Small Beginnings: Do They Matter? The Importance of Lymphovascular Invasion in Early Breast Cancer

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In the era of tailored therapy, the evaluation of systemic treatment of breast cancer has been increasingly dominated by consideration of biological features of the tumor and the host. Established breast cancer prognostic factors—those that determine natural history of breast cancer—include axillary nodal status, tumor size, histological grade, hormone receptor status, HER-2 expression, and presence of lymphovascular invasion. These factors often inform decisions about whether to use adjuvant systemic therapy. In contrast, predictive markers like expression of estrogen receptor (ER) alpha, progesterone receptor, and HER-2 protein are powerful tools to select certain types of therapy. Techniques to examine a myriad of genomic, transcriptional, or proteomic factors simultaneously, so-called ‘omics, currently dominate this field.

In this molecular age, it is important to reflect on the continuing importance of classic histopathology. One such feature is identification of lymphovascular invasion. Its importance in prognosis was suggested at the 2007 St. Gallen consensus conference (1) when extensive lymphovascular invasion was identified as a factor to identify women with moderate risk as opposed to low risk for recurrence. These classic histological studies have been amplified by immunohistochemical analysis. For example, immunohistochemical studies of microvascular density assessed by vascular markers such as CD31 and CD34 antigens have usually shown an association between extent of staining and a greater likelihood of subsequent metastatic disease (2), shorter relapse-free interval, and reduced overall survival in patients with node-negative, ER-negative breast cancers (3). The presence of tumor in peritumoral small lymphatic spaces, independent of lymphovascular density, has been shown to play a fundamental role in tumor progression (4). D2-40 or podoplanin, a novel antibody, selectively stains the endothelium of lymphatic vessels. The utility of this antibody as a specific marker for detection of lymphovascular invasion in the routine pathological workup is evolving (5,6). Recent studies (7,8) have demonstrated a higher sensitivity for detection of lymphovascular invasion by D2-40 than by routine histological detection or CD31-detected vascular invasion. Controversy continues to exist with regard to the process whereby tumor cells gain access via preexisting lymphatics or via newly formed lymphatics at the invasive front of the tumor; D2-40-detected lymph channel invasion along with high CD31 microvessel density has been associated with outcome in breast cancer as shown in univariate and multivariable analyses.

Several studies have consistently shown that lymphovascular invasion is an adverse prognostic factor for relapse and survival in node-negative patients in combination with other risk factors such as tumor grade and size and receptor status (9). The need for prospective research to define its individual role has been raised. In this issue of the Journal, Ejlertsen et al. (10) report a comprehensive analysis of the prognostic value of lymphovascular invasion in tumors from 15,659 women entered into the Danish Breast Cancer Cooperative Group registry from 1996 to 2002. The goal of the study was to assess whether lymphovascular invasion was a single independent prognostic factor in stratifying early breast cancer patients as low risk vs high risk for recurrence. The presence of lymphovascular invasion was noted in only 15% of tumors. A statistically significant difference in 5-year invasive cancer disease-free interval was seen: 79.5% (95% confidence interval [CI] = 78.7% to 80.2%) for patients without lymphovascular invasion vs 54.5% (95% CI = 52.4% to 56.6%) for patients with lymphovascular invasion. These differences were mirrored in the overall survival rates of 87.3% (95% CI = 86.7% to 87.8%) and 66.0% (95% CI = 64.1% to 67.9%) in patients without and with lymphovascular invasion, respectively, and they persisted in multivariable analysis. Finally, the study gives the unexpected and somewhat disappointing result that lymphovascular invasion was associated with adverse outcome in patients who are at high risk for recurrence by other recognized prognostic factors but not in those who are at low risk by the same criteria. It is therefore apparently not useful as a means to subdivide the low-risk group, the group in which many clinicians and patients would like assistance. This finding is at odds with the 2007 St. Gallen consensus recommendations, where extensive lymphovascular invasion was felt to be sufficient to upstage patients from low risk to moderate risk for recurrence.

The strengths of this study are several. It is derived from a population-wide database of virtually all women diagnosed with breast cancer in Denmark over a 7-year period, who were treated according to standard algorithms and whose tumors were analyzed in a prespecified way for multiple factors including lymphovascular invasion. It has shown the expected association between lymphovascular invasion and other poor prognostic features such as with positive nodal status, tumor size greater than 2 cm, ductal histology, grade 2 or 3, ER negativity, and use of adjuvant endocrine therapy and/or chemotherapy (P < .001 for each). This agreement with other work gives credence to the results of this study. Finally, the test is “low tech” and could theoretically be performed in virtually any diagnostic laboratory, although it does require two things—investment of valuable pathologist time and availability of standardized criteria that are easily reproduced across all pathology laboratories.

The limitations of the study are also real. Neither the reproducibility of the determination of lymphovascular invasion nor its extent was documented; rather a dichotomous cutoff of present or absent was used. HER-2 testing was not performed, and the study period preceded the routine use of several contemporary adjuvant...
therapies including aromatase inhibitors, anti–HER-2 therapy, and taxanes. Most importantly, even this large sample may be too small to make us secure about one of the primary conclusions of the study: that lymphovascular invasion is associated with a poorer outcome in every patient subset, except in those at low risk for recurrence. This last conclusion is based on the finding of lymphovascular invasion in 54 low-risk women out of the approximately 15,000 women studied. Thus, it is possible that this finding could simply represent the play of chance rather than a finding of substance, despite the statistical significance.

Two key questions for the future are determining the molecular determinants that play a role in lymphovascular invasion and the clinical implications of their alterations. This study provides an unparalleled opportunity to assess the clinical impact of newer markers of lymphovascular invasion like CD31 and D2-40 on well-annotated specimens from a very large and unselected population; it is conceivable that such staining could refine our ability to discriminate prognosis more precisely. In addition, the utility of anti-angiogenic therapies is under evaluation in breast cancer. A role for bevacizumab in conjunction with taxane therapy has been supported by two trials in metastatic breast cancer (11,12), and its utility in high-risk early-stage breast cancer is under evaluation. It has been suggested that low-dose weekly or metronomic chemotherapy might have anti-angiogenic qualities (13). Multitargeted small molecule inhibitors with anti-angiogenic effects are in clinical testing in breast cancer. Predictive markers for these approaches are sorely needed. Whether markers that are associated with lymphovascular invasion might also predict for success of antiangiogenic therapy is an area for investigation.

References
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