Re: Axillary Lymph Node Staging in Breast Cancer by 2-Fluoro-2-deoxy-D-glucose–Positron Emission Tomography: Clinical Evaluation and Alternative Management

Greco et al. *(1)* reported that 2-fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) is a reliable and accurate method to predict the axillary status in breast cancers of 1–2 cm in diameter: Histopathology detected axillary lymph node (ALN) metastases in 72 (43%) of 167 patients, and 68 ALN metastases were detected by PET (sensitivity = 94.4%).

To determine the sensitivity of FDG–PET to detect ALN metastases, the histopathologic methodology is crucial. Compared with other PET studies on this subject, a relatively detailed description was provided by Greco et al. *(1),* who stated, "each lymph node was sectioned into two or three parts, and one or more sections were prepared from each part," and who used only hematoxylin–eosin (H&E) staining. It remains unclear, however, how many sections were taken on average per ALN, which is important information. With step sectioning at regular intervals (e.g., five sections at 250 μm) and immunohistochemistry (e.g., against keratins by using CAM5.2 anti-keratin antibodies), the detection of ALN metastases is markedly increased *(2,3).* We reported previously *(4)* a detection difference (i.e., upstaging) of 20% (95% confidence interval [CI] = 11% to 28%) between one section stained with only

Table 1. Cumulative frequency distribution of the total axillary lymph node metastatic tumor load in 83 patients with invasive breast cancer*

	Total axillary lymph node metastatic tumor load, mm^2						
	0–1	0–2	0–4	0–8	0–15	0–20	>20
Cumulative frequency	42%	45%	53%	55%	65%	66%	100%

*At the hypothetical 3-mm (about 8 mm^2) positron emission tomography detection limit, metastases would be missed in the majority (55%) of patients.

H&E and five sections examined immunohistochemically. Eight percent of this difference was explained by H&E staining, and 12% was explained by immunohistochemistry. Thus, the less intensive histopathologic method used by Greco et al. is likely to overestimate the accuracy of PET because micrometastases are missed.

Furthermore, as Greco et al. *(1)* state in their report, the main pitfall in the detection of ALN metastases by PET is the limited spatial resolution and, therefore, the ability to detect metastases of only a few cells. Such small metastases are an important risk factor for axillary recurrence and have an impact on prognosis *(5)*. Consequently, they are generally considered to be an indication for further surgery or adjuvant therapy *(6)*.

PET is clearly able to detect tumors of less than 1 cm in diameter. However, even with very FDG-avid tumors, such as melanoma, this ability decreases with tumors of less than 6 mm in diameter, as reported by the same group *(7)*.

Using video morphometry, we have measured the total tumor load found in the ALNs of 83 patients with positive sentinel nodes. Lymph nodes were subjected to five-level step sectioning at 250-μm intervals and CAM5.2 immunohistochemistry if the initial H&E sections were negative. If all metastatic cells in the different ALNs are considered at one site, which is clearly an optimistic approach, the cumulative frequency distribution of the total ALN tumor load (Table 1) suggests that, even at a 3-mm (i.e., 8 mm^2) detection limit of PET, the majority of involved sites (55% [95% CI = 44% to 66%]) would have been false negative at imaging.

In conclusion, we think that the sensitivity of 94.4% as described by Greco et al. is overly optimistic because of the histopathologic method used. From the detection limits of PET and histopathology (one cell = approximately 150 μm^2), PET may miss a substantial number of patients with involved ALNs that could have been detected by surgical sentinel node-based staging. We admit that most of the metastases missed by PET would be micrometastases, but until it is proven that such metastases are not clinically important, we think that PET scanning cannot safely be used for ALN staging in patients with breast cancer.

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REFERENCES

(1) Greco M, Crippa F, Agresti R, Seregni E, Gerali A, Giovanazzi R, et al. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose–positron emission tomography: clinical evaluation and alternative management. J Natl Cancer Inst 2001;93:630–5.

(2) Torrenga H, Rahusen FD, Borgstein PJ, Meijer S, van Diest P. Immunohistochemical detection of lymph-node metastases [letter]. Lancet 2000;355:144.

(3) Cserni G. Metastases in axillary sentinel lymph nodes in breast cancer as detected by intensive histopathological work up. J Clin Pathol 1999;52:922–4.

(4) Torrenga H, Rahusen FD, Meijer S, Borgstein PJ, van Diest PJ. Sentinel node in breast cancer: detailed analysis of the yield from step sectioning and immunohistochemistry. J Clin Pathol 2001;54:550–2.

(5) International (Ludwig) Breast Cancer Study Group. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. Lancet 1990;335:1565–8.

(6) van der Wall E. The sentinel node in breast cancer: implications for adjuvant treatment? Eur J Nucl Med 1999;26(4 Suppl):S17–9.

(7) Crippa F, Leutner M, Belli F, Gallino F, Greco M, Pilotti S, et al. Which kinds of lymph node metastases can FDG PET detect? A clinical study in melanoma. J Nucl Med 2000;41:1491–4.

NOTES

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RESPONSE

The aim of our study *(1)* was to evaluate the role of positron emission tomography (PET) in lymph node staging of breast cancer as an alternative to surgical staging. The sensitivity of PET would be reduced if compared with serial sectioning (i.e., each section at a thickness of 250 μm) followed by systematic staining by immunohistochemistry. Even such a choice, however, can be considered arbitrary and still inadequate to evaluate the real condition of lymph nodes. In fact, because the diameter of the neoplastic cell can be less than 10 μm, the ideal distance between the two sections should be shorter than 10 μm to be sure of detecting any individual metastasized tumor cell. More sophisticated and accurate methods of lymph node evaluation (i.e., reverse transcription-coupled polymerase chain reaction) *(2)* have been described with the aim of reducing the rate of false-negative sentinel nodes. However, it is impractical to routinely use these procedures for lymph node staging even for a sentinel node. At this point, what is really crucial is to determine the cutoff of the lymph node tumor load that may used to compare an alternative procedure with the traditional axillary dissection.

Other methods reported for validation of the sentinel node procedure, in which a more accurate assessment was used for the sentinel node than for other axillary lymph nodes, lead to a bias in the evaluation of lymph node metastases. In our study, we chose the histopathologic method commonly used in clinical practice and uniformly applied to every lymph node removed.

Besides the fact that prognostic importance of micrometastases has yet to be defined completely, we must now consider the value of axillary lymph node staging with respect to treatment. Since 25% of lymph node-negative breast cancers have a poor prognosis, several authors look for a more accurate histologic method to detect lymph node metastases and convert a variable fraction of lymph node-negative breast cancers into lymph node-positive ones. Thus, it is reasonable to predict that an increased rate of lymph node-positive breast cancers will have a good prognosis, altering a prognostic stratification, which is the aim of the staging. It is also known that lymph node-positive breast cancers with favorable morphologic and biologic tumor variables show a better prognosis than lymph node-negative ones associated with adverse factors *(3).*

When lymph node staging is integrated with several biomolecular variables of tumors in the stratification of the risk *(4,5),* lymph node information (not lost with PET) influences the adjuvant treatment only in 6% of patients *(6).* Therefore, we believe that the lack of identification of lymph node micrometastases does not lead to an inadequate treatment. Even avoiding axillary dissection, it does not seem to lead to a suboptimal treatment *(7)* if the decision is supported by an adequate evaluation of the biology of the tumor.

Thus, in our institute, a randomized clinical trial is ongoing with the aim of redefining the role of lymph node staging in the multimodal treatment of stage T1N0 breast cancer. The study arm does not include any lymph node staging or any primary lymph node treatment, and the choice of a systemic adjuvant treatment is determined through more complex biologic evaluation of the primary tumor.

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References

(1) Greco M, Crippa F, Agresti R, Seregni E, Gerali A, Giovanazzi R, et al. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose–positron emission tomography: clinical evaluation and alternative management. J Natl Cancer Inst 2001;93:630–5.

(2) Bostick PJ, Huynh KT, Sarantou T, Turner RR, Qi K, Giuliano AE, et al. Detection of metastases in sentinel lymph nodes of breast cancer patients by multiple-marker RT–PCR. Int J Cancer 1998;79:645–51.

(3) Menard S, Bufalino R, Rilke F, Cascinelli N, Veronesi U, Colnaghi MI. Prognosis based on primary breast carcinoma instead of pathological nodal status. Br J Cancer 1994;70:709–12.

(4) Goldhirsch A, Glick JH, Gelber RD, Seen HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. J Natl Cancer Inst 1998;90:1601–8.

(5) Eifel P, Axelson JA, Costa J, Crowley J, Curran WJ Jr, Deshler A, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. J Natl Cancer Inst 2001;93:979–89.

(6) Greco M, Gennaro M, Valagussa P, Agresti R, Ferraris C, Ferrari B, et al. Impact of nodal status on indication for adjuvant treatment in clinically node negative breast cancer. Istituto Nazionale per lo Studio e las Cura dei Tumori. Ann Oncol 2000;11:1137–40.

(7) Greco M, Agresti R, Cascinelli N, Casalini P, Giovanazzi R, Maucione A, et al. Breast cancer patients treated without axillary surgery: clinical implications and biologic analysis. Ann Surg 2000;232:1–7.

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