Prospective Evaluation of Fluorine-18-FDG PET in Presurgical Staging of the Axilla in Breast Cancer

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Methods: The presurgical, noninvasive staging of axillary nodes for metastases was prospectively investigated in 68 patients who were diagnosed with primary breast cancer using PET with ^{18}F-fluorodeoxyglucose (FDG). Four patients had bilateral nodules; therefore, the total number of evaluable cases was 72. Visual analyses of attenuation-corrected PET images and standardized uptake values (SUVs) of FDG uptake in carcinomas were compared with histopathological surgical findings. The SUV distribution differences between carcinomas with and without axillary metastases were evaluated by means of statistical and receiver operating characteristics analyses. **Results:** PET correctly classified 64 of the 72 cases; four false-positive and four false-negative PET results were found. The overall sensitivity, specificity and accuracy of PET for axillary metastases were 85%, 91% and 89%, respectively. With respect to the clinical axillary stage of the patients (TNM, or tumor–node–metastasis, classification), we obtained the following results: N_0 patients, sensitivity = 70%, specificity = 92%, accuracy = 86%; N_{1a} patients, sensitivity = 85.5%, specificity = 100%, accuracy = 95%; and N_{1b-2} patients, sensitivity = 100%, specificity = 67%, accuracy = 87%. The median SUV in carcinomas with axillary metastases (4.6) was significantly higher than that in carcinomas without metastases (2.9), but there was a great SUV overlap between the two groups (interquartile ranges = 2.7–7.2 and 1.9–4.5, respectively). Analysis of the receiver operating characteristics curve showed that a high sensitivity of SUV in predicting axillary metastases was associated with a very low specificity and vice versa. With the best SUV cutoff value of 2.9, the sensitivity and specificity were 74% and 56%, respectively. **Conclusion:** PET showed good overall diagnostic accuracy in the detection of axillary metastases (86%). The very high accuracy (95%) in N_{1a} patients is of particular importance. False-negative PET findings, however, can be encountered. SUVs of breast carcinoma cannot predict the spread of the disease to the axilla, even if higher values are often associated with axillary metastases. Any decision on the use of PET in the presurgical staging of breast cancer should be incorporated into a more general debate on axillary management. In selected patients with a very low probability of axillary metastases (T_{1a}), in whom axillary surgery can already be avoided according to data from follow-up studies, ^{18}F-FDG PET could be proposed as a noninvasive imaging modality to improve the diagnosis of axillary relapses.

Key Words: breast cancer; axillary metastasis; PET; fluorine-18-fluorodeoxyglucose

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The management of axillary nodes is one of the most controversial areas in the treatment of breast cancer, and it is still intensely discussed in Europe, as well as in the U. S. (*1,2*). In most patients with breast cancer, surgery is performed to remove the mammary lesion, and the extent of the operation depends upon the size of the tumor with breast-conserving surgery being adopted for T_1 tumors. Routinely, the operation is combined with axillary lymph node dissection (ALND) because of the lack of an effective noninvasive method for the assessment of tumor spread to the axillary region and because of the importance of knowing the exact axillary status for prognosis and therapy planning. However, the frequency of axillary lymph node metastases decreases with tumor size, and histology is positive in only about 20% of T_1 breast cancers submitted to ALND (*3*). Moreover, ALND is not without morbidity and cost. Complications of ALND include postoperative seroma, arm edema, nerve injuries and shoulder dysfunction (*4*). ALND always requires hospitalization (at least 1 wk), general anesthesia and postoperative rehabilitation therapy of the shoulder and arm. Therefore, a noninvasive diagnostic procedure for the selection of a subpopulation of breast cancer patients with a low risk of axillary lymph node metastasis could be useful for ALND planning by reducing both the cost and the morbidity of breast cancer treatment without impairing patient care.

The clinical use of PET with ^{18}F-fluorodeoxyglucose (FDG) is being investigated for many human tumors including breast cancer (*5–13*). In a previous work in which we used ^{18}F-FDG PET, ^{99m}Tc-sestamibi SPECT and ^{111}In-DTPA-octreotide-SPECT in different groups of patients with breast cancer, the best results were obtained with ^{18}F-FDG PET, particularly in the detection of axillary metastases (*14*). Encouraged by these promising results, we planned this study to further evaluate the diagnostic accuracy of ^{18}F-FDG PET in the presurgical staging of the axilla in breast cancer. The patients enrolled in our study had palpable breast nodules and clinical and instrumental (mammography or ultrasound) diagnoses of primary cancer. Fluorine-18-FDG PET was performed during their hospitalization before surgery, which included ALND, if indicated, and the PET results were compared to the pathological results found at surgery. No treatment decisions were taken on the basis of the results of the PET examinations. This investigation was approved by the ethics committee of our institute, and all patients who were enrolled in this study gave their informed consent.

MATERIALS AND METHODS

Patients

Sixty-eight consecutive female patients (aged 29–84 yr; mean age = 56 yr) were studied. All patients were scheduled for breast surgery plus ALND, if indicated, based on the clinical and instrumental (mammography and/or ultrasonography) diagnosis of primary breast tumors. Sixty-four patients had unilateral disease (single nodules, n = 55 patients; bifocal nodules, n = 9 patients), and 4 had bilateral disease. Therefore, the total number of patients who were evaluable for axillary metastases was 72 (total number of breast nodules = 81). According to the TNM (tumor–node–metastasis) classification (*15*), the clinical stages of the breast nodules were T_1 (n = 45), T_2 (n = 30), T_3 (n = 2) and T_4 (n = 4),

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and the clinical stages of the axilla were N_0 (n = 36), N_{1a} (n = 21), N_{1b} (n = 13) and N_2 (n = 2).

Of the 64 patients with unilateral disease, 4 underwent lumpectomy without ALND, 49 underwent quadrantectomy (47 with ALND) and 11 underwent mastectomy (10 with ALND). In the four patients with bilateral nodules, bilateral surgery was performed (one lumpectomy, four quadrantectomies and three mastectomies), combined with unilateral ALND in two patients and bilateral ALND in one patient. The total number of ALNDs performed in our study was 61. In 11 cases, breast surgery was not combined with ALND because of an intraoperatory diagnosis of benign lesion (8) or in situ ductal carcinoma (3).

The pathology reports were the basis for the final classification of the breast nodules and for the evaluation of axillary spread.

FDG Synthesis and Administration

Fluorine-18-FDG was produced using a modified standard technique (*16*). About 400 MBq (11 mCi) of FDG were injected into a vein contralateral to the tumor side. Before the PET examination, patients fasted for at least 5 hr, and all patients showed normal blood glucose levels in fasting status.

Acquisition and Analysis of PET Images

Positron emission tomography studies were performed from 1 to 7 days before surgery. Data were obtained with a General Electric 4096 WB Plus scanner, which has an axial field of view of about 10 cm and produces 15 simultaneous contiguous axial slices, with a slice thickness of 6.5 mm. The average reconstructed transaxial and axial resolutions were 7.3 mm and 5.3 mm FWHM, respectively, corresponding to a volumetric resolution of 0.28 ml.

Positioning of the breast and axillary regions in the field of view of the scanner was checked by a built-in laser guide. Most of the patients were studied in the supine position with their arms raised. Before FDG injection, two contiguous bed position transmission scans (10 min each) were acquired with a rotating ^{68}Ge rod source for correction of attenuation of the mammary and axillary regions. Two 20-min static emission studies were acquired at the transmission positions, 45–60 min after FDG injection. Patients were repositioned by using skin markers that were placed before the transmission scans.

Analysis of the PET results was performed on attenuation-corrected emission images that were reconstructed by filtered backprojection using 2-mm pixels in a 256 × 256 matrix and a 4.2-mm Hanning filter. All PET interpretations were blinded to the histopathological findings at surgery. The images were read as positive if an increased localized FDG uptake, with respect to the surrounding tissue, was present. Additionally, semiquantitative analysis of the FDG uptake in breast carcinomas was performed by generating parametric images of standardized uptake values (SUVs), in which the concentration of radioactivity was divided by the ratio of total administered activity to body weight (*17*). For SUV calculation, the following procedure was adopted: for each breast carcinoma detected by PET, one region of interest was drawn within the uptake area, comprising the four contiguous pixels with the highest levels of activity, and the mean SUV was used.

We evaluated the distribution differences of SUVs between carcinomas with and without axillary metastases using the Mann-Witney U test; p values of less than 0.05 were considered significant. Afterwards, receiver operating characteristics (ROC) analysis was performed using the different SUVs of the two carcinoma groups to establish a relationship between the sensitivity and specificity of the SUV in predicting axillary spread.

TABLE 1
Histopathology of Breast Nodules

Histopathology	No. of lesions	Size (mm), mean (range)
Malignancies		
IDC	46	
ILC	9	
Mixed IDC + ILC	8	
In situ ductal carcinoma	7	
Other	3	
Total	73	20 (4–67)
Benign lesions		
Proliferative dysplasia	6	
Focal inflammatory lesion	2	
Total	8	15 (6–16)
Total breast nodules	81	20 (4–67)

IDC = infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma.

RESULTS

Of the 81 breast nodules, histopathology showed carcinomas in 73 cases and benign diseases in the remaining 8 (Table 1). The average size of the nodules was 20 mm (range = 4 mm–67 mm). Most of the malignancies were infiltrating ductal carcinomas (63%); the benign lesions were proliferative dysplasias without atypia (6) or focal inflammatory lesions (2). Of the 73 carcinomas, 69 were accurately visualized by PET. The average size of the four carcinomas that were not detected by PET was 6 mm (range = 5 mm–8 mm), and their histopathological types were in situ ductal carcinoma (2), mixed infiltrating ductal and lobular carcinoma (1) and infiltrating ductal carcinoma (1). Of the eight breast nodules with a histopathological diagnosis of benign disease, three dysplasias and two focal inflammatory lesions showed FDG uptake.

In the 61 ALNDs, the average number of dissected nodes was 21 (range = 12–38). Histopathology showed axillary metastases in 27 cases and was negative in 34 cases. Of the 27 cases with axillary metastases, macroscopic nodal involvement was found in 25 cases (plus perinodal infiltration in 14 cases), and microscopic nodal involvement (metastases of <0.2 cm) was found in 2 cases. Table 2 shows a summary of these findings and the PET results. The remaining 11 cases, which did not undergo ALND (8 benign lesions and 3 in situ ductal carcinomas), were classified as negative for axillary metastases.

Table 3 shows the summary of the PET results for axillary metastasis, both in the whole patient population and in subpopulations of patients distinguished according to axillary stage. The overall sensitivity, specificity and accuracy of PET in the detection of axillary metastases were 85% (23 of 27), 91% (41 of 45) and 89% (64 of 72), respectively (Fig. 1). Noteworthy results were obtained in the subpopulation of 21 N_{1a} patients, in which the accuracy of the method was 95% (20 of 21).

Positron emission tomography gave false-positive results in four patients (two N_0 and two N_{1b}), in whom there was no histopathological confirmation of metastases in the dissected nodes (mean = 22; range = 16–29). Moreover, there was no mention of inflammatory findings in the histopathological reports on the nodes. We reanalyzed the PET images of these cases, and in the two N patients, we were able to change the PET interpretation, attributing the results to vascular FDG uptake, but we had to confirm the abnormal axillary uptakes in the two N_{1b} patients (Fig. 2).

Positron emission tomography gave false-negative results in four patients (three N_0 and one N_{1a}), in whom histopathology

TABLE 2
Histopathology of Axillary Metastases*

Patient no.†	TNM	PET	No. of N^+/N_{tot}‡	Macroscopic metastases§	Microscopic metastases§	Perinodal infiltration
1	T_2N_0	+	2/21	2	0	No
6	T_1N_{1b}	+	20/31	19	1	Yes
7	T_2N_{1b}	+	11/19	11	0	Yes
9	T_4N_2	+	8/18	8	0	Yes
13	T_2N_{1a}	+	7/23	5	2	Yes
20	T_2N_{1a}	+	2/35	0	2	No
22	T_1N_0	+	1/21	0	1	No
23	T_2N_0	+	2/29	1	1	No
26	T_1N_{1a}	+	1/29	1	0	No
28	T_2N_{1a}	+	2/25	1	1	No
32	T_2N_{1b}	+	21/21	21	0	Yes
43	T_2N_{1b}	+	2/25	2	0	Yes
44	T_2N_{1b}	+	8/30	6	2	Yes
52	T_3N_0	−	23/23	23	0	Yes
56	T_2N_0	+	1/18	1	0	No
59	T_2N_{1b}	+	1/35	1	0	No
63	T_1N_0	−	1/16	0	1	No
66	T_4N_{1a}	+	8/19	4	4	Yes
69	T_1N_{1a}	+	15/22	15	0	Yes
71	T_4N_2	+	15/23	13	2	Yes
74	T_1N_0	+	1/12	1	0	No
76, left	T_2N_{1a}	−	4/19	4	0	Yes
76, right	T_2N_{1a}	+	19/21	19	0	Yes
77	T_1N_0	−	3/19	1	2	No
83	T_2N_0	+	1/24	1	0	Yes
84	T_2N_{1b}	+	17/34	11	6	No
86	T_1N_0	+	1/16	1	0	No

*Number of patients, n = 27.
†The identification number refers to a general database of the PET Center.
‡Number of metastases/total number of dissected nodes.
§Macroscopic metastases, size > 0.2 cm; microscopic metastases, size < 0.2 cm.

found an average number of 8 metastases (range = 1–23) in the dissected nodes (mean = 19; range = 16–23). Three of these patients had macroscopic nodal involvement, and one had a micrometastasis. Reevaluation of these cases did not allow any change in the initial negative findings (Fig. 3).

With regard to the semiquantitative analysis of FDG uptake in carcinomas, the median SUV in carcinomas with axillary metastases (4.6; n = 27) was significantly higher than that in carcinomas without axillary metastases (2.9; n = 45). However, a great SUV overlap was present between the two groups (interquartile ranges = 2.7–7.2 and 1.9–4.5, respectively). ROC analysis showed that the best cutoff value of SUV (2.9) was associated with a sensitivity and a specificity of 74% and 58%, respectively. Any change in the reading of the ROC curve was not useful in the management of patients referred for ALND. In fact, a high sensitivity was associated with an unacceptably low specificity (96% and 22%, respectively) and vice versa (specificity = 91% and sensitivity = 15%) (Fig. 4).

TABLE 3
PET Results in the Detection of Axillary Metastases

	N_0 (n = 36)	N_{1a} (n = 21)	N_{1b-2} (n = 15)	Total (n = 72)
Sensitivity	70% (7/10)	87.5% (7/8)	100% (9/9)	85% (23/27)
Specificity	92% (24/26)	100% (13/13)	67% (4/6)	91% (41/45)
Accuracy	86% (31/36)	95% (20/21)	87% (13/15)	89% (64/72)

n = number of patients.

DISCUSSION

Currently, FDG is the most interesting tumor-seeking agent in nuclear medicine imaging. To reduce cost and improve the investigational capacity, imaging techniques based on 511-KeV-collimated gamma cameras have been proposed, with promising results (*18,19*). Nevertheless, priority should be given to the PET technique, if it is available, because of its superior resolution and sensitivity, as compared to SPECT (*14,19*).

Several studies have addressed the imaging of breast cancer with ^{18}F-FDG PET, and FDG has shown the localization of primary carcinomas, regional metastatic nodes and distant metastases (*5–11*). Moreover, ^{18}F-FDG PET can be used to monitor tumor response to chemotherapy in patients with locally advanced disease (*12,13*).

In our study, the visualization of 94.5% (69 of 73) of the histopathologically confirmed carcinomas, with an average size of 20 mm (24% of the nodules were ≤10 mm), documented a sensitivity of PET in the detection of even small tumors. The false-negative PET results in four carcinomas may have been related to their size (mean = 6 mm; range = 5 mm–8 mm), which was close to the spatial resolution of our scanner. Five out of eight breast nodules with a histopathological diagnosis of benign disease accumulated FDG. Fluorine-18-fluorodeoxyglucose is not a very tumor-specific radiotracer, and false-positive results may occur because of tracer accumulation in benign lesions with increased glucose metabolism or containing inflammatory cells (*20*).

Clinical studies have demonstrated the prognostic value of FDG uptake: tumors with higher FDG uptakes appear to be more aggressive and to develop faster (*21–25*). On the basis of these findings, we evaluated the relationship between the SUV of the primary carcinomas and the axillary spread of the tumor, which is still the most important prognostic factor in breast cancer. We found that, even if carcinomas with high SUVs often have axillary metastases, there was a high degree of SUV overlap in carcinomas with and without axillary metastases. As a result, it was impossible to establish a useful SUV cutoff value for the management of patients referred for ALND.

With regard to the PET results in the detection of axillary metastases, the overall accuracy of the method was 89%, due to four false-positive and four false-negative PETs. As for the four false-positive PETs, in two patients vascular uptake was probably mistaken for axillary metastases, but in the other two patients, the reason for increased axillary uptake remains undetermined. In view of their clinical stage (N_{1b}), the PET results might have been due to FDG accumulation in inflammatory nodes, but the histopathological reports did not mention inflammatory findings in the dissected nodes. With regard to the four false-negative PETs, the result in one patient (Patient 63) may have been due to the size of the metastases (1 microscopic metastasis among 16 dissected nodes). However, PET was positive in one patient (Patient 20) with 2 microscopic metastases. In the other three patients (Patients 52, 76 left and 77) with macroscopic metastases, we carefully reexamined all the data without finding any explanation for the false-negative PET results. We probably have to consider other biological factors (e.g., subclinical disorders of the glucose metabolism) that cannot be estimated in this study.

On the whole, our findings showed a clear relationship between PET results and clinical axillary stage: the sensitivity rose from 70% in the N patients to 100% in the T_{1b-2} patients. The specificity also changed, being lower in N_{1b-2} patients than it was in N patients (67% compared to 92%, respectively). The reason could be that PET localization of palpable nodes is an

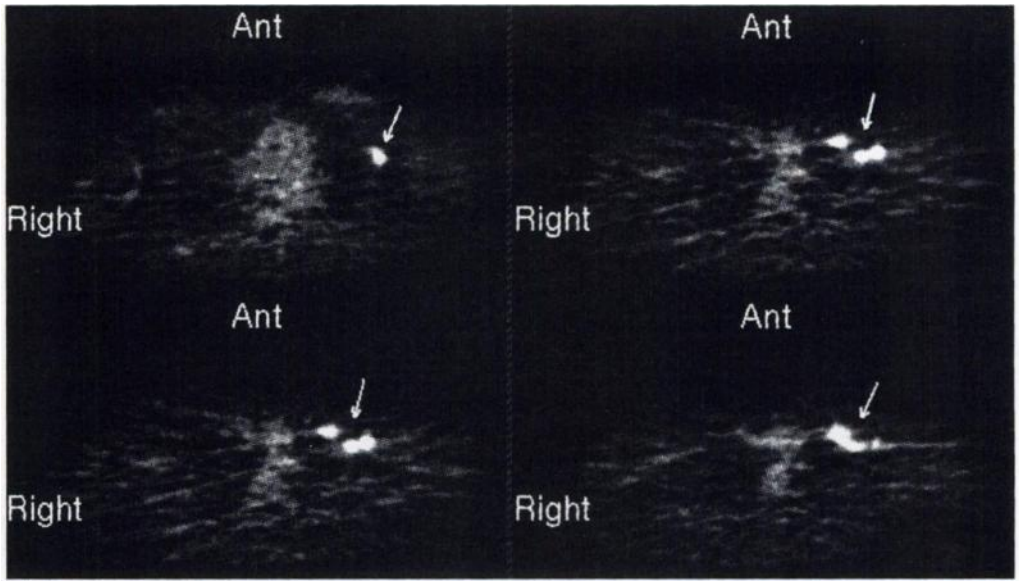

FIGURE 1. Transaxial slices of the axillary regions showing several FDG uptakes (arrows) on the left (true-positive finding; Patient 7, T_2N_{1b}, 11 axillary metastases documented by histopathology).

easy clinical finding, but the low tumor specificity of FDG can lead to false-positive results. Nevertheless, the results obtained in the N_{1a} subpopulation are of particular importance (accuracy = 95%) because the oncologist who finds palpable nodes in a patient may be compelled to perform unnecessary ALND, even if the patient is not suspected for metastases (here, histopathology found no axillary metastases in 62% of N_{1a} patients).

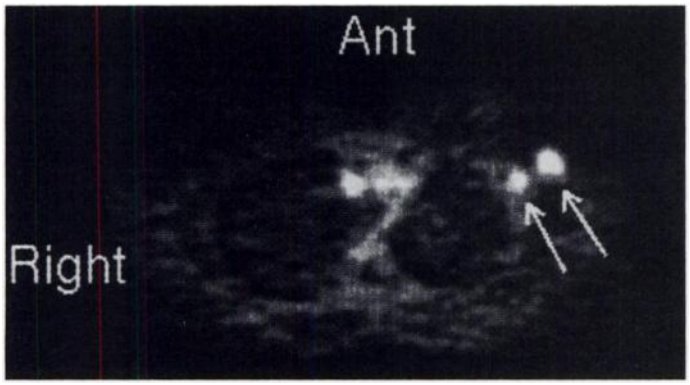

FIGURE 2. Transaxial slice of the axillary regions showing two FDG uptakes (arrows) on the left (false-positive finding; Patient 62, T_2N_{1b}, histopathology negative in the 25 dissected nodes).

Any conclusion on the use of ^{18}F-FDG PET in the presurgical staging of breast cancer should be incorporated in a more general debate regarding the management of axillary nodes. If the oncologist cannot afford even one false-negative result, the use of this imaging modality is to be questioned because, as shown by our study, false-negative PET results can and do occur despite its good overall diagnostic accuracy (86%), which is very high in N_{1a} patients (95%). However, recent follow-up studies have shown that axillary surgery can be avoided in early breast cancer, which has a very low incidence of axillary metastases at initial diagnosis, because of the minor risk of axillary relapse (<3%) and, above all, due to the efficacy of salvage surgery (*26*). Therefore, ^{18}F-FDG PET could be proposed in this category of patients to increase the accuracy of preoperative clinical staging and, particularly, as a follow-up modality for an early, noninvasive diagnosis of axillary relapse.

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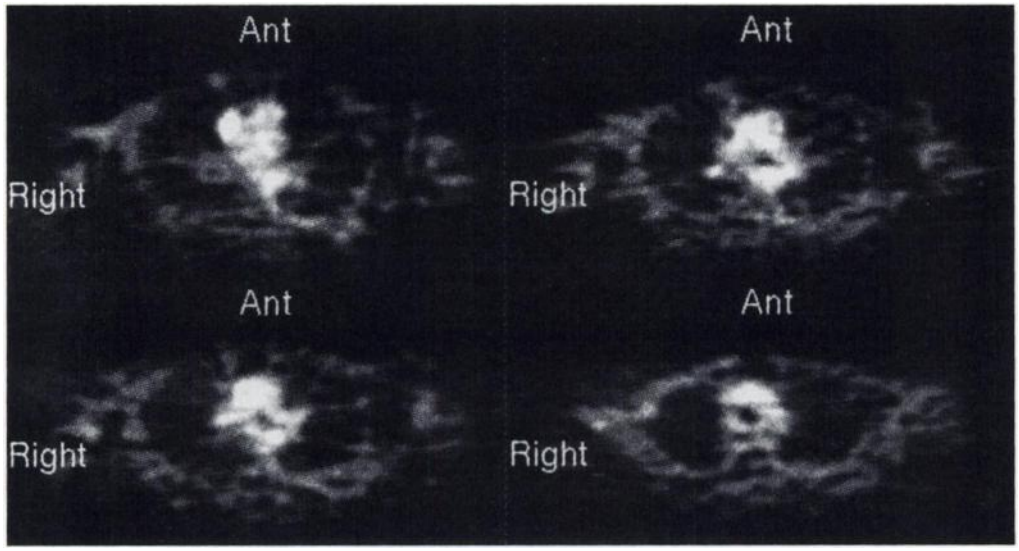

FIGURE 3. Transaxial slices of the axillary regions without any abnormal FDG uptake (false-negative finding; Patient 52, T_3N_0, 23 metastases in the left axilla documented by histopathology).

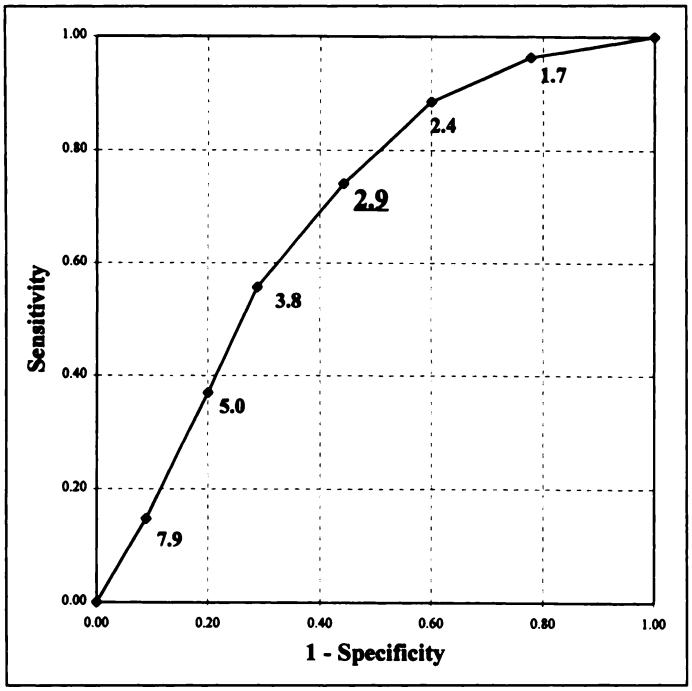

FIGURE 4. Sensitivity and specificity of different SUV cutoff values in primary carcinomas for predicting axillary metastases, determined by means of the ROC curve.

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