clinicians to the results of a test already in clinical use may create ethical challenges and will certainly limit interest on the part of both patients and clinicians to participate. Finally, blinding is impossible if the test in question is being billed and reimbursed as part of standard of care.

To calculate sensitivity, specificity, and likelihood ratios for an experimental diagnostic test, all positive and negative test findings must be adjudicated by the reference standard, but in clinical trials of imaging modalities, this is rarely possible. For example, in the case of the internal mammary node, confirmatory biopsy may be unsafe or technically infeasible. In many studies, the evolution of a lesion on follow-up is used to subsequently validate the test findings, but given the dynamic nature of cancer and cancer therapy, this approach may be misleading because interventions that impact the findings of the test may have occurred in the interim. Given the lack of a consistent, independent reference standard and a blinded approach or control group, it can be difficult to judge the prognostic impact of 18FDG PET/CT using data gleaned from emerging clinical practice.

The Groheux et al. study (6) is important in shedding light on the potential use of 18FDG-PET/CT in stage II and III breast cancer to accurately stage patients, a relevant clinical dilemma. Their results provide supportive evidence for a role for 18FDG-PET/CT in determining stage and prognosis of high-risk patients. However, the definitive evaluation of 18FDG-PET/CT as a prognostic biomarker in stage II and III breast cancer would require a confirmatory study with strict patient selection rules, independent reference standards, and blinding to imaging results or a control group. Such a study would be challenging, and likely expensive, but it would generate the important data needed to guide the use of a powerful but costly diagnostic imaging modality in a highly prevalent disease. This has been accomplished for 18FDG PET/CT for early-stage breast cancer, for which limited use was confirmed (10). Perhaps it is time to conduct a similar study to direct the appropriate use of what appears to be a useful test for higher-stage breast cancer.

References

Notes
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In the article “International Multicenter Tool to Predict the Risk of Nonsentinel Node Metastases in Breast Cancer,” Meretoja et al. (1) described a predictive tool that could be used to assess the risk of additional axillary metastases after a positive sentinel node biopsy. This model, which incorporated data from five centers and 1000 patients, has undergone extensive internal and external validation in identifying nine statistically significant factors for positive nonsentinel nodes.

Many questions about the management of the axilla in breast cancer, particularly questions about the role of axillary node dissection in the setting of a positive sentinel node, remain. Much of the debate centers around the still-uncertain impact of axillary node dissection on the incidence of regional recurrence, survival, and morbidity, particularly because the majority of patients with a positive sentinel node will not have additional positive axillary nodes found on completion of axillary node dissection.

Does Predicting Positive Nonsentinel Nodes Answer the Question of Axillary Dissection and Provide a Benefit?

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The primary endpoint analysis of the B-32 trial showed the safety of sentinel node biopsy alone in staging the axilla in women who are sentinel node negative, a procedure that resulted in a very low local/regional recurrence (2). The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (3) attempted to answer the question of whether axillary node dissection was necessary for women whose tumors were sentinel node positive. However, the latter trial, suffering from a low accrual rate and a low event rate, closed early because of concern about multiple factors affecting analysis (4). The results of this trial did show that there were no differences in local/regional recurrence between women with a positive sentinel node who underwent completion axillary node dissection and those who underwent no axillary node dissection (4). These results favored a low-risk population. That study also suggested that the whole-breast irradiation all these women underwent may have affected the low incidence of axillary recurrence (4).

The Oxford overview analysis (5) noted a benefit in disease-free survival and overall survival in women with positive nodes. The recent MA.20 trial showed that women with positive nodes or high-risk negative nodes after axillary node dissection who had axillary nodal radiation had improved disease-free survival compared with those who did not, although morbidity was higher in the treated group, particularly with respect to lymphedema (6).

The Meretoja et al. study (1) identified the approximately 30% of patients with a positive sentinel node who are likely to have additional positive nodes in the axilla and might benefit from an axillary node dissection. The factor used in Meretoja et al.’s predictive model (1) was the baseline prevalence of positive nonsentinel axillary nodes reported from each participating center, 32.7%, which was lower than the 42.2% of the validated series and higher than the 25% in the ACOSOG Z0011 trial. The use of preoperative axillary ultrasound with needle biopsy of nodes eliminated some women from proceeding to sentinel node biopsy and, therefore, affected the rate of nonsentinel node positivity. This model includes factors not seen in other models, such as size of nodal metastases. How readily this model can be applied in centers where this rate cannot be easily identified remains to be seen. The model also used isolated tumor cells, which is controversial when performing an axillary node dissection, but the cells were predictors of outcome in NSABP B-32 (7).

The Meretoja et al. model (1) may be useful for predicting the existence of additional positive axillary nodes after sentinel node biopsy, and the authors should be applauded for their efforts. The value of complete axillary node dissection in terms of its impact on recurrence in the axilla, overall survival, and morbidity continues to remain controversial. In the absence of definitive information, selecting women who have additional positive nonsentinel nodes and reducing the morbidity of axillary node dissection for those for whom the sentinel node is the only node that is positive will continue to be a quest and may have an impact on the treatment, morbidity, and outcomes of these patients.

References

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