



TITLE: **Positron Emission Tomography (PET) for
the Evaluation of Breast Lesions for
Staging Axillary Lymph Nodes**

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POSITRON EMISSION TOMOGRAPHY FOR THE EVALUATION OF BREAST LESIONS FOR STAGING AXILLARY LYMPH NODES

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: Axillary Lymph Node Staging

In patients with an initial diagnosis of breast cancer, staging evaluation of the axillary lymph nodes is used to define prognosis and to determine appropriate therapy. In addition to providing information on nodal status, axillary lymph node dissection (ALND) may be therapeutic: removing tumor-involved nodes may improve local control. This hypothesis is being investigated by ongoing clinical trials. Results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial did not find that axillary dissection improves survival, although the data were insufficient to rule out the possibility of a small, but clinically meaningful benefit (Rokkette *et al.* 1982).

The presence of tumor in the axillary nodes frequently influences the decision to use adjuvant systemic chemotherapy or hormonal therapy. Furthermore, the number of positive axillary nodes influences the selection of more aggressive treatment. The presence of 4 or more positive axillary nodes may indicate the need for radiation therapy. However, the evidence on axillary node status and treatment is evolving.

BACKGROUND, continued

Breast cancer: Axillary Lymph Node Staging (continued)

Chronic lymphedema is common following ALND and strategies for reducing the morbidity of axillary node staging are being developed (Ververs *et al.* 2001; Burak *et al.* 2002; Golshan *et al.* 2003). Sentinel node biopsy, a more limited surgical approach to axillary lymph node staging, has been introduced as an alternative surgical technique. More recently, PET has been proposed as a non-invasive method for determining the presence of axillary lymph node involvement and for selecting patients for ALND.

Adjuvant chemotherapy or hormonal therapy

Adjuvant systemic therapy has been reported to reduce recurrence and improve survival in patients with breast cancer. Improved outcomes occur in patients with positive axillary nodes and also in patients without axillary involvement. However, the absolute reduction in recurrence rate or mortality is greater for those with axillary nodal disease. Compared to patient without axillary involvement, node-positive patients are at greater baseline risk of recurrence and disease related mortality and thus have greater potential for benefit (Henderson 1994). In 1992, the Early Breast Cancer Trialists' Collaborative Group published an overview of 133 randomized clinical trials on the effect of adjuvant chemotherapy or hormonal therapy (EBCTCG 1992).

Women with positive axillary nodes reduced the odds of recurrence by about a third and reduced the odds of dying with either chemotherapy or hormonal therapy. Median survival was increased about 2 years compared with controls. For premenopausal women < 50, the absolute differences in 10-year survival are 12% for disease-free survival and 10% for overall survival. A separate analysis including all age groups found a 6.8% absolute difference in 10-year survival associated with chemotherapy.

For postmenopausal women older than age 50 with positive nodes, tamoxifen reduces the odds of recurrence by at least 29% and the odds of death by at least 20%. Absolute differences in 10-year survival rates are 9% for disease free survival and 7% for overall survival (EBCTCG 1992). For women without nodal disease, chemotherapy was associated with a 29% reduction in the odds of recurrence and a 16% reduction in the odds of death. The absolute difference in 10-year survival was 4%.



BACKGROUND, continued

Adjuvant chemotherapy or hormonal therapy (continued)

Similarly, tamoxifen was associated with a 27% reduction in the odds of recurrence, a 17% reduction in the odds of death, and an absolute difference in 10-year survival of 3.5% (EBCTCG 1992).

Decisions on the use of adjuvant therapy in patients with node-negative disease is complicated by uncertainties in balancing potential benefits and toxicity of systemic therapy, as well as by variation in patient preferences (Fisher 1999). Axillary node status is essential information needed to estimate the absolute benefits that a patient may receive from adjuvant therapy.

Sentinel Node Biopsy (SNB)

Sentinel node biopsy is an emerging technology that has been used as an alternative to complete ALND in patients requiring axillary staging. SNB may be an attractive alternative to ALND as the surgery is less extensive and there is a lower risk of chronic lymphedema in the arm on the affected side.

While there is uncertainty about whether axillary lymph node dissection produces therapeutic benefit, its potential morbidity is well established. The morbidity depends on the extent of removal of lymph nodes, which are categorized into three levels: I (most superficially located), II, and III (most deeply located). Most staging axillary lymph node dissections involve removal of at least 10 nodes from levels I and II, which is called a partial ALND. Reported procedure related morbidity from partial ALND varies. Chronic lymphedema is estimated to occur in 8-25% of patients with half of patients experiencing chronic pain. Other adverse effects of axillary lymph node dissection include wound complications (8%) and limitations in shoulder movement (2%). Major complications such as injury to axillary motor nerves or the axillary vein are infrequent (Ververs *et al.* 2001; Burak *et al.* 2002; Swenson *et al.* 2002; Golshan *et al.* 2003; Schijven *et al.* 2003).



BACKGROUND, continued

Sentinel Node Biopsy (SNB) (continued)

Sentinel node biopsy uses a tracer injected into the breast tissue around the primary tumor, which drains through the lymphatics towards the axilla. The earliest lymph node identified by the tracer is designated the “sentinel” node. The sentinel node is surgically removed and directly analyzed for the presence of tumor. It is postulated that the absence of tumor in the sentinel node can reliably predict the absence of tumor in the axilla. Unlike axillary node dissection, SNB does not seem to be associated with the development of chronic lymphedema and has very low morbidity (Burak *et al.* 2002; Swenson *et al.* 2002; Golshan *et al.* 2003; Schijven *et al.* 2003).

Commonly used tracers include a blue dye that is visible to the surgeon and/or a radioactive colloid that can be detected with a gamma camera for overall imaging or a hand held gamma detector probe for localization. Both tracers have been used in the available studies of SNB.

Several systematic reviews of the diagnostic performance of SNB have been performed. The specificity, by definition, is always 100%, as a positive result on SNB is based on the pathologic finding of cancer in the sentinel node. The two published meta-analyses report summary sensitivities of 95% (Miltenburg *et al.* 1999) and 91% (Fraile *et al.* 2000). A more extensive review performed by the BCBSA TEC reported their summary estimate of the sensitivity to be 89% (95% CI 86%-91%). The NCI consensus statement concluded that before SLN can replace axillary lymphadenectomy, randomized trials are needed to confirm that both procedures yield comparable survival rates.



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 population for this review includes patients with confirmed primary breast malignancy without palpable axillary lymph node metastases and no evidence of distant metastases. Patients with palpable lymphadenopathy would likely undergo axillary node dissection even if the results of PET were negative. The reference standard for axillary lymph node status is ALND. The proposed role for PET is to allow patients who are candidates for breast conserving surgery and who have negative PET results to avoid ALND.

Patients would benefit from PET if the scan correctly suggests no lymph node spread, as the patient could avoid the pain and other potential complications associated with ALND. True positive results on PET would not result in additional benefit since patients would still undergo ALND and received accurate staging diagnosis. False negative PET results would be associated with potential harm as the patient would not have the benefit of accurate staging information and might not receive adjuvant systemic therapy for node-positive disease. Such under treatment would reduce the probability of 10-year survival by about 8% or by about 2 years on average. In addition, a patient with a false-negative PET who does not undergo ALND would not drive any therapeutic benefit from removing the involved lymph nodes.

TA Criterion 2, continued

The literature search found 24 studies of the test characteristics of PET when used to stage the axilla prior to surgery for breast cancer. 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; Crowe *et al.* 1994; Crippa *et al.* 1998; Yutani *et al.* 1999). The 19 remaining studies (Hoh *et al.* 1993; Avril *et al.* 1996; Bassa *et al.* 1996; Scheidhauer *et al.* 1996; Utech *et al.* 1996; Adler *et al.* 1997; Palmedo *et al.* 1997; Noh *et al.* 1998; Smith *et al.* 1998; Rostom *et al.* 1999; Ohta *et al.* 2000; Yutani *et al.* 2000; Greco *et al.* 2001; Schirrmeister *et al.* 2001; Yang *et al.* 2001; Guller *et al.* 2002; Kelemen *et al.* 2002; Rieber *et al.* 2002; van der Hoeven *et al.* 2002) are summarized in Tables 5 (Methods) and Table 6 (Results). 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 19 studies included a total of 965 patients. Three studies (Adler *et al.* 1997; Noh *et al.* 1998; Ohta *et al.* 2000) used the region as the unit of analysis (n=106 patients, 114 regions) while 16 studies used the patient as the unit of analysis (n=859 patients) The study design was prospective in 14 studies, retrospective in 3 studies, and unclear in 2.

It was difficult to assess the quality of the studies because the publications often omitted the information needed to make the assessment (Table 5). Seven studies were free of verification bias, one was not, but 11 did not provide enough information to make a determination. In 14 studies, it was clear that the interpreters of PET images were blinded to the reference standard results and in the remaining 5 studies it was unclear. Only 2 of the 16 studies reported that investigators who assessed the reference standard were blinded to PET results, 2 studies reported that they were not blinded, and there was no information given for the remaining 15 studies.



TA Criterion 2, continued

The population that needs to be studied in order to answer the question about the utility of PET in avoiding ALND is patients without clinical evidence of lymph node involvement (stage cN0). Only 6 of the 19 studies provided information on the diagnostic performance of PET in patients without palpable axillary lymph nodes (Crowe *et al.* 1994; Smith *et al.* 1998; Greco *et al.* 2001; Ohta *et al.* 2001; Guller *et al.* 2002; Kelemen *et al.* 2002). These include 249 of the 965 patients studied.

TA criterion 2 is met.

Level of evidence: 3

Table 5: Methodologic characteristics of studies of PET for the staging of axillary lymph nodes

Reference	N	Design	Patient selection	Mean Age (SD), y	Mean tumor Size (SD), cm	PET Interpretation	AC	Verification bias avoided	blinded to RS	RS blinded to PET
Guller 2002 Basel, Switzerland	31	Prospective	Invasive breast cancer. No palpable LN (cN0 100%)	64.8	T1 61% T2 39%	?	?	Yes	Yes	?
Van der Hoeven 2002 Amstelveen, Netherlands	70	Prospective	Operable breast cancer. 47 SNB, 23 ALND cN0(71%), cN+(29%)	58 (13)	2.3 (1.1)	Qualitative	Yes	Yes	Yes	Yes
Kelemen 2002 St. Louis, MO	15	Prospective	Invasive breast cancer. No palpable LN (cN0 100%). SNB 100%.	60 (med)	1.5 (med)	Qualitative	Yes	Yes	Yes	Yes
Rieber 2002 Munich, Germany	40	Prospective	BIRADS 5 by palpation, MM, or US	52.9	T2 (2-5 cm, med), 67%>2cm	Qualitative	No	?	Yes	No
Greco 2001 Milan, Italy	167	Prospective	T1/T2 breast cancer scheduled to receive ALND.	54.0	2.1 T1 59% T2 41%	Qualitative	Yes	Yes	Yes	?
Schirrmester 2001 Ulm, Germany	113	Prospective	Palpable breast mass, suspicious Mammogram or U/S	56.8	-	Qualitative	No	?	Yes	?
Yang 2001 Seoul, South Korea	18	?	Breast cancer, underwent ALND. cN0(94%), cN+(6%)	44.7	3.5 (2.0)	Quantitative	No	?	?	?

Reference	N	Design	Patient selection	Mean Age (SD), y	Mean tumor Size (SD), cm	PET Interpretation	AC	Verification bias avoided	PET blinded to RS	RS blinded to PET
Ohta 2000 Isehara, Japan	32 33R	Prospective	Breast cancer with PET, US, ALND in 30, node sampling in 1. cN0(70%), cN+(30%)	50.0 (med)	-	Qualitative	Yes	?	?	?
Yutani 2000 Osaka, Japan	38	Prospective	Consecutive patients with suspicious lesions on PE, MM, US.	50.9 (13.4)	2.1 (1.0)	Qualitative	Yes	Yes	Yes	?
Rostom 1999 Saudi Arabia	74	Retrospective	Consecutive patients attending breast clinic, pathology + cancer	40.3	-	Qualitative	Yes (50%)	Yes	Yes	?
Noh 1998 Seoul, South Korea	24, 27R	?	Breast cancer	-	2.0 (med)	?	Yes	?	?	No
Smith 1998 Aberdeen, Scotland	50	Prospective	Breast cancer. cN0(70%), cN+(30%)	67.0	T1 20% T2 42% T3 18% T4 20%	Qualitative	No	?	Yes	?
Adler 1997 Cleveland, Ohio	50 52R	Prospective	Operable breast cancer, PET available, ALND, Tumor > 5 mm	-	T1 61% T2 33% T3 6%	Qualitative	No	?	Yes	?
Palmedo 1997 Bonn, Germany	20	Prospective	Palpable mass or abnormal Mammogram: cN0(65%), cN+(35%)	58.4	2.8 (1.6)	Qualitative, quantitative	Yes	?	Yes	?
Avril 1996 Munich, Germany	51	Prospective	Operable breast cancer. cN0(55%), cN+(45%)	49.9 (10.3)	-	Qualitative	Yes	?	Yes	?
Bassa 1996	16	Retrospective	Consecutive patients with	43.8	T2 12%	Qualitative	Yes	Yes	?	?

Reference	N	Design	Patient selection	Mean Age (SD), y	Mean tumor Size (SD), cm	PET Interpretation	AC	Verification bias avoided	PET blinded to RS	RS blinded to PET
Houston, Texas		e	locally advanced BC to receive neoadjuvant chemotherapy: cN0(13%), cN+(87%)	(9.5)	T3 50% T4 38%					
Scheidhauer 1996 Cologne, Germany	18	Prospective	Surgery scheduled for suspicion of BC based on palpation, MM, US	57	-	Qualitative	Yes	?	Yes	?
Utech 1996 Peoria, Illinois	124	Prospective	Breast cancer. cN0(64%), cN+(36%)	59.0	T1 67% T2 29% T3 4%	Qualitative	Yes	?	Yes	?
Hoh 1993 Los Angeles, CA	14	Retrospective	Had whole body PET and biopsy data	-	-	Qualitative	No	?	?	?

Table 6: Results of studies of PET for the staging of axillary lymph nodes

Reference	N	Prevalence of disease		Sensitivity (%)	Specificity (%)	Comments
		(%)				
Guller 2002	31	45		43	94	PET cN0
Basel, Switzerland						
Van der Hoeven 2002	70	46		25	97	PET
Amstelveen, Netherlands						
Kelemen 2002	15	33		20	90	PET cN0
St. Louis, MO						
Rieber 2002	40	50		80	95	PET
Munich, Germany						
Greco 2001	167	43		94	86	PET
		33		93	87	PET cN0
Milan, Italy		79		97	75	PET cN+
Schirrmeister 2001	113	30		79	92	PET
Ulm, Germany						
Yang 2001	18	33		50	100	PET
Seoul, South Korea						
Ohta 2000	32	61		70	100	PET
	33R	43		40	100	PET cN0
Isehara, Japan		100		100	100	PET cN+
Yutani 2000	38	42		50	100	PET
Osaka, Japan						
Rostom 1999	74	66		86	100	PET
Saudi Arabia						

Reference	N	Prevalence of disease		Sensitivity (%)	Specificity (%)	Comments
		(%)				
Noh 1998	24, 27R	56		93	100	PET
Seoul, South Korea						
Smith 1998	50	42		90	97	PET
		28		90	96	PET cN0
Aberdeen, Scotland		79		91	100	PET cN+
Adler 1997	50 52R	38		95	66	PET
Cleveland, Ohio						
Palmedo 1997	20	30		83	100	PET
Bonn, Germany						
Avril 1996	51	47		79	96	PET
		33		33	100	PET pT1
Munich, Germany		78		94	100	PET >pT1
Bassa 1996	16	81		77	100	PET
Houston, Texas						
Scheidhauer 1996	18	50		100	89	PET
Cologne, Germany						
Utech 1996	124	35		100	75	PET
Peoria, Illinois						
Hoh 1993	14	64		67	100	PET
Los Angeles, CA						



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

In order to be used to avoid ALND, Pet should provide a highly sensitive evaluation for axillary node involvement. The rate of false-negative PET results is the most important factor when considering whether the risk of under treatment by forgoing adjuvant therapy is worth the benefit of avoiding axillary node dissection. Breast cancer tumors in general do not appear to be as metabolically active as melanomas or lung cancers, thus they have lower uptake of FDG, leading to concerns about low sensitivity of PET for breast cancer detection.

Among patients with nonpalpable nodes, the sensitivity in individual studies ranged from 20% to 93% and the specificity ranged from 87% to 100%. The summary sensitivity from a random-effects meta-analysis was 74% (95% CI 56%-94%) and the summary specificity was 91% (95% CI 86%-95%). Note that the width of the confidence interval for sensitivity is almost 40 percentage points in contrast to the 5-percentage point width for SNB. This reflects both the wide range in estimates of sensitivity from the 6 studies and the relatively small sample sizes. If all studies are included (adding in some patients with clinically palpable axillary nodes), the summary sensitivity for PET is 79% (95% CI 70%-84%) and the summary specificity is 89% (95% CI 83%-93%).

Knowing the sensitivity, specificity, and prevalence of disease, we can estimate the potential benefits of PET (women without axillary node involvement who avoid ALND) and the potential harms (women who have axillary node disease who are under-treated because the PET scan is negative). We can also estimate the likelihood that a woman with a negative PET has occult axillary disease (negative predictive value of the test). The pooled prevalence for patients without palpable lymphadenopathy was 35% and ranged from 28% to 45%. This is consistent with published estimates of 30% to 50% in early breast cancer. Assuming a sensitivity of 74% and a specificity of 91%, 59% of women tested with PET would appropriately avoid ALND, but 9.1% of women tested would inappropriately not undergo ALND. Of all women testing negative, 13.3% would actually have positive axillary lymph nodes. If the actual prevalence were as high as 50%, 22% of the women with a negative PET would have axillary node disease.



TA Criterion 3, continued

The available body of evidence is too sparse to draw any firm conclusions regarding the diagnostic performance of PET for staging of axillary lymph node metastases. In addition, no studies reported on whether PET was able to predict the extent of nodal involvement (≥ 4 nodes), which could be useful in selecting patients for radiation therapy.

TA criterion 3 is not met.

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

Sentinel lymph node biopsy is a technique currently under intensive investigation as an alternative to ALND. Three of the studies reviewed included information on patients who received both PET and SNB (Guller *et al.* 2002; Keleman *et al.* 2002; van der Hoeven *et al.* 2002). In all three studies, the sensitivity of PET was less than 50% when compared with SNB. There is a larger body of literature on the utility of SNB for evaluation of the axilla in early breast cancer with evidence of a better sensitivity of specificity than PET. Furthermore, PET 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 found at that time 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. The ASBS has been asked to provide representation at the meeting.

California Radiological Society

The Society indicated that they do not have a formal position on the use of PET for this indication. The CRS has been asked 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 and has been asked to provide representation at the meeting.

American College of Surgeons, California Chapter

The College does not have a formal position or opinion and has been asked to provide representation at the meeting.

Society of Nuclear Medicine

The Society does not have a position regarding the use of PET for this indication. The SNM 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

19 studies including 965 patients were identified. Among patients with nonpalpable nodes, the sensitivity in individual studies ranged from 20% to 93% and the specificity ranged from 87% to 100%. The summary estimate of sensitivity from a random-effects meta-analysis was 74% and the summary estimate of specificity was 91%. If all studies are included, the summary sensitivity is 79% (95% CI 70%-84%) and the summary specificity is 89% (95% CI 83%-93%).

Most studies of PET for the staging of axillary lymph nodes included patients with palpable lymph nodes. Patients with palpable lymphadenopathy would undergo ALND even if the PET scan were negative as the sensitivity of PET is not 100% for either primary tumors or involved lymph nodes. Only six studies presented data specifically on the diagnostic performance of PET in patients with clinically node negative disease.



CONCLUSION, continued

Given the limited data on PET in this population, the 95% confidence interval for the estimate of sensitivity is wide (56% to 94%), especially when compared to a comparable estimate for sentinel node biopsy (86% to 91%). The low sensitivity of PET is likely due to a combination of the limited spatial resolution of the technique resulting in volume averaging and the fact that breast tumors tend to be less metabolically active than other tumors, resulting in less uptake of FDG.

In order to avoid ALND, 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 11% to 22%. This is unacceptably high. Given the relatively low sensitivity of PET with limited data in the population of interest and the availability of sentinel node biopsy, an alternative with better test characteristics, it is unlikely that FDG PET will prove useful for the staging of axillary lymph nodes in women with operable breast cancer.

RECOMMENDATION

FDG PET for the staging of axillary lymph nodes in breast cancer 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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