included: the menstrual flow phase; the proliferative phase of estrogen action; the mid cycle, or ovulation; the secretory phase of progesterone action. In the current study, increased FDG uptake in the endometrium or ovaries was found in premenopausal patients with a normal menstrual cycle and no gynecological malignancy, while ovulating and during menstruation. Glucose phosphorylation is an important rate-limiting step in the estrogenic stimulation of uterine glycolysis [15]. Increased FDG uptake in the endometrium or ovaries suggests a malignancy in postmenopausal patients. In premenopausal patients, however, it can be interpreted as either malignant or functional. Many functional benign ovarian cysts have SUVs that overlap with malignant disease. Correlative CT findings with the menstrual cycle may assist in differentiating physiological from malignant FDG uptake.

High FDG uptake in normal fat can be a common source of potentially misleading false-positive PET imaging in the neck, thorax, and abdomen. Brown adipose tissue (BAT) represents a thermogenic organ; it produces heat to maintain body temperature. BAT has the ability to generate heat in response to cold exposure (non shivering thermo-

Table 3 Benign disease with increased FDG uptake

FDG avid sites	Value, n(%)	Mean maxSUV	Range of maxSUV	Clinical characteristics	
				Age	Disease
1 Chest wall and breast	39(27%)	2.1±1.3	1.2–5.8	46.2±7.4	Granulomatous tissue or surgical scar, fat necrosis, seroma, postoperative inflammation and radiotherapy-induced fibrosis.
2 Mediastinal LNs	24(16%)	2.5±0.5	1.7–3.4	58.9±10.9	Reactive hyperplasia
3 Cervical LNs	14(10%)	2.6±0.2	2.4–2.9	52.8±11.2	Reactive hyperplasia
4 Axillary LNs	9(6%)	1.3±0.4	0.7–1.8	56.4±16.0	Reactive hyperplasia
5 Thyroid	26(18%)	3.8±1.2	2.2–6.8	51.1±10.8	Benign nodules and/or chronic thyroiditis
6 Joint	12(8%)	2.8±0.3	2.4–3.2	55.1±9.9	Degenerative osteoarthritis
7 Bone	14(9%)	1.7±0.4	1.4–2	57.1±13.7	Healed fracture (rib and spine)
8 Lung	9(6%)	1.7±0.6	1–2.2	50.1±11.6	Radiation pneumonitis or radiotherapy-induced fibrosis, subsegmental atelectasis, inflammatory nodule and inactive pulmonary tuberculosis

genesis), or ingestion of food (diet-induced thermogenesis), associated with increased glucose uptake [16]. Hypermetabolic BAT on PET imaging is observed most commonly in the winter and noted in the supraclavicular regions, mid axillary line, and paraspinal regions in the posterior mediastinum, usually in pediatric and female patients [17, 18]. The data in this study showed that patients with hypermetabolic BAT had higher maxSUVs with a mean of 4.1 ± 1.0 and were younger than the patients without hypermetabolic BAT. Therefore, in younger female patients, it is essential to warm the body to inhibit FDG uptake in the BAT and also to interpret the results with a simultaneously performed CT.

FDG is excreted in part through the gastrointestinal tract, with uptake in the distal esophagus, stomach, small intestine, and large intestine representing normal patterns of tracer distribution [12]. This physiologic tracer activity in the gastrointestinal tract has been attributed to uptake by smooth muscles (mainly in the bowel), swallowed secretions, or excretion and intraluminal concentration of the FDG. [13] Abnormal accumulation of FDG in the lymph nodes can also be a consequence of accidental tracer extravasation into the tissue drained by regional lymph nodes. Because of this possibility, and whenever possible, the site of FDG injection, into an antecubital vein, should be contralateral when evaluating conditions such as breast cancer that may metastasize to the regional lymph nodes.

Early detection of local-regional recurrence after surgery for breast cancer is clinically important and crucial to the selection of the most appropriate therapy. However, surgical intervention and radiation therapy for breast cancer is occasionally compromised by local-regional granulomatous tissue or scar formation, infectious disease, radiation-induced fibrosis and lymphadenopathy [19–21]. Despite advances in morphological imaging, the differentiation of recurrent lesions from these local-regional compromised benign lesions is occasionally difficult. FDG PET has been introduced to overcome this problem. However, significant FDG uptake in compromised benign lesions after surgery for breast cancer results in false positives, as seen in the present study. It can be assumed that abundant inflammatory/fibroblast cells and the increased extra-cellular component of FDG that results from enhanced vascular permeability in these active benign lesions can cause intensive FDG uptake regardless of the relatively lower ratio of hexokinase to glucose-6-phosphatase compared with malignant cells [22]. Increased uptake of FDG with inflammation may be explained by the recruitment of activated granulocytes, lymphocytes and macrophages. These cells have enhanced levels of glucose transporters (GLUTs), especially GLUT 3 and to a lesser extent, GLUT 1 [23]; they have an increased affinity for FDG with the various cytokines and growth factors.

The ratio of diffusely increased FDG uptake in the thyroid gland was higher in patients with breast cancer than in healthy subjects on the PET/CT [24]. The etiology of diffuse FDG uptake can include patients with hypothyroidism on hormone replacement, Hashimoto's or autoimmune thyroiditis, hyperthyroidism and Graves' disease, and normal variants [25].

FDG uptake in lymph nodes is not specific for a malignant neoplasm, since active granulomatous diseases such as tuberculosis and sarcoidosis may cause very intense FDG uptake in the involved lymph nodes [26]. The response of regional lymph nodes to infection is also a common source of elevated FDG uptake in non-malignant lymph nodes. False-positive lymphadenopathy from inflammatory or granulomatous lesions continue to be a problem for the accurate interpretation of FDG PET images in regions with a high prevalence of granulomatous disease.

In the current study, the mean maxSUV of physiologic uptake was higher than that of benign lesions in patients with breast cancer. These findings derived from the high physiologic uptake in brown fat tissue and gastrointestinal tracts. Moreover, the patients enrolled in the present study had a longer time interval with a mean of 21.2 months after surgery/radiation therapy and showed low FDG uptake with a mean maxSUV 2.1 ± 1.3 . Therefore, reduced populations of active inflammatory/fibroblast cells, and a decreased extra-cellular component of FDG in repaired compromised benign lesions, can result in low FDG uptake.

The present study was retrospective in nature, and included the number of women patients with breast cancer. Larger comparative studies are required in patients with other malignancies to determine the frequent physiologic uptake or that due to benign lesions in breast cancer. In addition, anatomical imaging methods with high resolution, such as MRI, may be necessary for differential diagnosis of hypermetabolic breast lesions following surgery or radiotherapy.

Conclusions

On the whole-body FDG PET/CT scans for breast cancers, we identified that several normal or altered physiologic foci and various benign lesions demonstrated significant FDG uptake in patients with breast cancer; altered physiologic uptake in the lower neck muscles following ipsilateral breast surgical and/or radiation therapy, functional ovary and uterus during normal menstruation cycle, brown adipose tissue associated with cold-induced thermogenesis, surgery or radiotherapy-induced sequelae of breast or chest wall, and benign disease in thyroid could be predominant findings on FDG PET/CT in women patients with breast cancer. The accurate interpretation of these findings can be

challenging for clinicians. To avoid misinterpretations, we suggest that careful attention to these normal or altered physiologic FDG uptake patterns and hypermetabolic benign disease is required for more accurate image interpretation for the correct staging and detection of disease recurrence in patients with breast cancer.

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