

Impact of Whole-Body ^{18}F -FDG PET on Staging and Managing Patients with Breast Cancer: The Referring Physician's Perspective

Cecelia S. Yap, Marc A. Seltzer, Christiaan Schiepers, Sanjiv S. Gambhir, Jyotsna Rao, Michael E. Phelps, Peter E. Valk, and Johannes Czernin

Ahmanson Biological Imaging Center/Nuclear Medicine Clinic, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, University of California, Los Angeles; and Northern California PET Imaging Center, Sacramento, California

FDG PET has emerged as an important clinical imaging modality for diagnosing and staging cancer. However, the impact of FDG PET on staging and managing patients with breast cancer from the referring physician's point of view is unknown. **Methods:** The referring physicians of 160 breast cancer patients received standardized questionnaires inquiring if and how PET findings altered their patient's stage and their clinical management decisions. Management changes were classified as intermodality if the change was from one modality to another (e.g., medical to surgical, surgical to radiation, medical to no treatment, and vice versa) or as intramodality if the change was within the same modality (e.g., altered medical or radiotherapy approach). **Results:** Fifty of the 160 surveys were completed (31% response rate). PET changed the clinical stage in 36% of patients (28% upstaged, 8% downstaged) and resulted in intermodality changes in 28% of patients and intramodality changes in 30% of patients. **Conclusion:** The results of this prospective survey show that FDG PET has a major impact on the management of breast cancer patients, influencing both clinical stage and management in more than 30% of patients.

Key Words: PET; breast cancer; staging; survey

J Nucl Med 2001; 42:1334–1337

Although lung cancer has surpassed breast cancer as the leading cause of cancer deaths in American women since 1987, breast cancer alone is expected to account for 182,800, or nearly one third, of all new female cancer cases this year. It is also estimated that breast cancer will account for 15% of cancer mortality among American women (1).

As with other cancers, management decisions are complex and are often affected by the judgment of the physician and by the desires of the patient. Accurate staging is therefore critical to determining the best therapeutic approach for breast cancer patients.

PET with ^{18}F -FDG detects metabolic alterations that occur in malignant tumor cells. Compared with normal tissues, neoplastic cells have an increased glucose metabolism (2–5), the extent of which correlates with the aggressiveness of tumor growth (2,6). Because oxidative metabolism is nearly absent, tumor cells rely on glucose metabolism to meet the energy requirements of rapidly dividing tissues. Markedly accelerated rates of the hexose monophosphate shunt result in large amounts of ribose-6-phosphate, which provides the carbon backbone for DNA and RNA synthesis in tumor cells. These alterations can be imaged and detected with FDG PET (2–5).

Several studies have shown that FDG PET detects and stages breast cancer with a high diagnostic accuracy (7–11). FDG PET has also been used to monitor the effects of treatment in these patients (12,13). However, whether PET findings alter the clinical stage and cause referring physicians to change the management of their patients are unknown. This prospective survey was designed to determine the impact of whole-body FDG PET imaging on the staging and management of breast cancer patients from the referring physician's perspective.

MATERIALS AND METHODS

Referring Physicians and Patients

The referring physicians of 160 breast cancer patients who underwent whole-body FDG PET at the Ahmanson Biological Imaging Center/Nuclear Medicine Clinic of the University of California, Los Angeles (UCLA) ($n = 115$; 72%) and the Northern California PET Imaging Center, Sacramento, CA (NCPIC) ($n = 45$; 28%), between October 1998 and August 2000 were surveyed. Completed questionnaires were received from 32 referring physicians for 50 patients (age range at PET, 30–79 y; mean age \pm SD, 57 ± 12 y). Thirty-eight (76%) of these patients were referred to UCLA and 12 (24%) to the NCPIC.

Image Acquisition and Reconstruction

The patients were instructed to fast for at least 6 h before PET imaging (14). Emission scans of the body starting 45 min after intravenous administration of approximately 555 MBq (15 mCi) FDG were acquired for 6–9 bed positions (6 min per bed position)

Received Dec. 12, 2000; revision accepted Apr. 9, 2001.

For correspondence or reprints contact: Johannes Czernin, MD, Ahmanson Biological Imaging Center/Nuclear Medicine Clinic, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, AR-259 CHS, Los Angeles, CA 90095-6948.

for each patient. Scanning was performed using an EXACT or HR+ system (CTI, Knoxville, TN/Siemens Medical Systems, Inc., Hoffman Estates, IL). The resolution of reconstructed images is approximately 8–12 mm for these devices (15–17). The acquired image sets were displayed in transaxial, coronal, and sagittal planes and were evaluated clinically along with the 3-dimensional projection images on a computer screen. At UCLA, images were reconstructed using standard filtered backprojection without attenuation correction (18). At the NCPIC, iterative image reconstruction algorithms were used and transmission scans were obtained so that attenuation-corrected images were also available for evaluation (19,20).

Image Interpretation

The clinical PET images were interpreted and the corresponding PET reports generated on the basis of all available clinical information. Quantitative or semiquantitative analysis of FDG uptake in lesions, such as region-of-interest analysis or calculation of standardized uptake value, was not performed because such analyses are not part of the protocol for routine interpretation of clinical images at either of the institutions involved.

The impact of PET imaging on patient management was evaluated through pre-PET and post-PET questionnaires (21), which were sent as a single fax to the referring physicians, along with the official interpretive PET report, within 1 wk of the PET study. This simple, straightforward approach was chosen to minimize the administrative burden for referring physicians and to increase the likelihood of response. The pre-PET portion of the questionnaire asked physicians to specify the clinical stage of each patient. The updated scheme of the American Joint Committee on Cancer (22) on TNM staging of breast cancer was attached to the questionnaire. Further, the pre-PET questionnaire asked about the intended management plan before PET. The post-PET questionnaire asked if PET caused any changes in the cancer stage and patient management. Further, the referring physicians were asked to specify the management changes prompted by the PET findings.

When the completed surveys were received, the PET-induced management changes were classified as intermodality changes, intramodality changes, or no change in modality. Intermodality changes refer to alterations from one treatment modality to another, such as from surgery to radiation therapy or from medical treatment to no treatment. Intramodality changes encompass those that were made within a treatment modality, such as from one chemotherapeutic agent to another, and those that involved adding or removing a chemotherapeutic agent.

RESULTS

One hundred sixty patients with breast cancer were referred to the 2 study centers for whole-body PET. Thirty-two different physicians responded to the survey, and 50 completed questionnaires were received, resulting in a response rate of 31% (38/115, or 33%, for patients scanned at UCLA; 12/45, or 27%, for patients scanned at the NCPIC).

The specialties of the responders were as follows: medical oncologists (63%), surgeons (16%), radiation oncologists (6%), and general practitioners (16%). The distribution of specialties did not differ significantly between the physicians who responded and those who did not or between the 2 institutions involved.

Whole-body FDG PET was ordered most frequently for more accurate staging of breast cancer (52%). In fact, all these patients were referred for restaging. In 16% of the patients, PET was ordered for a more accurate diagnosis. Monitoring the course of disease (14%), monitoring therapy (8%), and a combination of 2 or more of the above reasons (8%) accounted for the indications in the remaining patients. The referring physician of 1 patient (2%) did not provide an answer. The clinical indications for PET did not differ significantly between the 2 study centers or between responders and nonresponders.

PET resulted in changes in clinical stage in 36% of the patients. The disease was upstaged for 14 (28%) and downstaged for 4 (8%). PET did not result in changes in clinical stage in 60% of the patients. The referring physicians of the remaining 2 patients (4%) did not respond to this question. The PET-induced changes in stage are listed in Table 1.

PET resulted in intermodality management changes for 14 patients (28%), intramodality changes for 15 (30%), and no change for 13 (26%). One patient (2%) underwent both intermodality and intramodality changes, 3 patients (6%) underwent other unspecified changes, and this question remained unanswered for the remaining 4 patients (8%).

Six (43%) of the 14 patients whose cancer was upstaged by PET underwent intermodality changes, whereas another 6 (43%) underwent intramodality changes. One patient (7%) whose cancer was upstaged had both intermodality and intramodality changes, whereas another patient (7%) whose cancer was upstaged had no management change. Intermodality changes occurred in 2 (50%) of 4 patients whose cancer was downstaged, whereas intramodality changes occurred in the remaining 2 patients.

Clinical management was changed for some of the 30 patients whose stage was not altered by PET: 6 (20%) of these had intermodality changes, 7 (23%) had intramodality changes, and 3 (10%) had other, unspecified changes. Table 2 specifies the management changes for the study group.

DISCUSSION

This prospective survey showed PET to have a considerable impact on staging and managing breast cancer patients. PET altered the clinical stage in 36% of patients and the clinical management in 60%. This study also supports the notion that referring physicians accept FDG PET as an important diagnostic staging modality for the care of their patients.

TABLE 1
Impact of PET on Clinical Stage

Clinical stage	<i>n</i>	%
Upstaged	14	28
Downstaged	4	8
No change	30	60
Question unanswered	2	4

TABLE 2
Impact of PET on Clinical Management

Change	<i>n</i>	%
Intermodality	14	28
From surgery to medical treatment	2	4
From surgery to radiation	0	0
From surgery to no treatment	1	2
From medical treatment to surgery	2	4
From medical treatment to radiation	1	2
From medical treatment to no treatment	0	0
From radiation to surgery	0	0
From radiation to medical treatment	0	0
From radiation to no treatment	0	0
From no treatment to surgery	1	2
From no treatment to medical treatment	4	8
From no treatment to radiation	1	2
From no treatment to radiation and from no treatment to medical treatment	1	2
From medical treatment to surgery and from medical treatment to radiation	1	2
Intramodality	15	30
Change in surgical approach	2	4
Change in medical approach	9	18
Change in radiation approach	1	2
Change in surgical approach and change in radiation approach	2	4
Change in medical approach and change in surgical approach	1	2
Combination of management	1	2
From no treatment to medical treatment and change in medical approach	1	2
None	13	26
Other management changes	3	6
Question unanswered	4	8

The results are in keeping with a previous report suggesting that FDG PET added information on the extent of disease in 29% of the 41 patients studied (23), mainly through detection of additional lymph node involvement. Importantly, in the current study PET uncovered unknown lymph node metastases ($n = 5$) and unknown distant metastases ($n = 8$) (Fig. 1 shows a case example) in 10 patients (20% of the entire population; both unknown lymph node metastases and unknown distant metastases were found in 3 of these patients).

The fact that 53% of those patients whose stage was not altered by PET nevertheless were managed differently after PET is noteworthy and suggests that PET provided the referring physicians with additional pertinent staging information. For instance, in patients with stage IV disease, additional nodal or distant metastatic disease detected by PET may not result in a stage change but may result in different management plans.

The current study has several limitations. First, whether all the management changes that were intended really took place is unknown. A study addressing this issue and further evaluating the outcome of these patients is currently under way. Second, the 31% response rate likely introduced a "responder bias." Only those referring physicians who be-

lieved PET had provided useful information for the management of their patients might have responded to the survey. Those who did not respond might have believed that PET did not add useful information. However, even in the unlikely event that all nonresponders believed PET had no effect on stage or management, 11% and 21% of the entire population of 160 patients would have incurred a change in stage and management, respectively, because of the PET findings.

The issue of responder bias was addressed by a recent study by Sjöström et al. (24), who reported that questionnaire studies tend to have a bias caused by both nonresponse and incorrect answers and that this bias can be substantial. Although such factors should not be dismissed, one should be aware that those authors conducted a parallel survey to



FIGURE 1. A 73-y-old woman with history of mastectomy for cancer of right breast. She was examined with PET because of rising tumor markers. Anterior coronal cut showed intense hypermetabolic focus (arrow) at inferior tip of right liver lobe, consistent with large, solitary liver metastasis. Cancer was up-staged, and clinical management was changed from medical treatment to surgery.

validate their findings and found that even higher response rates of 60%–70% (their actual response rate was 43%) would not have altered their findings.

The low response rate of the current study can be accounted for by several factors, such as varying degrees of interest among referring physicians in the subject of the survey, the length of the questionnaires, and their 2-component (pre- and post-PET) aspect. The response rate was slightly higher at UCLA (33%) than at the NCPIC (27%); however, this difference was not statistically significant. Also, the impact of PET on stage and clinical management did not differ between the 2 study sites. An important finding is that the clinical specialty and level of training did not vary between the responders and nonresponders (25); hence, the possibility of a bias based on specialty can be ruled out.

The breast cancer in this study was classified as stage IV in 36% of patients before PET but in 52% after PET. Thus, PET revealed unknown distant metastases in 8 patients. This finding shows the value of PET, as a whole-body imaging technique, in providing additional information about the extent of metastatic involvement, which in turn affects clinical management in many patients.

CONCLUSION

The current survey of referring physicians showed that whole-body FDG PET affected clinical stage and management in 36% and 58%, respectively, of their breast cancer patients.

REFERENCES

- Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin*. 2000;50:7–33.
- Warburg OH. *The Metabolism of Tumors*. London, U.K.: Constable; 1930.
- Monakhov NK, Neistadt EL, Shavlovskil MM, Shvartsman AL, Neifakh SA. Physicochemical properties and isoenzyme composition of hexokinase from normal and malignant human tissues. *J Natl Cancer Inst*. 1978;61:27–34.
- Weber MJ, Nakamura KD, Salter DW. Molecular events leading to enhanced glucose transport in Rous sarcoma virus-transformed cells. *Fed Proc*. 1984;43:2246–2250.
- Brown RS, Wahl RL. Overexpression of Glut-1 glucose transporter in human breast cancer: an immunohistochemical study. *Cancer*. 1993;72:2979–2985.
- Warburg OH. On the origins of cancer cells. *Science*. 1956;123:309–314.
- Utech CI, Young CS, Winter PF. Prospective evaluation of fluorine-18-fluoro-deoxyglucose positron emission tomography in breast cancer for staging of the axilla related to surgery and immunocytochemistry. *Eur J Nucl Med*. 1996;23:1588–1593.
- Smith IC, Ogston NK, 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*. 1998;228:220–227.
- Crippa F, Agresti R, Seregni E, et al. Prospective evaluation of fluorine-18-FDG PET in pre-surgical staging of the axilla in breast cancer. *J Nucl Med*. 1998;39:4–8.
- Adler LP, Crowe JP, al-Kaisi NK, et al. Evaluation of breast masses and axillary lymph nodes with [F-18]2-deoxy-2-fluoro-D-glucose PET. *Radiology*. 1993;187:743–750.
- Avril N, Dose J, Jänicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol*. 1996;14:1848–1857.
- Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol*. 1993;11:2101–2111.
- Bassa P, Kim EE, Inoue T, et al. Evaluation of preoperative chemotherapy using PET with fluorine-18-fluorodeoxyglucose in breast cancer. *J Nucl Med*. 1996;37:931–938.
- Minn H, Leskinen-Kallio S, Lindholm P, et al. [18F]Fluorodeoxyglucose uptake in tumors: kinetic vs. steady-state methods with reference to plasma insulin. *J Comput Assist Tomogr*. 1993;17:115–123.
- Wienhard K, Eriksson L, Grootenck S, Casey M, Pietrzyk U, Heiss WD. Performance evaluation of the positron scanner ECAT EXACT. *J Comput Assist Tomogr*. 1992;16:804–813.
- Dahlbom M, Hoffman EJ, Hoh CK, et al. Whole-body positron emission tomography. Part I. Methods and performance characteristics. *J Nucl Med*. 1992;33:1191–1199.
- Adam LE, Zaers J, Ostertag H, Trojan H, Bellmann ME, Brix G. Performance evaluation of the whole body PET scanner ECAT EXACT HR+ following the IEC standard. *IEEE Trans Nucl Sci*. 1997;44:1172–1179.
- Bengel FM, Ziegler SI, Avril N, Weber W, Laubenbacher C, Schwaiger M. Whole-body positron emission tomography in clinical oncology: comparison between attenuation-corrected and uncorrected images. *Eur J Nucl Med*. 1997;24:1091–1098.
- Meikle SR, Dahlbom M, Cherry SR. Attenuation correction using count-limited transmission data in positron emission tomography. *J Nucl Med*. 1993;34:143–150.
- Meikle SR, Hutton BF, Bailey DL, Hooper PK, Fulham MJ. Accelerated EM reconstruction in total-body PET: potential for improving tumour detectability. *Phys Med Biol*. 1994;39:1689–1704.
- Meta J, Seltzer M, Schiepers C, et al. Impact of 18F-FDG PET on managing patients with colorectal cancer: the referring physician's perspective. *J Nucl Med*. 2001;42:586–590.
- Fleming ID, Cooper JS, Henson DE, et al. *AJCC Cancer Staging Manual*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1997.
- Avril N, Dose J, Janicke F, et al. Assessment of axillary lymph node involvement in breast cancer patients with positron emission tomography using radiolabeled 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. *J Natl Cancer Inst*. 1996;88:1204–1209.
- Sjöström O, Holst D, Lind SO. Validity of a questionnaire survey: the role of non-response and incorrect answers. *Acta Odontol Scand*. 1999;57:242–246.
- Cartwright A. Professionals as responders: variations in and effects of response rates to questionnaires, 1961–77. *Br Med J*. 1978;2:1419–1421.



The Journal of
NUCLEAR MEDICINE

Impact of Whole-Body ^{18}F -FDG PET on Staging and Managing Patients with Breast Cancer: The Referring Physician's Perspective

Cecelia S. Yap, Marc A. Seltzer, Christiaan Schiepers, Sanjiv S. Gambhir, Jyotsna Rao, Michael E. Phelps, Peter E. Valk and Johannes Czernin

J Nucl Med. 2001;42:1334-1337.


This article and updated information are available at:
<http://jnm.snmjournals.org/content/42/9/1334>

Information about reproducing figures, tables, or other portions of this article can be found online at:
<http://jnm.snmjournals.org/site/misc/permission.xhtml>

Information about subscriptions to JNM can be found at:
<http://jnm.snmjournals.org/site/subscriptions/online.xhtml>

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

© Copyright 2001 SNMMI; all rights reserved.

 SOCIETY OF
NUCLEAR MEDICINE
AND MOLECULAR IMAGING