EDITORIAL

Assessing the Significance of Occult Micrometastases in Axillary Lymph Nodes from Breast Cancer Patients

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The presence or absence of metastatic breast cancer in the axillary lymph nodes has historically been considered to be the most important prognostic factor in planning treatment and predicting outcome for women afflicted with this disease. A report of negative nodes is as welcome as the brightest day, while positive nodes are regarded as gloomily as the darkest night. This on or off approach may have been practical in a time or place when breast cancer was likely to present as advanced disease. However, with modern screening and diagnostic modalities, this is not a valid approach. The full spectrum of nodal tumor burden must be measured and the task of detecting and quantifying micrometastases is equally as challenging as marking the subtle moment to moment transitions from night to day. When minimal nodal disease is detected, is this significantly different from undetected occult nodal disease or is this analogous to a mere moment later in the twilight spectrum of dawning day?

This question of minimal and occult disease has fascinated us for more than half a century. In this issue of The Breast Journal, Kahn et al. report their institution’s experience with occult nodal metastases and clinical outcome (1). The study also addresses one important deficiency in some similar previous investigations by quantifying nodal tumor burden, in this case according to the nodal classifications in the 6th edition of the American Joint Committee on Cancer (AJCC) staging manual (2). A cohort of 214 patients with negative axillary lymph nodes on initial pathologic examination was identified. Paraffin tissue blocks were retrieved, recut, and an additional routine stain and anticytokeratin immunohistochemical (IHC) stain were performed. Occult metastases were identified in the lymph nodes from 29 patients (14%). These metastases were apparent on routine and IHC stains in 10 patients. More importantly, 27 patients had micrometastases identified (larger than 0.2 mm, but not larger than 2.0 mm) and 2 patients had only isolated tumor cells or cell clusters identified (no cluster larger than 0.2 mm). Occult micrometastases were identified in only one node in 23 patients and two nodes were involved in 4 patients. Macronodules (larger than 2.0 mm) were not identified in any lymph nodes. These women had undergone surgery between 1977 and 1986 and the median follow-up time was 8 years. Both disease-free interval and disease specific survival were evaluated and correlated with metastasis size and primary tumor characteristics.

In a univariate analysis, factors with statistically significant correlation with disease-free survival (p < 0.05) were tumor size, tumor grade, nuclear grade, lymphatic vascular invasion, HER-2/neu overexpression, and elevated S-phase fraction. Excepting nuclear grade, the same factors had statistically significant correlation with disease specific survival. Occult micrometastases were not associated with a decrease in disease-free interval or disease specific survival in both univariate and multivariate analyses. In other words, in the setting of axillary dissection, this is a negative study with respect to the clinical significance of occult micrometastases.

Advocates of the importance of micrometastases are often critical of small studies with limited follow-up. Those factors have been addressed in this study of more than 200 patients that have been followed for a long period of time. Further, toward this end, the authors demonstrate reasonable statistical power to demonstrate a 20% difference in disease-free interval. Another interesting element in this study is the observation that only 11 patients received adjuvant systemic therapy, effectively removing systemic therapy as a confounding variable. Patients with “poor clinical pathologic features” were offered adjuvant therapy; however, the authors explain...
that tumor size would have been the variable most likely to influence this decision, as the modern array of prognostic factors was not reported at their institution during this time period. Within the subset of patients receiving no chemotherapy, micrometastases were not a significant factor for predicting outcome. Although no single study, particularly a retrospective study, can address all the issues surrounding the clinical significance of micrometastases, this group of investigators has done their best to control for primary tumor variables, size of occult micrometastases, and the effect of treatment with chemotherapy.

Virtually all studies evaluating the clinical impact of occult micrometastases are actually asking the question, “How thoroughly should we examine a lymph node?” Huvos et al. (3) in 1971, followed by Fisher et al. (4) in 1978, set the threshold for clinically significant metastases at 2.0 mm by demonstrating that women with metastases no larger than 2.0 mm did not have a significant survival disadvantage compared to women with no metastases detected. Interestingly, these two studies did not engender within pathologists a systematic evaluation of lymph nodes designed to identify all metastases larger than 2.0 mm, and it was not until 2000 that it was generally recommended that the entire lymph node be submitted for histopathologic evaluation (5). This creates uncertainty in retrospective studies evaluating occult metastases because we do not know how completely (in some instances a portion of the nodes were discarded) or thoroughly the lymph node was initially examined: more thorough initial examination is likely to exclude the largest, most significant metastases, while a less thorough initial examination may not have detected some clinically significant metastases. Primarily for this reason, the clinical significance of micrometastases is best addressed by prospective study with a defined initial lymph node evaluation strategy that includes slicing the lymph nodes as close to 2.0 mm in greatest thickness as possible prior to embedding in paraffin. This has not been, and probably never will be, formally tested within the context of an axillary dissection, given the general acceptance of sentinel node biopsy as an alternative to axillary dissection (6).

Sentinel nodes are routinely sectioned at approximately 2.0 mm intervals and a relatively superficial examination of each paraffin tissue block will exclude metastases larger than 2.0 mm when nodes are negative. The question then remains, in the negative sentinel node examination, how thoroughly should we look for metastases smaller than 2.0 mm? This question is not entirely analogous to retrospective analysis of pathologically negative axillary lymph nodes where more extensive axillary surgery has already been performed. In other words, undetected axillary metastases have already been removed in the case of axillary dissection and these metastases could never be the source of future systemic dissemination; they can only be a marker of systemic dissemination at the time of diagnosis. In contrast, a negative sentinel node examination, by virtue of a defined false-negative rate, will leave some patients with undetected axillary disease that could potentially give rise to future systemic metastases. Adjuvant chemotherapy and tangent field radiation would be expected to treat some of this disease.

These tenets have guided the design of sentinel node trials comparing axillary dissection to sentinel node biopsy alone: we first must determine conclusively whether performing less than an axillary dissection confers a higher risk for axillary recurrence, systemic recurrence, or decreased overall survival. Detection of occult micrometastases is an essential part of this evaluation. If the presence of occult metastases ultimately predict for axillary recurrence, systemic recurrence, or survival, then a more thorough examination of sentinel nodes may be warranted. Any significance demonstrated for occult metastases in initially negative sentinel nodes must be evaluated concomitantly with primary tumor variables, as these variables may potentially be more important predictors than the presence of minute metastases in regional lymph nodes. This may be particularly true if molecular evaluation of the primary tumor can routinely predict a metastatic phenotype in a manner that is more cost effective than sampling of regional nodes (7).

A final subtle issue that is not routinely discussed, but is raised by the title of the article by Kahn et al., is biologic versus clinical significance of regional metastatic disease. For example, most clinicians diagnosing and treating breast cancer would accept the observation that a well-differentiated tumor is biologically less aggressive than a poorly differentiated tumor. However, there are additional variables that would help predict the likelihood of recurrence, including such factors as tumor size, grade, hormone receptor expression, and yet to be defined new markers. Some biologically aggressive tumors may actually respond better to cytotoxic chemotherapy than a less aggressive tumor. The exact combination of prognostic factors that accurately predicts which tumors will recur and which will not is probably not attainable in the context of modern clinical trials and may require tens of thousands of patients or more, considering the degrees of statistical freedom that exist within our current and expanding set of prognostic variables. Clinical significance evaluates outcome in the context of diagnosis and
treatment, whereas biologic significance implies and perhaps should be reserved for outcome in the absence of treatment, and ideally in the absence of diagnostic intervention such as removal of the tumor.

In breast cancer we have very few opportunities to assess intrinsic biologic significance and these are mainly anecdotal. An excellent example of this conundrum is present within the population studied in this article. Two of the patients had only isolated tumor cells or clusters no larger than 0.2 mm present as occult metastatic disease (both had pathologically negative lymph nodes on the initial examination utilized 20 years ago for purposes of clinical management). One of these patients died from breast cancer and did not receive chemotherapy; the other patient received chemotherapy and was alive without evidence of distant recurrence. We are unable to assess whether the outcome in these two patients was due to innate tumor biology or clinical intervention, yet we tend to cling to the anecdotal observation that the patient receiving chemotherapy was cured. We also tend to forget that patients receiving chemotherapy and having no detected occult metastases died from their disease probably due to innate tumor biology that was generally set long before clinical detection of the primary tumor. Our role as clinicians and investigators is to define the general parameters of clinical significance, while recognizing that innate biology and situational complexity will constantly confound our best efforts to alter innate biologic behavior.

Although it is unlikely that micrometastases represent the proverbial silver bullet of prognostication, micrometastases will most likely have some role in influencing the prognosis and management of breast cancer, given the long-standing value of knowing the tumor status of axillary lymph nodes. Defining to what extent we should look for them and to what extent they contribute to outcome and management is just one of many important tasks to be completed in the field of breast cancer research.

REFERENCES
