



TITLE: **Positron Emission Tomography (PET) for the Evaluation of Breast Lesions for Diagnosis of Breast Cancer**

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POSITRON EMISSION TOMOGRAPHY FOR THE EVALUATION OF BREAST LESIONS FOR DIAGNOSIS OF BREAST CANCER

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of Positron Emission Tomography (PET) for evaluating breast cancer in clinical practice. Specifically, we will review the evidence for the use of the glucose analog, 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) as a tracer in PET imaging for (1) the evaluation of breast lesions for diagnosis of breast cancer and (2) staging axillary lymph nodes. Subsequent reviews will focus on the detection of locoregional recurrence or distant metastases/recurrence and the evaluation of response to chemotherapy.

BACKGROUND

Breast cancer

In 2002, there were an estimated 203,500 new cases of invasive breast cancer in the United States and an estimated 40,000 deaths from this cancer. This represents approximately 31% of all new cancer cases in women and 15% of all cancer deaths in women (2002;ACS 2002). In addition to invasive breast cancer, 54,300 new cases of in situ breast cancer were estimated to be diagnosed in women in 2002. Cancer of the breast is the most common form of cancer in women. The average American woman is estimated to have a 1 in 8 chance of developing breast cancer at some time during her life.

Most patients with breast cancer present with the complaint of a breast mass or an abnormal screening mammogram. A fine-needle aspiration, core needle biopsy, or open surgical biopsy can be used to obtain a definitive tissue diagnosis of breast cancer.

Once breast cancer has been diagnosed, staging depends on assessment of both the tumor size and regional lymph node involvement. A patient's prognosis is directly related to the initial stage of her breast cancer. Prior to the initial surgical management of breast cancer and after making a tissue diagnosis of breast cancer, the patient undergoes a clinical staging evaluation.

BACKGROUND, continued

Breast cancer (continued)

This includes bilateral mammography (to evaluate for synchronous cancer), a complete physical examination, chest radiography, and liver function tests. Further testing is done only if abnormalities are found during this evaluation.

Based on this presurgical evaluation the patient is assigned a clinical stage for her breast cancer using the TNM staging system (AJCC 1997) of the American Joint Committee on Cancer (Table 1). This classification describes tumor size (T), node involvement (N), and evidence of metastasis (M). Initial treatment options are then determined using the presurgical tumor stage. Patients with early stage invasive cancers (defined as stage I or II) usually undergo some form of local surgical excision to completely remove the tumor.

Table 1: TNM Staging for Breast Cancer

Tumor:	Tis	Carcinoma in situ
	T0	No evidence of primary tumor
	T1	Tumor ≤ 2 cm
	T2	Tumor > 2 cm but ≤ 5 cm
	T3	Tumor > 5 cm
	T4	Tumor with direct extension to chest wall or skin
Nodes:	N0	No regional node metastases
	N1	Metastases to ipsilateral axillary nodes, mobile
	N2	Metastases to ipsilateral axillary nodes, fixed
	N3	Metastases to ipsilateral internal mammary nodes
Metastases:	M0	No distant metastases
	M1	Metastases present
Stage:	0	Tis, N0, M0
	I	T1, N0, M0
	II A	T0 or T1, N1, M0 or T2, N0, M0
	II B	T2, N1, M0 or T3, N0, M0
	III A	T0 or T1 or T2, N2, M0 or T3, N1 or N2, M0
	III B	Any T, N3 M0 or T4, Any N, M0
	IV	Any T, any N, M1

BACKGROUND, continued

Breast cancer (continued)

Options for surgical management of the primary tumor include breast-conserving therapy with radiation therapy, mastectomy plus reconstruction, and mastectomy alone. Surgical staging of the axilla is usually performed. Survival is equivalent with any of these options as documented in randomized prospective trials and meta-analyses of the trials (1995; van Dongen *et al.* 2000; Fisher *et al.* 2002; Veronesi *et al.* 2002). Selection of a local therapeutic approach depends on the location and size of the lesion, analysis of the mammogram, breast size, and the patient's attitude toward preserving the breast. The presence of multi-focal disease in the breast or a history of collagen vascular disease are relative contraindications to breast-conserving therapy (Abrams *et al.* 1995).

Initial diagnosis of breast cancer

Screening mammography has improved the detection of primary breast cancer. However, the majority of abnormalities identified on screening mammography and referred for biopsy are benign (Consensus 1997). Estimates of the proportion of biopsies that are negative for cancer range from 70 to 90% (Meyer *et al.* 1990; Bassett *et al.* 1991; Thompson *et al.* 1991). Concern about the number of biopsies resulting from false positive mammograms has stimulated efforts to improve the selection of patients referred for biopsy diagnosis.

Mammographic findings are usually reported according to the Breast Imaging Reporting and Data System (BI-RADS) criteria established by the American College of Radiology. BI-RADS classifies the results into 5 categories (ACR 1995).

- 1 Normal mammogram
- 2 Benign finding
- 3 Probably benign finding
- 4 Suspicious abnormality
- 5 Highly suggestive of malignancy

BACKGROUND, continued

Initial diagnosis of breast cancer (continued)

In a recent study of 688 biopsies (Lacquement *et al.* 1999), 47% were BI-RADS category 3, 34% were BI-RADS category 4, and 15% were BI-RADS category 5. Only 3% of the biopsies for category 3 were positive for cancer compared to 23% for category 4 and 92% for category 5. Similar findings were reported in other series (Lieberman *et al.* 1998; Orel *et al.* 1999).

Needle biopsy techniques provide a minimally invasive alternative to conventional surgical biopsy for many patients. Nevertheless, undergoing a breast biopsy may be psychologically difficult for the patient and the scarring resulting from a biopsy may complicate future mammographic evaluation of that area of the breast. Thus, FDG PET imaging has been proposed as an additional diagnostic test following a suspicious mammogram in order to reduce the number of breast biopsies.

Positron Emission Tomography

Positron emission tomography (PET) is an imaging technology that can reveal both anatomical and metabolic information in various tissue sites. The metabolic information is what distinguishes it from other imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) that provide primarily anatomic information. PET uses organic compounds labeled with positron-emitting isotopes as radiotracers. Several radiotracers have been used in cancer imaging, but by far the most common is the glucose analog FDG. Once injected into a patient, it is metabolized in both normal and malignant tissue in proportion to the rate of glucose metabolism. FDG is potentially useful in cancer imaging because tumor cells show increased utilization of glucose (Wahl 1998).

After injection, PET tracer isotopes undergo a process of decay, emitting positrons that lose energy as they pass through tissue and combine with electrons. During this reaction, the total mass is converted into energy that is released in the form of two high-energy photons. A detection device registers the photons simultaneously and localizes the annihilation event (Mandelkern *et al.* 2002).

BACKGROUND, continued

Positron Emission Tomography, (continued)

After the patient fasts for at least 4 hours, a dose of FDG is injected intravenously. A transmission scan is performed either before tracer injection or after FDG imaging with an external ring of a positron-emitting isotope to allow for correction of photon attenuation. Attenuation corrected PET images provide better data for quantitative analysis and qualitative interpretation. However the correction has not been consistently available in clinical investigations using PET. Image acquisition usually begins 30-60 minutes after injection of FDG and lasts 10-20 minutes. Scanning can be focused on one area of the body or performed over the whole body.

The most common method of PET image analysis is visual interpretation, which is qualitative and based on recognition of areas of increased tracer uptake relative to background. Quantitative interpretation begins after the operator draws a region of interest (ROI) over the suspicious area, sometimes based on other imaging. Tracer uptake counts within the ROI are usually corrected for injected dose and body weight. Quantitative indices mentioned in published reports include: standardized uptake value (SUV); distribution absorption ratio (DAR); differential uptake ratio (DUR); tumor-to-normal tissue (TNT) ratio; and regional metabolic rate of glucose (rMRglu). Tracer uptake varies across different types of tissue and some quantitative indices compare uptake in the suspicious area with “normal background” uptake in either a contralateral comparison site or a predetermined distal site common to all patients.

Quantitative interpretation would be expected to be more precise and possibly more accurate than qualitative interpretation because it relies less on operator judgment. With quantitative analysis, the criterion for interpretation of a positive test is a numerical value along a continuous function. A threshold can be established for a particular quantitative index to separate benign from malignant lesions based on the desired sensitivity or specificity.

BACKGROUND, continued

Systematic reviews of diagnostic tests

Guidelines for the systematic assessment of studies of diagnostic tests have been developed (Irwig *et al.* 1994; Cochrane 1996). They emphasize the importance of the following in order to assess study quality:

- Gold standard: Was a valid reference standard used?
- Blinding: Were both the test and the reference standard assessed without knowledge of the results of the other test?
- Was verification bias (test results influence performance of the reference standard) avoided?
- Was the spectrum of disease adequately described for both disease and non-disease?
- Were patient characteristics adequately described?
- Were the details of how the test was performed described including interpretation and estimates of reproducibility?
- Was the study design prospective or retrospective?

For the studies evaluated in this review, PET technique was classified as either qualitative and/or quantitative and whether attenuation correction was employed. Verification bias was considered to have been avoided if consecutively enrolled patients were imaged with PET, the reference standard was obtained independent of the results of the PET study, and all enrolled patients were included in the final analysis. Blinding of the readings of PET and the reference standard with respect to each other was also recorded. A study was considered to be high quality if data were collected prospectively, verification bias was avoided, and the assessment of PET and the reference standard were blinded.



TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate regulatory bodies.

There are several manufacturers of PET scanners that have received FDA clearance for marketing. FDG is considered by the FDA as a drug that is safe and effective for the evaluation of glucose metabolism in malignancy. Due to the short half-life of this radiotracer it is frequently produced in the clinical setting. The FDA intends to regulate PET centers for production of FDG and other radiotracers.

TA criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The literature search found 21 studies of the test characteristics of PET when used to evaluate suspicious breast lesions. Five of the articles were not included in this summary as the participants appeared to overlap with those included in later reports from the same institution (Tse *et al.* 1992; Adler *et al.* 1993; Avril *et al.* 1996; Avril *et al.* 1997; Yutani *et al.* 1999). The 16 remaining studies (Hoh *et al.* 1993; Nieweg *et al.* 1993; Crowe *et al.* 1994; Bassa *et al.* 1996; Scheidhauer *et al.* 1996; Kole *et al.* 1997; Palmedo *et al.* 1997; Noh *et al.* 1998; Rostom *et al.* 1999; Avril *et al.* 2000; Murthy *et al.* 2000; Yutani *et al.* 2000; Brix *et al.* 2001; Brix *et al.* 2001; Schinmeister *et al.* 2001; Rieber *et al.* 2002; Levine *et al.* 2003) are summarized in Tables 2 (Methods) and Table 3 (Results). One systematic review and meta-analysis of this topic (Samson *et al.* 2002) summarizes the data from 13 of the 16 studies included in Table 1. There were no studies comparing the management and outcome of women with suspicious lesions who received PET with those who did not receive PET.

The 16 studies included a total of 679 patients. Four studies (Palmedo *et al.* 1997; Noh *et al.* 1998; Avril *et al.* 2000; Levine *et al.* 2003) used the lesion as the unit of analysis (n=207 patients, 256 lesions) while 12 studies used the patient as the unit of analysis (n=472 patients) The study design was prospective in 12 studies, retrospective in 3 studies, and unclear in 1.

TA Criterion 2, continued

Sensitivity estimates in the studies ranged from 79% to 100% and specificity estimates were between 50% and 100%. Samson et al performed a meta-analysis (Samson *et al.* 2002) that included 13 of the 16 studies and 606 of the 679 patients found in this literature search. Using a random effects model, the pooled estimate of sensitivity was 88% (95% CI 83%-92%) and the pooled estimate of specificity was 79% (95% CI 71%-85%). They could not perform the planned sensitivity analysis based on high quality studies as only one (Yutani *et al.* 2000) was prospective, free of verification bias, and used blinded interpretation of PET. Addition of the 3 studies (Brix *et al.* 2001; Rieber *et al.* 2002; Levine *et al.* 2003) published since the meta-analysis was performed is unlikely to change the estimates substantially. The new studies would add only about 10% more patients and the estimates of sensitivity and specificity in these studies were similar to the pooled estimates of the meta-analysis.

It was difficult to assess the quality of the studies because the publications often omitted the information needed to make the assessment (Table 2). Five studies were free of verification bias, but 11 did not provide enough information to make a determination. In 8 studies, it was clear that the interpreters of PET images were blinded to the reference standard results; in one study they were not blinded; and in the remaining 7 studies it was unclear. Only 1 of the 16 studies mentioned whether investigators who assessed the reference standard were blinded to PET results.

The patient populations in these studies of PET for the differential diagnosis of breast lesions have a much higher prevalence of malignancy than that reported for the general population. Only one small study had a prevalence of less than 50% (Levine *et al.* 2003) and the pooled average was 76%. Most studies in the literature report between 20 to 30% of biopsies are positive for cancer (Meyer *et al.* 1990; Bassett *et al.* 1991; Thompson *et al.* 1991). This apparent bias of the spectrum of disease is further supported by the fact that the mean tumor size in the study was relatively large (2-4 cm).



The published studies that are available omit a critical segment of the biopsy population: those with indeterminate mammograms and small non-palpable lesions. The sensitivity of PET in such patients, compared with patients who have suspicious mammograms or palpable masses, might be as high, but is likely to be lower. Volume averaging becomes a significant issue when evaluating smaller masses. In the absence of evidence in this important segment of the population, it is not possible to generalize from the study populations to those with prevalence of malignancy lower than 50%. Thus, there is no evidence here to evaluate the utility of PET for avoiding biopsy in patients presenting with mamographically identified lesions classified as BIRADS category 3 or 4 (prevalence of cancer 3% and 23% respectively) (Lacquement *et al.* 1999).

TA criterion 2 is not met.

Level of evidence: 3

Table 2: Methodologic characteristics of studies of PET for the evaluation of suspicious breast lesions

Reference	N	Design	Patient selection	Mean Age (y)	Mean tumor Size (cm)	PET interpretation	AC	Reference standard	Verification bias avoided	PET blinded to RS	RS blinded to PET
Levine 2003 Winston-Salem, NC	16, 18L	Prospective	Suspicious mammogram	57	1	Semi-quantitative	Yes	Histology	Yes	No	Yes
Rieber 2002 Munich, Germany	43	Prospective	BIRADS 5 by palpation, MM, or US	52.9	T2 (2-5 cm, med), 67%>2cm	Qualitative	No	Histology	?	Yes	?
Brix 2001 Heidelberg, Germany	14	Prospective	Palpable breast mass, suspicious Mammogram or U/S. Lesion> 1 cm	49	67%>2cm	Quantitative	Yes	Histology	Yes	?	?
Schirrmeister 2001 Ulm, Germany	117	Prospective	Palpable breast mass, suspicious Mammogram or U/S	56.8	-	Qualitative	No	Histology	?	Yes	?
Avril 2000 Munich, Germany	144, 185 L	Prospective	Palpable breast mass, suspicious Mammogram or U/S	50.6 (10.3)	3.1 (2.1)	Qualitative	Yes	Histology	?	Yes	?
Murthy 2000 Montreal, Canada	16	Prospective	Suggestive mass	54.8 (med)	-	Qualitative; semi-quantitative	No	Histology	?	?	?
Yutani 2000 Osaka, Japan	40	Prospective	Consecutive patients with suspicious Lesions on PE, MM, US	50.9 (13.4)	2.1 (1.0)	Qualitative	Yes	Histology	Yes	Yes	?
Rostom 1999 Saudi Arabia	93	Retrospective	Consecutive patients attending breast clinic	40.3	-	Qualitative	Yes (50% (86%), FNAB)	Histology (14%)	Yes	Yes	?
Noh 1998	27, 31L	?	Breast mass, had both PET and pathology data	-	2.0 (med)	?	Yes	Histology (96%), FNAB	?	?	No

Reference	N	Design	Patient selection	Mean Age (y)	Mean tumor Size (cm)	PET interpretation	AC	Reference standard	Verification bias avoided	PET blinded to RS	RS blinded to PET
Seoul, South Korea								(4%)			
Kole 1997	13	Prospective	Palpable mass or abnormal Mammogram	-	3.8 (2.3)	Quantitative	Yes In 7	Histology	?	?	?
Groningen, Netherlands											
Palmedo 1997	20, 22L	Prospective	Palpable mass or abnormal Mammogram	58.4	2.8 (1.6)	Qualitative, quantitative	Yes	Histology	?	Yes	?
Bonn, Germany											
Bassa 1996	16	Retrospective	Consecutive patients with locally Advanced BC to receive neoadjuvant Chemotherapy	43.8 (9.5)	-	Qualitative	Yes	Histology	Y	?	?
Houston, Texas											
Scheidhauer 1996	30	Prospective	Surgery scheduled for suspicion of BC based on palpation, MM, US	57	-	Qualitative	Yes	Histology	?	Yes	?
Cologne, Germany											
Crowe 1994	37	Prospective	Breast lesion \geq 1 cm on palpation or MM	55 (14)	2.9 (1.5)	Qualitative	Yes	Histology	?	Yes	?
Cleveland, Ohio											
Hoh 1993	34	Retrospective	Had whole body PET and Biopsy data	-	-	Qualitative	No	Histology	?	?	?
Los Angeles, CA											
Nieweg 1993	19	Prospective	Mixed	49.0 (med)	3.6 (2.8)	?, AC		Histology	?	?	?
Houston, Texas											

Table 3: Results of studies of PET for the evaluation of suspicious breast lesions

Reference	N	Prevalence of disease (%)	Sensitivity (%)	Specificity (%)	Comments
Levine 2003 Winston-Salem, North Carolina	16, 18L	39	86	89	Novel device: dedicated breast PET
Rieber 2002 Munich, Germany	43	100	93	-	Spectrum bias, all BIRADS 5, all + histology
Brix 2001 Heidelberg, Germany	14	64	89	60	
Schirrmeister 2001 Ulm, Germany	117	76	93	75	
Avril 2000 Munich, Germany	144, 185 L	71	64	94	Second set of numbers use "sensitive" vs. conventional PET. Sensitivity dependent on size of tumor: T1 tumors 68%, T2 tumors 92%.
Murthy 2000 Montreal, Canada	16	71	80	100	
Yutani 2000 Osaka, Japan	40	95	79	100	
Rostom 1999 Saudi Arabia	93	81	91	83	

Reference	N	Prevalence of disease (%)	Sensitivity (%)	Specificity (%)	Comments
Noh 1998	27, 31L	71	100	89	
Seoul, South Korea					
Kole 1997	13	77	100	67	
Groningen, Netherlands					
Palmedo 1997	20, 22L	71	80	83	
Bonn, Germany					
Bassa 1996	16	94	100	100	
Houston, Texas					
Scheidhauer 1996	30	77	91	86	
Cologne, Germany					
Crowe 1994	37	70	100	100	
Cleveland, Ohio					
Hoh 1993	34	76	92	75	
Los Angeles, California					
Nieweg 1993	19	58	91	100	
Houston, Texas					

TA Criterion 3: The technology must improve the net health outcomes.

In order to be used to avoid biopsy, PET should provide a highly sensitive evaluation for malignancy. The rate of false-negative PET results weighs heavily in considering whether the risk of delayed or missed diagnosis of breast cancer is worth the benefit of avoiding biopsy of a benign lesion. Women who test negative on PET would be expected to delay biopsy and thus have a later diagnosis of their breast cancer and potentially a worse prognosis. The benefits would primarily accrue to women who test negative and thus avoid a biopsy. We can use the summary estimate from the meta-analysis to calculate the number of women in each of these two categories. The numbers will depend on the prevalence of disease in the population being studied. For the studies summarized, the pooled prevalence of breast cancer is 76%. Using a sensitivity of 88% and specificity of 79%, the proportion of all women tested who have a negative PET, but harbor cancer is 9.1%. This is offset by the 19% of all women tested who avoid biopsy. Is it worth avoiding biopsy in 19% of women at a cost of 9% of the women having a delayed diagnosis?

How does this look from the perspective of a woman with a mammographic lesion who is evaluated with PET? If she tests positive, she must have a biopsy and gets no benefit from PET. She may have lost a few days in making the final diagnosis, but this should not greatly affect prognosis. If she tests negative, either she has cancer or she is one of the women who avoided biopsy. What is the probability that she has cancer, given that she has tested negative? It is the proportion of women with cancer among those who have a negative test: $9.1\% / (19.0\% + 9.1\%) = 32.5\%$. Will the woman and her physicians be comfortable not proceeding with a biopsy when there is a 32% chance that the lesion is malignant? Most women would probably opt for a biopsy; thus nothing will have been gained with PET, as few biopsies will be avoided.

Table 4: Estimates of potential benefits, harms and negative predictive value for a range of estimates for the prevalence of cancer , sensitivity and specificity of PET

Prevalence*	Sensitivity	Specificity	False negatives†	True negatives‡	NPV
0.6	88.0%	79.0%	7.2%	31.6%	18.6%
0.7	88.0%	79.0%	8.4%	23.7%	26.2%
0.76	88.0%	79.0%	9.1%	19.0%	32.5%
0.8	88.0%	79.0%	9.6%	15.8%	37.8%
0.25	88.0%	79.0%	3.0%	59.3%	4.8%
0.25	80.0%	79.0%	5.0%	59.3%	7.8%
0.25	68.0%	79.0%	8.0%	59.3%	11.9%
0.25	50.0%	79.0%	12.5%	59.3%	17.4%

* Prevalence of malignancy at biopsy of suspicious breast lesions. In the studies of PET it was 76%; population base studies range from 20-30%.

† Potential harms: the percentage of all women having PET who test negative but have a malignant breast lesion.

‡ Potential benefits: the percentage of all women having PET who test negative and do not have a malignant breast lesion.

NPV Negative predictive value: the percentage of women with a negative PET who have a malignant breast lesion.

These numbers are very sensitive to the prevalence of disease in the population being studied. As the prevalence goes down, the number of false positives will go down as well (Table 3). In population-based studies, it appears that the prevalence of cancer in all breast biopsies is between 20% and 30% (Meyer *et al.* 1990; Bassett *et al.* 1991; Thompson *et al.* 1991). If we use the same sensitivity and specificity, 59% of women receiving PET will avoid a biopsy and only 3% of women with cancer will have a negative PET scan; 5% of all women with negative tests will have malignant lesion. However, as noted above, the estimate of sensitivity derived from the studies in Tables 1 and 2 is only valid in populations with a prevalence of cancer > 50% and overestimates the sensitivity of PET for small lesions. Avril *et al.* noted that even using a modification of conventional PET to enhance sensitivity, the sensitivity for T1 tumors (< 2 cm) was 68%, much lower than the 92% sensitivity for T2 tumors (2-5 cm) (Avril *et al.* 2000). If the true sensitivity is 68%, then 12% of women from the same population who test negative on PET will have cancer in the lesion.

TA Criterion 3, continued

It is important to note that there are no data on the sensitivity or specificity of PET in populations with a prevalence of 20-30%, so we are unable to make estimates of benefits or harms for this population with any confidence. The known limitations of PET at imaging small areas due to volume averaging effects has led some investigators to develop a device specific to the breast which has better spatial resolution (Levine *et al.* 2003).

TA criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

At this time, there are no accepted alternatives for avoiding biopsy, once it has been recommended. However, the technology has not been shown to improve net health outcomes.

TA criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational setting

PET is generally performed at institutions that have considerable expertise in the imaging modality. However, there is no agreed upon approach to imaging breast lesions with PET. Many different protocols were used at the various institutions represented in the publications reviewed. No improvements have been documented in the investigational setting, so it remains unclear whether improvements will be attainable outside the investigational setting.

TA criterion 5 is not met.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCB SA)

The BCBSA last reviewed the use of FDG PET for the diagnosis and staging of breast cancer in 2001 and determined that BCBSA TEC criteria were not met.

Centers for Medicare and Medicaid Services

CMS made the determination on October 1, 2002 that FDG PET would be considered reasonable and necessary as an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with locoregional recurrence or metastasis; as an adjunct to standard imaging modalities for monitoring tumor response to treatment for women with locally advanced and metastatic breast cancer when a change in therapy is anticipated.

CMS will continue to have a national noncoverage policy for the use of FDG PET for the initial diagnosis of breast cancer and the staging of axillary lymph nodes as noted in CMS National Coverage Analysis as of January 24, 2003.

American Society of Breast Surgeons

The Society does not have a formal position or opinion on the use of PET and was not able to send a representative to the meeting.

California Radiological Society

The Society does not have a formal opinion on the use of PET for this indication. The CRS was not able to provide representation at the meeting.

Association of Northern California Oncologists

The Association does not have a formal position on the use of FDG PET for breast cancer but has indicated that they agree with the CMS position regarding the use of this technology as an adjunct to other imaging modalities for staging and restaging local/regional breast cancer recurrence or metastasis.



RECOMMENDATIONS OF OTHERS, continued

Medical Oncology Association of Southern California

The MOASC Board of Directors endorses the CMS coverage position. The Association will not be sending representation to the meeting.

American College of Surgeons, California Chapter

The College chapter does not have a formal position or opinion on the use of PET for this indication. The ACS will not be able to provide a representative to the meeting.

Society of Nuclear Medicine

The Society does not have a formal position regarding the use of PET for this indication has been asked to provide representation at the meeting.

American Society of Therapeutic and Radiation Oncology

The Society has been asked to provide a position statement and representation at the meeting.

CONCLUSION

Studies of PET for the evaluation of suspicious breast lesions included women with suspicious mammograms or palpable masses. The population studied had a notably higher prevalence of malignancy (76%) than that reported in the general population (20%-30%). The studied population also had relatively large average tumor size at initial diagnosis. No published studies are available on the diagnostic performance of PET on a more representative population. This group consists of patients with indeterminate mammograms and smaller, non-palpable lesions. Without evidence on the diagnostic performance of PET in the lower portion of the biopsy population, no conclusions can be reached. Given that the test characteristics are likely to be different, it is not prudent to generalize from the available studies.

Sixteen studies including 679 patients were identified. The prevalence of malignancy ranged from 39% to 100% compared with 20% to 30% in the general population. Sensitivity estimates in the studies ranged from 79% to 100% and specificity estimates were between 50% and 100%. Samson et al performed a meta-analysis that included 13 of the 16 studies and 606 of the 679 patients found in this literature search. Using a random effects model, the pooled estimate of sensitivity was 88% (95% CI 83%-92%) and the pooled estimate of specificity was 79% (95% CI 71%-85%).

In order to avoid biopsy, PET must be highly sensitive or else the harm from false negative results causing a delay in the diagnosis of malignancy will outweigh the benefit. Using the sensitivity and specificity values from the meta-analysis, the estimates of the proportion of women testing negative who have cancer ranged from 5% to 48%. The only examples with the negative predictive value below 10% are those with a low prevalence of malignancy. There are no studies available to assess the sensitivity of PET in this population, but the sensitivity is likely to be lower because volume-averaging effects are large when evaluating small volumes. At lower sensitivities, the negative predictive value is again greater than 10%.

There is no evidence on the diagnostic performance of PET for the evaluation of suspicious breast lesions in populations with a low prevalence of malignancy. Furthermore, PET is likely to be less sensitive in that population than in the high prevalence populations that have been studied. Among patients with a higher prevalence of malignancy, the risk of a false-negative diagnosis is too high relative to the benefit of avoiding the biopsy of a benign lesion.



RECOMMENDATION

FDG PET for the evaluation of suspicious breast lesions does not meet California Technology Assessment Forum TA criteria.

The California Technology Assessment Forum voted to accept the recommendation as stated.

June 11, 2003

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