VOLUME 26 · NUMBER 5 · FEBRUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Is There a Role for Positron Emission Tomography in Breast Cancer Staging?

Nicole C. Hodgson and Karen Y. Gulenchyn

From the Departments of Surgery, Oncology, and Radiology, McMaster University; and Department of Nuclear Medicine, Hamilton Health Sciences, Hamilton, Ontario, Canada.

Submitted August 2, 2007; accepted November 13, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Nicole C. Hodgson, MD, Department of Surgical Oncology, Juravinski Cancer Centre, 699 Concession St, Hamilton, Ontario L8V 5C2, Canada; e-mail: nicole.hodgson@hrcc.on.ca.

0732-183X/08/2605-712/$20.00

DOI: 10.1200/JCO.2007.13.8412

ABSTRACT

Positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) is a radiotracer imaging method that is used in the care of patients with cancer. We conducted a nonsystematic review of the literature regarding the applicability of this technique in patients with breast cancer, encompassing the impact of FDG-PET on surgical management, including axillary node staging and sentinel lymph node biopsy; the use of FDG-PET in the evaluation of the primary tumor; the role of FDG-PET in the evaluation of distant metastases both at diagnosis and in the investigation of suspected recurrence; and the ability of FDG-PET to predict treatment response. FDG-PET is not sufficiently sensitive to replace histologic surgical staging of the axilla. Although FDG avidity of the primary tumor has been shown to be an unfavorable indicator, there is insufficient information to recommend its routine use for this indication. FDG-PET is more sensitive than conventional imaging in the detection of metastatic or recurrent disease, but the impact of increased sensitivity on patient care and outcome has not been demonstrated. The data regarding prediction of treatment response are insufficient to reach any conclusion. There are a number of prospective, adequately powered clinical trials currently in progress that should provide more definitive answers regarding the role, if any, of this technique in the management of patients with breast cancer.

J Clin Oncol 26:712-720. © 2008 by American Society of Clinical Oncology

INTRODUCTION

The role of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) in the preoperative management of early-stage breast cancer has yet to be defined. With dramatic improvement in imaging modalities such as mammography, magnetic resonance imaging, and computed tomography (CT), is there, in fact, a need for another diagnostic test such as PET in breast cancer staging? A recent National Comprehensive Cancer Network taskforce report concluded that PET was not indicated for diagnosis or screening of breast cancer; staging of the primary tumor, axilla, or metastatic disease in patients with clinically early-stage disease; or post-treatment surveillance.[1] Furthermore, PET is not suited for screening purposes because of its high expense and modest whole-body radiation exposure. A review of 20 studies evaluating PET and axillary staging noted a wide variability of sensitivities and specificities, but this analysis mixed retrospective and prospective studies and cannot provide a quantitative analysis.[2] No randomized studies have been published to date, and overall existing prospective trial sample sizes have been exceedingly small. Also, few studies have assessed dual-modality PET/CT imaging in breast cancer. Our objective was to review the utility of FDG-PET in axillary staging, in identifying local recurrence and distant metastases, and in assessing response to therapy and to identify future possible avenues for research.

INTRODUCTION TO PET

FDG-PET is a prototypical molecular imaging technique. FDG is a structural glucose analog labeled with the positron emitter fluorine-18. Substitution of fluorine for a hydroxyl group blocks the metabolism of the tracer. Thus, the level of FDG uptake reflects the rate of trapping of phosphorylated FDG and is an indication of the rate of glycolysis. In general, malignant cells use more glucose, leading to increased accumulation of fluorodeoxyglucose. This increased uptake of glucose by tumors was demonstrated by Warburg[3] in 1930, but the development of FDG-PET imaging for cancer applications did not begin until the development of instruments capable of whole-body imaging in 1993.[4] In 2000, integrated PET/CT instrumentation capable of providing both functional and anatomic information with accurate image registration was introduced to clinical practice[5]; virtually all units sold at present are PET/CT scanners. Gamma cameras modified for

coincidence imaging have been used for FDG-PET imaging; however, it has been demonstrated that these units are less sensitive than dedicated PET instrumentation in the detection of abnormal uptake, and these units are no longer manufactured, although some may continue in clinical use.[6]

Careful attention to detail is required to maximize study quality. To minimize tracer uptake in normal tissues, patient preparation is critical. Particular attention must be paid to ensure that the patient avoids strenuous exercise in the 24 hours before the study and rests quietly after the injection of FDG during the uptake period. The patient must be fasting, and blood glucose levels must be normal. FDG uptake can occur in benign pathologies such as inflammatory conditions, infections, trauma, and granulomatous disease. Careful documentation of the patient history and correlation with other imaging tests are critical to the correct interpretation of the study.[7] The patient presented in Figure 1 illustrates this point.

Both absolute and semiquantitative measurements of glucose metabolism can be made. The standardized uptake value (SUV) is a semiquantitative measurement that calculates regional tracer uptake normalized to the administered dose of tracer and can be used to assist in the interpretation of FDG-PET imaging. The SUV may be particularly useful when imaging is used to monitor response to therapy. The SUV is usually normalized to body weight or body-surface area, and either the average or maximum SUV within the tumor volume may be determined. SUV determinations can vary among PET centers by up to 15%, even when the same acquisition protocol is used, as a result of technical and calibration factors. Each PET center needs to develop its own reference values and use SUVs as a clinical adjunct.[8]

STAGING THE AXILLA

Breast cancer staging includes detecting cancer spread to regional lymph nodes, both in the axilla and internal mammary chain, and also distant metastases to such sites as lung, liver, bone, and other organs. Of these sites, the status of the axillary lymph nodes is important for prognosis and determining adjuvant therapy. The introduction of sentinel lymph node biopsy (SLNB) for minimal axillary staging has

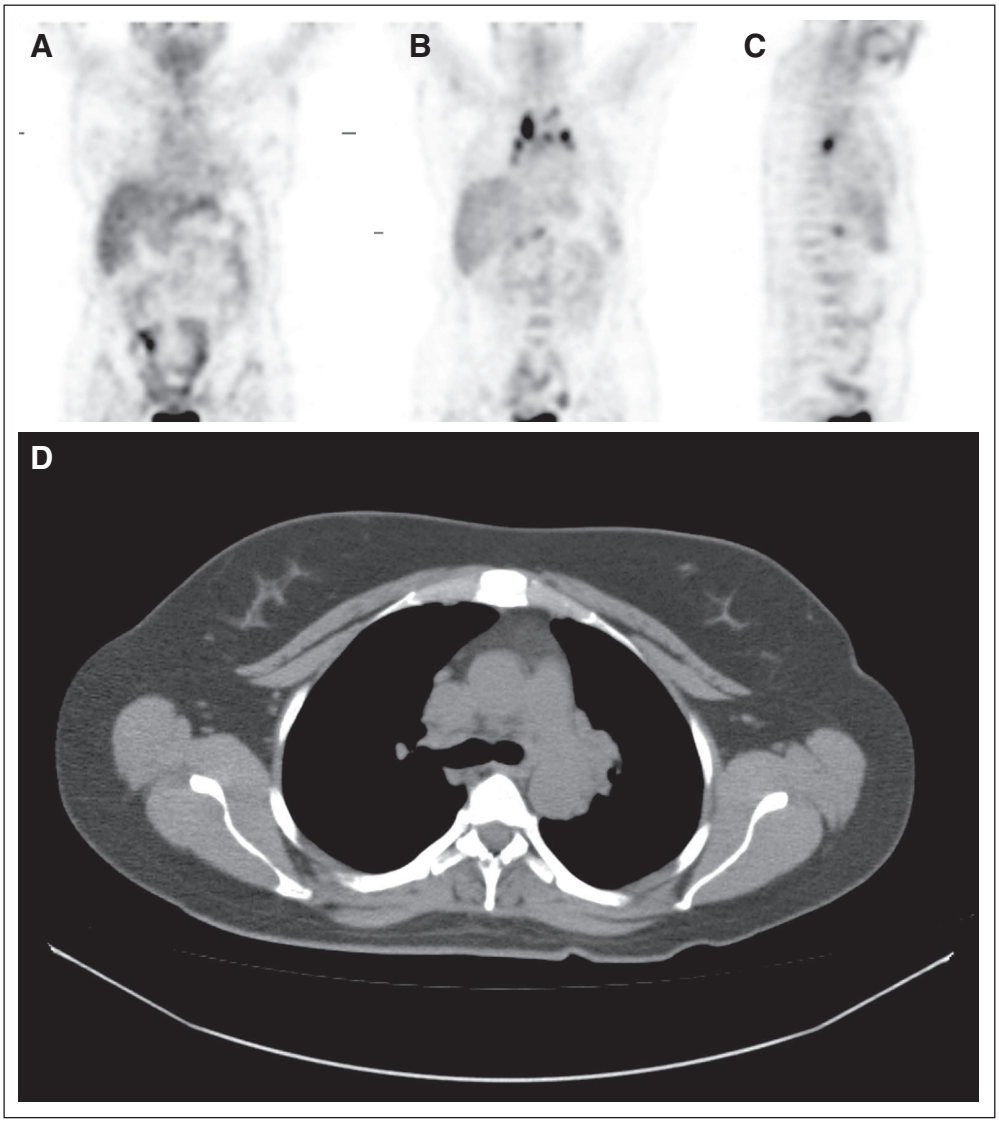

Fig 1. Breast cancer patient in whom the primary tumor did not accumulate fluorodeoxyglucose (FDG). FDG-positron emission tomography imaging shows abnormal activity in hilar, mediastinal, and para-aortic lymph nodes. Computed tomography imaging shows enlarged left hilar nodes. This pattern is consistent with sarcoidosis. Clinical and radiologic correlation is required to avoid false-positive upstaging.

reduced some of the morbidity of axillary surgery for early breast cancer patients.[9,10] Randomized trials such as the Axillary Lymphatic Mapping Against Nodal Axillary Clearance trial have reported lymphedema rates of 5% with SLNB compared with 13% for standard axillary dissection.[11] The National Surgical Adjuvant Breast and Bowel Project-32 trial results are still pending. However, a subset of patients undergoing SLNB require subsequent completion of axillary dissection, resulting in a second surgical procedure as well as associated psychological distress and higher risk of associated shoulder and arm morbidity. The use of FDG-PET to identify this subset of patients could potentially aid in triaging patients to the most definitive surgery. Early studies of FDG-PET for axillary staging showed a sensitivity of 85% to 90% and higher.[12-14] However, these studies included patients with more advanced primary tumors, increasing the pretest likelihood of a positive PET. A literature search of studies evaluating FDG-PET in assessing axillary nodal status was undertaken for the period from 1997 to 2007. The search was confined to English-language studies with at least 15 patients and with axillary lymph node dissection, SLNB, or both as the reference standard. The results are listed in Table 1. More recent series with a larger proportion of T1 primary lesions have demonstrated much lower sensitivity for axillary metastases, as low as 20%. The specificity of PET has been consistently high across studies, ranging from 85% to 100%. The identification of subsets of patients or specific circumstances in which this high specificity could prove useful could be an avenue for further research. For example, in the clinical setting, some centers routinely use preoperative axillary ultrasound with needle biopsy in the presence of abnormal sonographic adenopathy in preoperative planning. In this setting, PET could be useful in the clinically and sonographically negative axilla to determine the best surgical procedure.

PET and SLNB

SLNB has gained widespread acceptance over the last 10 years to minimize the invasiveness of axillary staging. In a recent prospective study, Veronesi et al[15] evaluated 236 patients with breast cancer with preoperative PET imaging and performed SLNB; in patients with a positive PET scan or a positive SLNB, a completion axillary lymph node dissection was carried out. This larger study reported, again, a low sensitivity of FDG-PET (37%), whereas the specificity and positive predictive value were high at 96% and 88%, respectively. The results of this study are listed in Table 2. Of note, the false-negative rate of PET was 35%, and PET showed increased overall accuracy in women of older age and with postmenopausal status.

The stated accuracy of FDG-PET can also be impacted by the method of pathologic assessment of nodal tissue used for comparison. Serial sectioning and immunohistochemistry applied to sentinel lymph nodes improve the detection of micrometastases, which are often missed by PET/CT imaging. Figure 2 demonstrates a case of missed micrometastases. In the study by Gil-Rendo et al[16] of 275 women, there were 22 false negatives, and of these, six were micrometastases. There were five false negatives in which there was significant nodal disease (pN2, pN3). The failure of PET to detect significant nodal burden is concerning. Some studies have suggested that this may be a result of inherent tumor characteristics such as tumor grade and type. Possibly, necrotic or extensive macrometastases have less avidity for FDG. In summary, these studies (Table 1) indicate that PET cannot replace histologic surgical staging of the axilla.

FDG-PET AND THE PRIMARY TUMOR

Although early PET trials suggested high sensitivity and specificity, the sensitivity of PET for detecting small breast cancers (< 1 cm) and in situ lesions, such as ductal carcinoma in situ, is low.[32] This may be linked to tumor biology because in situ cancers such as ductal carcinoma in situ may have decreased vascularity and glycolytic activity. In the largest series, the sensitivity was 57% for lesions less than 1 cm compared with 91% for tumors more than 1 cm. For in situ cancers,

Table 1. Tabulated Summary of Studies Assessing Axillary Staging

Study	Year	No. of Patients	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Veronesi et al[15]*	2006	236	37	96	88	66
Gil-Rendo et al[16]*	2006	245	84.5	98.5	98.4	85.6
Chung et al[18]*	2006	51	60	100	—	—
Kumar et al[19]*	2005	80	44	95	—	—
Zornoza et al[20]*	2004	200	84	98	62	79
Lovrics et al[21]*	2004	80	40	97	90	78
Fehr et al[22]	2004	24	20	93	67	62
Wahl et al[23]	2004	360	61	80	62	99
Barranger et al[24]*	2003	32	20	100	—	—
van der Hoeven et al[25]*	2002	70	25	97	63	95
Guller et al[26]*	2002	31	43	94	86	67
Kelemen et al[27]*	2002	15	20	90	50	69
Yang et al[28]	2001	18	50	100	—	—
Schirrmeister et al[17]	2001	117	79	93	82	79
Greco et al[14]	2001	167	94	86	84	95
Yutani et al[29]	2000	38	50	100	100	100
Crippa et al[30]	1998	72	85	91	—	—
Noh et al[31]	1998	27	93	100	—	—
Smith et al[13]	1998	50	90	97	95	95
Crippa et al[12]	1997	82	84	85	—	—

*These studies included a comparison with sentinel lymph node biopsy.

Table 2. Diagnostic Accuracy of FDG-PET Compared With SLNB in 236 Patients

Measure	FDG-PET	SLNB
Sensitivity, %	37	96
Specificity, %	96	100
Positive predictive value, %	88	100
Negative predictive value, %	66	97
Overall accuracy, %	70	98

NOTE. Data adapted.[15]
Abbreviations: FDG-PET, fluorodeoxyglucose-positron emission tomography; SLNB, sentinel lymph node biopsy.

the sensitivity was only 25%. A specific evaluation has been performed in a few studies to consider the uptake of FDG in the primary tumor compared with the uptake in the axilla.[15] In all cases where FDG-PET was negative in the primary carcinoma, the axilla was also PET negative. Because of the demonstrated low sensitivity of PET in the detection of axillary disease, it is uncertain whether FDG negativity on the primary tumor may be considered a good predictive marker. Among 187 patients in the study by Veronesi et al[15] in whom PET was positive for the primary breast tumor, axillary metastases were present in 88 (47%); thus, PET positivity of the primary tumor seemed to be an unfavorable indicator. There are too few studies to draw definitive conclusions on the utility of PET and the primary tumor.

PET AND DISTANT METASTASES

Baseline Staging

In patients with breast cancer, correct staging of the disease is important in guiding patients and physicians towards the most appropriate treatment option. However, in stage I or early stage II disease, the extensive use of imaging studies is not recommended because of the low yield and the cost and distress associated with the need to investigate detected abnormalities, which, for the most part, are false-positive results.[33-35] However, there is limited evidence to support the use of imaging tests in the staging of patients with more advanced cancer at diagnosis, such as locally advanced (including inflammatory) breast cancer.[35]

Three reports have described the use of FDG-PET imaging in the staging of patients with locally advanced breast cancer at the time of diagnosis.[36-38] The number of patients in each study is small (n = 7, n = 17, and n = 48). The detection rates of confirmed metastatic disease are reported as 14%, 12%, and 8%, respectively. The rates of false-positive results in these studies were reported as 0%, 12%, and 21%, respectively. Two additional reports are available that describe the utility of FDG-PET imaging in patients at all disease stages at the time of diagnosis. Schirrmeister et al[17] (n = 117) and Weir et al[39] (n = 84) report the detection of distant metastatic disease in 6% and 5% of patients, respectively. Neither reported false-positive results. Figure 3 illustrates a patient example with unexpected metastases at diagnosis.

FDG-PET is superior to CT in the detection of internal mammary and mediastinal lymph node metastases.[40-42] In studies comparing FDG-PET with CT directly, the overall sensitivity, specificity, and accuracy in the detection of internal mammary and mediastinal lymph node metastases have been demonstrated to be 85%, 90%, and 88%, respectively, for PET compared with 54%, 85%, and 73%, respectively, for CT.[43] The impact of increased sensitivity on staging and the prescription of treatment has not been determined.

Recurrent Disease

Despite advances in breast cancer care, a significant proportion of patients will develop recurrent or metastatic disease. To date, early detection of metastases by repeated conventional imaging tests (CT, ultrasound, and bone scintigraphy) has not been shown to be of benefit over routine follow-up in terms of patient survival.[44] However, the early detection of recurrence may offer the opportunity to begin therapy when the tumor volume is smaller, thus reducing or delaying

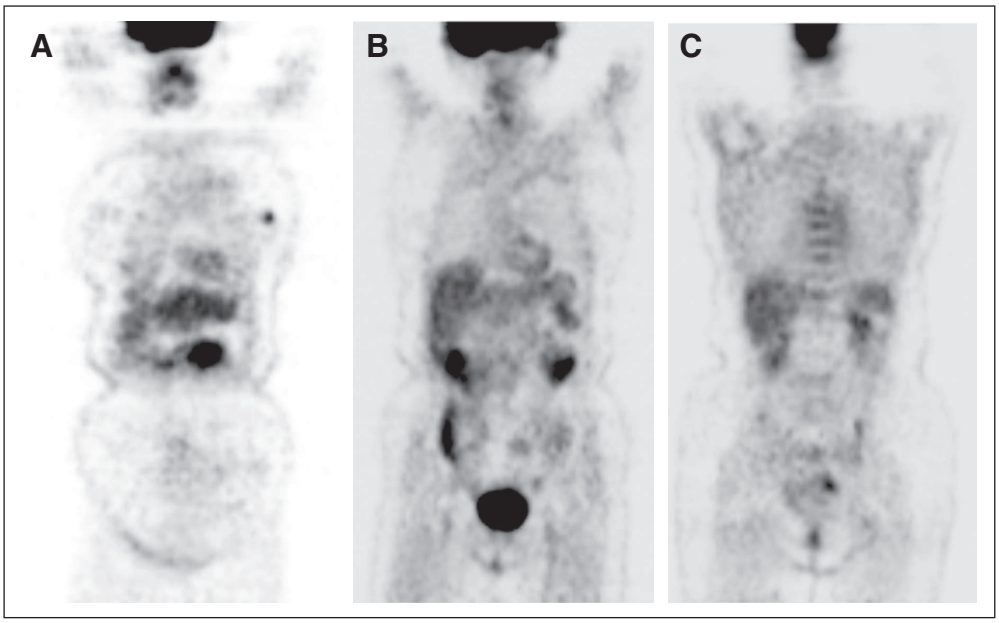

Fig 2. Fluorodeoxyglucose (FDG) -positron emission tomography images showing increased activity in primary tumor with no abnormal accumulation of FDG at axillae, bone, or other organs. Sentinel lymph node biopsy revealed a micrometastatic deposit.

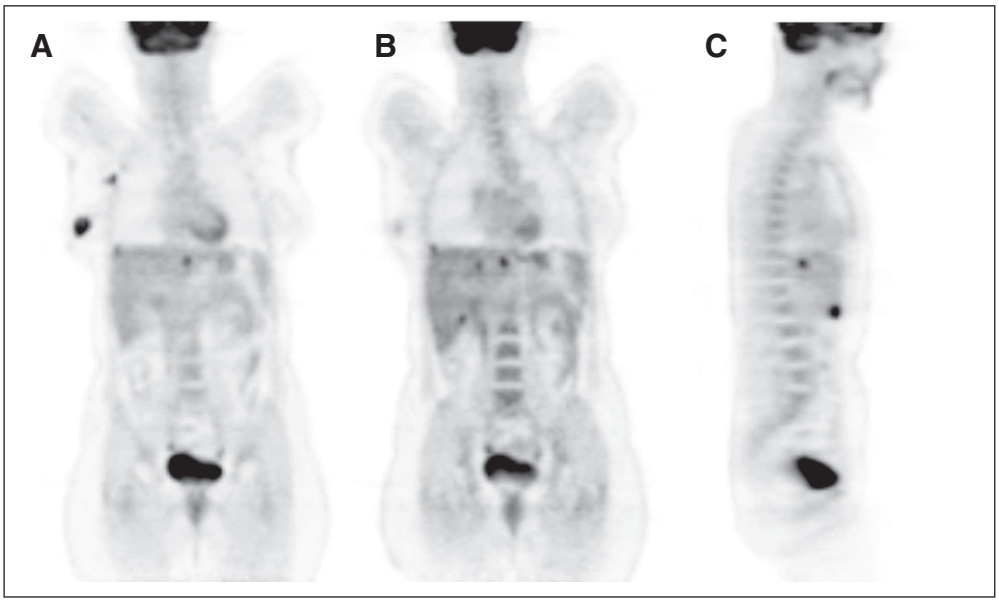

Fig 3. Patient presenting with breast cancer for preoperative staging showing axillary lymph node and liver metastases but no evidence of bone metastases. Fusion imaging demonstrates that axillary activity is localized in a lymph node as opposed to a rib.

tumor-related symptoms. For many tumors, FDG-PET has been shown to be more sensitive than conventional imaging in the detection of recurrent or metastatic malignancy.[45] As a result, FDG-PET has been evaluated by a number of authors regarding the detection of local or distant recurrent breast cancer. Twenty-two studies, describing 1,023 patients, have been identified in this nonsystematic review and are listed in Table 3. A number of these publications were included in a meta-analysis published in 2005.[64] That analysis excluded publications that used modified gamma camera technology; however, those publications have been included in this review because they included a significant proportion (25%) of the patients studied to date.[46,47] Four publications included in the meta-analysis have been excluded from this review[13,38,65,66] because they described a mixture of patient studies, including those performed for primary staging.

All studies, except two describing a total of 144 patients, were retrospective in nature. Dedicated PET technology was used in the majority of studies, and integrated PET/CT technology was used in two of the most recent studies. The prevalence of cancer recurrence in the populations studied ranged from 57% to 93%, indicating that these studies were carried out in populations highly likely to have metastatic disease. In the detection of nodal or distant metastases, sensitivity ranged from 78% to 100%, specificity ranged from 20% to 100%, negative predictive value ranged from 50% to 100%, positive predictive value ranged from 50% to 96%, and accuracy ranged from 80% to 99%. The two publications describing the use of PET/CT technology indicated only a marginal improvement in diagnostic accuracy, reporting sensitivity, specificity, and accuracy rates of 94%, 84%, and 99%[48] and 90%, 71%, and 83%,[49] respectively.

Four of these studies[47,49-51] were conducted on otherwise asymptomatic patients with elevated tumor markers (CA 15-3 and/or carcinoembryonic antigen). In this group of studies, the sensitivity and positive predictive value ranged from 90% to 96% and 84% to 93%, respectively, operating in the high range of the total group of studies.

Table 4 lists the subset of studies that directly compared FDG-PET with various forms of conventional imaging in the same patient. When the parameter evaluated is the detection of disease at any site, FDG-PET is seen to exhibit increased sensitivity, specificity, and accuracy compared with conventional imaging and with CT alone. However, in the detection of bone metastases, the four available studies[52-54,66] provide conflicting information. The sensitivity of FDG-PET in the detection of metastatic sites is noted to be similar in three publications and substantially lower in one publication. In three publications, the specificity of FDG-PET is higher than that of bone scintigraphy, and in one study, the specificity is the same. The presence of conflicting data is not unexpected because breast cancer can cause metastases that are either osteolytic or osteoblastic. Cook et al[68] showed that FDG-PET detected the osteolytic metastases often missed by bone scanning, whereas FDG-PET often missed osteoblastic metastases, for which bone scanning has high sensitivity.

There is one study comparing FDG-PET with magnetic resonance imaging in the detection of local recurrence; it indicates improved sensitivity for FDG-PET but reduced specificity.[55] Overall diagnostic accuracy of the two modalities was comparable, but they seemed to provide complementary information.

Finally, four studies, all retrospective, attempted to assess the effect of FDG-PET on patient management. Three studies obtained this information from chart review,[49,56,57] and one obtained the information from a questionnaire sent to the referring physician at the time of retrospective review.[46] Although management changes were reported in between 32% and 51% of patients, this data should be viewed with caution in view of its retrospective nature and potential for recall bias.

FDG-PET seems to have reasonable sensitivity and specificity in the detection of recurrent and metastatic breast cancer, particularly in the subset of patients presenting with elevated tumor markers. However, in view of the information available regarding disparate results between phosphonate bone scanning and FDG-PET imaging, radionuclide bone scanning remains the most appropriate examination for evaluation of the entire skeleton for bone metastases. It is possible that FDG-PET using modern PET/CT technology might serve as a single additional test to assess patients with suspected metastases for local

Table 3. Summary of Studies Assessing Diagnostic Accuracy of FDG-PET in Disease Recurrence

Study	Year	No. of Patients	Imaging	Study Type	Recurrence						
					Site	Prevalence (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Radan et al[49]	2006	46	Discovery LS PET/CT	R	Distant	65	90	71	80	84	83
Weir et al[39]	2005	27*	ECAT EXACT 47	R	Distant	89	89	88	NC	NC	NC
Fueger et al[48]	2005	58	REVEAL RT PET/CT	R	Distant	57	94	84	91	89	99
Landheer et al[37]	2005	25*	ECAT EXACT	P	Distant	NS	95	20	50	83	NC
Eubank et al[56]	2004	61	GE Advance	R	Distant	82	94	91	77	98	92
Grahek et al[46]	2004	75	PRISM2000/Irix Gamma Camera	R	Distant	76	84	78	61	92	83
Goerres et al[55]	2003	32	GE Advance	P	Local	44	100	72	100	74	84
Kamel et al[58]†	2003	57	GE Advance	R	Distant	70	100	97	100	96	98
					Local	59	89	84	84	89	87
Gallowitsch et al[52]†	2003	62	ECAT ART	R	Distant	55	97	82	96	87	90
					Bone	34	92	92	96	86	92
Lin et al[59]†	2002	36	GE Advance	R	LN	4	80	100	97	100	97
					Distant	11	83	85	89	79	84
					Local	11	100	97	100	80	97
Yang et al[53]†‡	2002	40	ECAT HR+	R	Bone	NS	95	91	80	98	95
Liu et al[50]†	2002	30	ECAT HR+	R	All	93	96	NC	NC	93	90
Suarez et al[51]†	2002	38	ADAC C-PET	R	Distant	68	92	75	82	89	87
Pecking et al[47]	2001	119	GE Varicam Gamma Camera	P	Distant	83	93	30	46	87	82
Eubank et al[42]	2001	33	GE Advance	R	Distant	NS	85	90	NC	NC	88
Kim et al[57]†	2001	27	ECAT EXACT 47	R	Distant	63	94	80	89	89	89
					Local	30	88	100	80	100	92
Ohta et al[54]†	2001	51	ECAT EXACT 47	R	Bone	18	78	98	95	88	94
Lonneux et al[60]†	2000	39	ECAT EXACT HR	R	Distant	85	94	50	60	91	87
Hathaway et al[61]†	1999	10	GE Advance	R	Local	90	100	100	100	100	100
Moon et al[62]†	1998	57	ECAT 931,961	R	Distant	51	93	79	82	92	86
Bender et al[63]†	1997	75	ECAT EXACT 927, 47	R	LN	29	97	91	98	88	93
					Bone	15	100	98	100	94	99
					Lung	6	83	97	99	71	96
					Liver	2	100	97	100	50	97
					Local	27	80	96	93	89	92

Abbreviations: FDG-PET, fluorodeoxyglucose-positron emission tomography; NPV, negative predictive value; PPV, positive predictive value; CT, computed tomography; R, retrospective; NC, not calculable; P, prospective; NS, not stated; LN, lymph node.
*Only assessable patients studied for recurrence have been included.
†Included in 2005 meta-analysis.
‡Determined on the basis of lesions.

recurrence or metastases to organs other than bone. However, prospective randomized controlled trials are required to determine the appropriateness of such an approach compared with the use of conventional imaging. Such a trial or trials could also assess cost effectiveness, the impact on patient management, and the ability of potentially more accurate assessment to reduce tumor-related symptoms.

ASSESSING RESPONSE TO THERAPY

Locally Advanced Breast Cancer

PET may be useful in determining response to therapy in patients with locally advanced breast cancer. A multidisciplinary approach is important in managing patients with locally advanced breast cancer. These patients routinely undergo neoadjuvant chemotherapy, and PET has shown promise in predicting response to therapy.[69] In a study of 22 patients, after an initial course of therapy, all responding (based on SUV changes) tumors were identified through a decrease in SUV of greater than 55% below baseline (sensitivity, 100%; specificity, 85%).[70] Another study of 30 patients used PET at midtherapy assessments and reported a complete response correlating with a 50% to 60% reduction from baseline SUV.[71] A positive PET at the completion of therapy indicates residual macroscopic disease. In this clinical setting, PET may be useful in determining the timing of surgery for nonresponding or chemotherapy-resistant tumors. PET imaging may have future clinical application as an in vivo test for chemotherapy sensitivity. The pretreatment PET imaging may also be important for radiation planning because extent of disease may change for patients responding to chemotherapy.

Metastatic Disease

Although metastatic breast cancer is considered to be an incurable disease, patients who achieve a complete response to chemotherapy have a chance to become long-term survivors.[72,73] The best response to regimens, usually containing a combination of taxanes and anthracyclines, is usually reached after six or more courses of chemotherapy. This means administering treatment that is highly costly, both in terms of toxicity and economic cost, to a percentage of patients who will not benefit from it. The ability to use FDG-PET

Table 4. Summary of Studies Comparing Diagnostic Accuracy of PET With Conventional Imaging in Detection of Recurrent Disease

Study	Conventional Imaging	Site	Conventional Imaging Diagnostic Parameters			PET or PET/CT Diagnostic Parameters		
			Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Radan et al[49]	CT	All	70	47	59	85	76	81
Goerres et al[55]	MRI	Local	79	94	88	100	72	84
Gallowitsch et al[52]	CT, MRI, US, mammography, bone scan	All	84	60	74	97	82	90
	Bone scan (lesion based)	Bone	90	74	87	57	89	63
Yang et al[53]	Bone scan	Bone	93	35	78	95	91	95
Dose et al[66]	CXR, bone scan, US	All	36	95	61	86	90	88
	CXR	Lung	42	100	—	79	90	—
	Bone scan	Bone	89	92	—	83	89	—
	US	Liver	60	95	—	86	98	—
	CXR	MLN	0	100	—	100	100	—
Eubank et al[56]	CT	All	54	85	73	85	90	88
Ohta et al[54]	Bone scan	Bone	78	81	80	78	98	94
Hubner et al[67]	CT	All	71	54	51	85	73	80
Bender et al[63]	CT, MRI	Local	91	98	97	73	96	90
		LN	74	95	88	95	93	94
		Bone	46	98	87	100	96	97
		Lung	83	96	95	83	96	95
		Liver	50	95	91	100	99	99

Abbreviations: PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound; CXR, chest x-ray; MLN, mediastinal lymph node; LN, lymph node.

imaging as a predictive assay for treatment response in the case of metastatic disease has been evaluated by a number of authors.[74-77] Somewhat conflicting results have been described. Both Gennari et al[74] (n = 9) and Dose Schwarz et al[76] (n = 11) observed a decrease in tumor SUV after one or two cycles of chemotherapy in patients who responded to therapy. In each case, there was a trend to longer survival in metabolic responders. The most recent trial by Couturier et al[77] studied 20 patients. A decline in SUV determined from FDG-PET performed after one cycle of therapy was not predictive, but SUV decline after three cycles of therapy was predictive of treatment response and improved overall survival. Visual assessment of the images alone was insufficient to make this determination; SUV calculation was required. Given the small sample sizes and conflicting results presented, there is insufficient information available to recommend that FDG-PET imaging be used to predict treatment response either in the case of locally advanced breast cancer or metastatic disease.

FUTURE OF PET/CT

The literature regarding the application of PET and PET/CT to date is largely representative of the majority of publications in the radiologic field, in that most studies are retrospective and, as such, are not designed to address specific research questions. A search of the clinical trials registry (http://clinicaltrials.gov) identifies six open prospective clinical trials evaluating FDG-PET in breast cancer. Three trials will evaluate preoperative diagnosis with comparison made to pre- and postoperative staging; these trials have planned enrollments of 100, 320, and 400 patients and should contribute significant information regarding the role of preoperative PET. It is highly unlikely that non-invasive PET imaging will replace surgical axillary staging (axillary dissection or SLNB) because overall sensitivity is poor and false negatives are high for lesions less than 1 cm. It is possible, however, that these studies will provide evidence for the use of preoperative PET in a specific subset of patients. Specifically, in the case of positive preoperative PET, triaging patients directly to axillary dissection rather than SLNB is likely to be a strong recommendation.

The remaining three smaller prospective trials will evaluate response to therapy using FDG and other markers, fluorine-labeled estrogen, and iodine-labeled iododeoxyuridine. Breast cancer treatment continues to evolve, with therapies targeted to more specific cell receptors becoming more important. Examples of targeted therapies include tamoxifen for estrogen receptor–positive tumors and trastuzumab for *HER2*-positive tumors. Other targets include epidermal growth factor receptor and angiogenesis factors. More specific PET and single-photon emission CT radiopharmaceuticals that can identify specific targets and predict response to treatment could increase the importance of molecular imaging in the care of patients with breast cancer. Current examples include fluorine-labeled estrogen, which can be useful in measuring response to hormonal therapy. It is crucial that, as these agents are introduced and evaluated, well-designed, prospective, adequately powered clinical trials with well-defined response criteria be used to evaluate the imaging methodology. The failure to properly assess FDG-PET imaging in breast cancer and, indeed, most cancers over the last 10 years has resulted in confusion regarding the role of this technology in medical care and, in many jurisdictions, has delayed its implementation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Nicole C. Hodgson, Karen Y. Gulenchyn
Collection and assembly of data: Nicole C. Hodgson, Karen Y. Gulenchyn
Data analysis and interpretation: Nicole C. Hodgson, Karen Y. Gulenchyn
Manuscript writing: Nicole C. Hodgson, Karen Y. Gulenchyn
Final approval of manuscript: Nicole C. Hodgson, Karen Y. Gulenchyn

REFERENCES

1. Podoloff DA, Advani RH, Alfred C, et al: NCCN task force report: Positron emission tomography (PET)/computed tomography (CT) scanning in cancer. J Natl Compr Canc Netw 5:S1–S22, 2007 (suppl 1)

2. Sloka JS, Hollett PD, Mathews M: A quantitative review of the use of FDG-PET in the axillary staging of breast cancer. Med Sci Monit 13:RA37-RA46, 2007

3. Warburg O: Metabolism of tumors, in: On the Metabolism of Tumors in the Body. London, United Kingdom, Constable, 1930, pp 254-270

4. Hoh CK, Hawkins RA, Glaspy JA, et al: Cancer detection with whole-body PET using 2-[18F]fluoro-2-deoxy-D-glucose. J Comput Assist Tomogr 17: 582-589, 1993

5. Beyer T, Townsend DW, Brun T, et al: A combined PET/CT scanner for clinical oncology. J Nucl Med 41:1369-1379, 2000

6. Tunis SR, Londner MS, Burken M, et al: Decision memo for positron emission tomography scanner technology (CAG-00090N). Baltimore, MD, Center for Medicare and Medicaid Services, June 29, 2001

7. Delbeke D, Coleman RE, Guiberteau MJ, et al: Procedure Guideline for SPECT/CT Imaging 1.0. J Nucl Med 47:1227-1234, 2006

8. Young H, Baum R, Cremerius U, et al: Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations—European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 35:1773-1782, 1999

9. Lyman GH, Giuliano AE, Somerfield MR, et al: American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 23:7703-7720, 2005

10. Chao C, McMasters K: The current status of sentinel lymph node biopsy for breast cancer. Adv Surg 36:167-192, 2002

11. Fleissig A, Fallowfield LJ, Langridge CI, et al: Post-operative arm morbidity and quality of life: Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 95:279-293, 2006

12. Crippa F, Agresti R, Donne VD, et al: 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 83:542-543, 1997

13. Smith IC, Ogston KN, Whitford P, et al: 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 228:220-227, 1998

14. Greco M, Crippa F, Agresti R, et al: 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 93:630-635, 2001

15. Veronesi U, De Cicco C, Galimberti VE, et al: A comparative study on the value of FDG-PET and sentinel node. Ann Oncol 18:473-478, 2007

16. Gil-Rendo A, Zornoza G, Garcia-Velloso MJ, et al: Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. Br J Surg 93:707-712, 2006

17. Schirrmeister H, Kuhn T, Guhlmann A, et al: Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: Comparison with the standard staging procedures. Eur J Nucl Med 28:351-358, 2001

18. Chung A, Liou D, Karlan S, et al: Preoperative FDG-PET for axillary metastases in patients with breast cancer. Arch Surg 141:783-788, 2006

19. Kumar R, Zhuang H, Schnall M, et al: FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. Nucl Med Commun 27:231-236, 2006

20. Zornoza G, Garcia-Velloso MJ, Sola J, et al: 18F-FDG PET complemented with sentinel lymph node biopsy in the detection of axillary involvement in breast cancer. Eur J Surg Oncol 30:15-19, 2004

21. Lovrics PJ, Chen V, Coates G, et al: A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer. Ann Surg Oncol 11:846-853, 2004

22. Fehr MK, Hornung R, Varga Z, et al: Axillary staging using positron emission tomography in breast cancer patients qualifying for sentinel lymph node biopsy. Breast J 10:89-93, 2004

23. Wahl RL, Siegel BA, Coleman RE, et al: Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: A report of the Staging Breast Cancer With PET Study Group. J Clin Oncol 22:277-285, 2004

24. Barranger E, Grahek D, Antoine M, et al: Evaluation of fluorodeoxyglucose positron emission tomography in the detection of axillary lymph node metastases in patients with early-stage breast cancer. Ann Surg Oncol 10:622-627, 2003

25. van der Hoeven JJ, Hoekstra OS, Comans EF, et al: Determinants of diagnostic performance of [F-18]fluorodeoxyglucose positron emission tomography for axillary staging in breast cancer. Ann Surg 236:619-624, 2002

26. Guller U, Nitzsche E, Moch H, et al: Is positron emission tomography an accurate non-invasive alternative to sentinel lymph node biopsy in breast cancer patients? J Natl Cancer Inst 95:1040-1043, 2003

27. Kelemen PR, Lowe V, Phillips N: Positron emission tomography and sentinel lymph node dissection in breast cancer. Clin Breast Cancer 3:73-77, 2002

28. Yang JH, Nam SJ, Lee TS, et al: Comparison of intraoperative frozen section analysis of sentinel node with preoperative positron emission tomography in the diagnosis of axillary lymph node status in breast cancer patients. Jpn J Clin Oncol 31:1-6, 2001

29. Yutani K, Shiba E, Kusuoka H, et al: Comparison of FDG-PET with MIBI-SPECT in the detection of breast cancer and axillary lymph node metastasis. J Comput Assist Tomogr 24:274-280, 2000

30. Crippa F, Agresti R, Seregni E, et al: Prospective evaluation of fluorine-18-FDG PET in presurgical staging of the axilla in breast cancer. J Nucl Med 39:4-8, 1998

31. Noh DY, Yun IJ, Kim JS, et al: Diagnostic value of positron emission tomography for detecting breast cancer. World J Surg 22:223-227, 1998

32. Avril N, Rose CA, Schelling M, et al: Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: Use and limitations. J Clin Oncol 18:3495-3502, 2000

33. Ravaioli A, Pasini G, Polselli A, et al: Staging of breast cancer: New recommended standard procedure. Breast Cancer Res Treat 72:53-60, 2002

34. Myers RE, Johnston M, Pritchard K, et al: Baseline staging tests in primary breast cancer: A practice guideline. CMAJ 164:1439-1444, 2001

35. Puglisi F, Follador A, Minisini AM, et al: Baseline staging tests after a new diagnosis of breast cancer: Further evidence of their limited indications. Ann Oncol 16:263-266, 2005

36. Baslaim MM, Bakheet SM, Bakheet R, et al: 18-Fluorodeoxyglucose-positron emission tomography in inflammatory breast cancer. World J Surg 27:1099-1104, 2003

37. Landheer ML, Steffens MG, Klinkenbijl JH, et al: Value of fluorodeoxyglucose positron emission tomography in women with breast cancer. Br J Surg 92:1363-1367, 2005

38. van der Hoeven JJ, Krak NC, Hoekstra OS, et al: 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. J Clin Oncol 22:1253-1259, 2004

39. Weir L, Worsley D, Bernstein V: The value of FDG positron emission tomography in the management of patients with breast cancer. Breast J 11: 204-209, 2005

40. Bernstein V, Jones A, Mankoff DA: Assessment of internal mammary lymph nodes by fluorodeoxyglucose positron emission tomography (FDG-PET) in medial hemisphere breast cancer. J Nucl Med 41:289, 2000 (abstr)

41. Bellon JR, Livingston RB, Eubank WB, et al: Evaluation of the internal mammary lymph nodes by FDG-PET in locally advanced breast cancer (LABC). Am J Clin Oncol 27:407-410, 2004

42. Eubank WB, Mankoff DA, Takasugi J, et al: 18-Fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. J Clin Oncol 19:3516-3523, 2001

43. Wu D, Gambhir SS: Positron emission tomography in diagnosis and management of invasive breast cancer: Current status and future perspectives. Clin Breast Cancer 4:S55–S63, 2003 (suppl 1)

44. The GIVIO Investigators: Impact of follow-up testing on survival and health-related quality of life in breast cancer patients: A multicenter randomized controlled trial. JAMA 271:1587-1592, 1994

45. Hoh CK, Schiepers C, Seltzer MA, et al: PET in oncology: Will it replace other modalities? Semin Nucl Med 27:94-106, 1997

46. Grahek D, Montravers F, Kerrou K, et al: [18F]FDG in recurrent breast cancer: Diagnostic performances, clinical impact and relevance of induced changes in management. Eur J Nucl Med Mol Imaging 31:179-188, 2004

47. Pecking AP, Mechelany-Corone C, Bertrand-Kermorgant F, et al: Detection of occult disease in breast cancer using fluorodeoxyglucose camera-based positron emission tomography. Clin Breast Cancer 2:229-234, 2001

48. Fueger BJ, Weber WA, Quon A, et al: Performance of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography and integrated PET/CT in restaged breast cancer patients. Mol Imaging Biol 7:369-376, 2005

49. Radan L, Ben-Haim S, Bar-Shalom R, et al: The role of FDG-PET/CT in suspected recurrence of breast cancer. Cancer 107:2545-2551, 2006

50. Liu CS, Shen YY, Lin CC, et al: Clinical impact of [(18)F]FDG-PET in patients with suspected recurrent breast cancer based on asymptomatically elevated tumor marker serum levels: A preliminary report. Jpn J Clin Oncol 32:244-247, 2002

51. Suarez M, Perez-Castejon MJ, Jimenez A, et al: Early diagnosis of recurrent breast cancer with FDG-PET in patients with progressive elevation of serum tumor markers. Q J Nucl Med 46:113-121, 2002

52. Gallowitsch HJ, Kresnik E, Gasser J, et al: F-18 fluorodeoxyglucose positron-emission tomography in the diagnosis of tumor recurrence and metastases in the follow-up of patients with breast carcinoma: A comparison to conventional imaging. Invest Radiol 38:250-256, 2003

53. Yang SN, Liang JA, Lin FJ, et al: Comparing whole body (18)F-2-deoxyglucose positron emission tomography and technetium-99m methylene diphosphonate bone scan to detect bone metastases in patients with breast cancer. J Cancer Res Clin Oncol 128:325-328, 2002

54. Ohta M, Tokuda Y, Suzuki Y, et al: Whole body PET for the evaluation of bony metastases in patients with breast cancer: Comparison with 99Tcm-MDP bone scintigraphy. Nucl Med Commun 22:875-879, 2001

55. Goerres GW, Michel SC, Fehr MK, et al: Follow-up of women with breast cancer: Comparison between MRI and FDG PET. Eur Radiol 13:1635-1644, 2003

56. Eubank WB, Mankoff D, Bhattacharya M, et al: Impact of FDG PET on defining the extent of disease and on the treatment of patients with recurrent or metastatic breast cancer. Am J Roentgenol 183:479-486, 2004

57. Kim TS, Moon WK, Lee DS, et al: Fluorodeoxyglucose positron emission tomography for detection of recurrent or metastatic breast cancer. World J Surg 25:829-834, 2001

58. Kamel EM, Wyss MT, Fehr MK, et al: [18F]-fluorodeoxyglucose positron emission tomography in patients with suspected recurrence of breast cancer. J Cancer Res Clin Oncol 129:147-153, 2003

59. Lin WY, Tsai SC, Cheng KY, et al: Fluorine-18 FDG-PET in detecting local recurrence and distant metastases in breast cancer: Taiwanese experiences. Cancer Invest 20:725-729, 2002

60. Lonneux M, Borbath I, Berliere M, et al: The place of whole-body PET FDG for the diagnosis of distant recurrence of breast cancer. Clin Positron Imaging 2:45-49, 2000

61. Hathaway PB, Mankoff DA, Maravilla KR, et al: Value of combined FDG PET and MR imaging in the evaluation of suspected recurrent local-regional breast cancer: Preliminary experience. Radiology 210:807-814, 1999

62. Moon DH, Maddahi J, Silverman DH, et al: Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med 39:431-435, 1998

63. Bender H, Kirst J, Palmedo H, et al: Value of 18fluoro-deoxyglucose positron emission tomography in the staging of recurrent breast carcinoma. Anticancer Res 17:1687-1692, 1997

64. Isasi CR, Moadel RM, Blaufox MD: A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat 90:105-112, 2005

65. Rostom AY, Powe J, Kandil A, et al: Positron emission tomography in breast cancer: A clinicopathological correlation of results. Br J Radiol 72:1064-1068, 1999

66. Dose J, Bleckmann C, Bachmann S, et al: Comparison of fluorodeoxyglucose positron emission tomography and "conventional diagnostic procedures" for the detection of distant metastases in breast cancer patients. Nucl Med Commun 23:857-864, 2002

67. Hubner KF, Smith GT, Thie JT, et al: The potential of F-18-FDG PET in breast cancer: Detection of primary lesions, axillary lymph node metastases, or distant metastases. Clin Positron Imaging 3:197-205, 2003

68. Cook GJ, Houston S, Rubens R, et al: Detection of bone metastases in breast cancer by 18FDG PET: Differing metabolic activity in osteoblastic and osteolytic lesions. J Clin Oncol 16:3375-3379, 1998

69. Krak NC, Hoekstra OS, Lammertsma AA: Measuring response to chemotherapy in locally advanced breast cancer: Methodological considerations. Eur J Nucl Med Mol Imaging 31:S103–S111, 2004 (suppl 1)

70. Schelling M, Avril N, Nahrig J, et al: Positron emission tomography using [(18)F]fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. J Clin Oncol 18:1689-1695, 2000

71. Smith IC, Welch AE, Hutcheon AW, et al: Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. J Clin Oncol 18:1676-1688, 2000

72. Falkson G, Holcroft C, Gelman RS, et al: Ten-year follow-up study of premenopausal women with metastatic breast cancer: An Eastern Cooperative Oncology Group study. J Clin Oncol 13:1453-1458, 1995

73. Rahman ZU, Frye DK, Smith TL, et al: Results and long term follow-up for 1581 patients with metastatic breast carcinoma treated with standard dose doxorubicin-containing chemotherapy: A reference. Cancer 85:104-111, 1999

74. Gennari A, Donati S, Salvadori B, et al: Role of 2-[18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) in the early assessment of response to chemotherapy in metastatic breast cancer patients. Clin Breast Cancer 1:156-161, 2000

75. Stafford SE, Gralow JR, Schubert EK, et al: Use of serial FDG PET to measure the response of bone-dominant breast cancer to therapy. Acad Radiol 9:913-921, 2002

76. Dose Schwarz J, Bader M, Jenicke L, et al: Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG PET. J Nucl Med 46:1144-1150, 2005

77. Couturier O, Jerusalem G, N'Guyen JM, et al: Sequential positron emission tomography using [18F]fluorodeoxyglucose for monitoring response to chemotherapy in metastatic breast cancer. Clin Cancer Res 12:6437-6443, 2006