Re: Population-Based Study of Peritumoral Lymphovascular Invasion and Outcome Among Patients With Operable Breast Cancer

In a comprehensive analysis performed using data from the Danish breast cancer registry, Ejlertsen et al. (1) conclude that lymphovascular invasion (LVI) has no prognostic significance within a clearly defined low-risk subgroup of patients. In an extensive multivariable analysis, they also show that the prognostic value of LVI for disease-free survival is slightly influenced by estrogen receptor (ER) status but not by tumor size, nodal status, menopausal status, or systemic therapy. These parameters broadly define the low-risk population, and consequently, it is surprising that LVI loses its prognostic significance within this subgroup. Because these patients were also selected based on having low tumor grade, we performed a similar multivariable analysis, including LVI, size, age, mitotic index, and ER status, in a previously published large series of node-negative invasive ductal carcinoma (2). With a mean follow-up of 15.6 years, the prognostic value of LVI remained, regardless of tumor grade (Figure 1).

The results of Ejlertsen et al. raise several comments. Although patient and tumor characteristics are not specified within each risk group, the 1884 lobular carcinomas may represent a substantial portion of the 3271 low-risk patients, considering that lobular carcinomas that are grade 3, hormone receptor negative, or occur in patients aged 35 years and younger are rare. Because LVI is seldom observed and its prognostic impact probably limited in these tumors, combined analysis may lead to inaccurate conclusions for the well-delineated subgroup of low-grade ductal carcinomas.

Second, the percentage of patients with LVI in the Danish series was low compared with ours or with other published series: 28% vs 40%–78% in patients with node-positive tumors (3,4) and 1.6% vs 8.1% in low-risk patients [complementary analysis from (2)]. Considering the large number of laboratories that participated in the study by Ejlertsen et al., an external quality control program, a central review of cases, and/or systematic immunochemical analyses (5) would have been helpful.

Third, the conclusions of the authors are based on relapse analysis of 54 LVI-positive low-risk patients (ie, 1.65% of the low-risk patients and 0.33% of the whole population). A twofold higher number of LVI-positive low-risk patients should have been analyzed to potentially show a statistically significant hazard ratio of 2.26, similar to the hazard ratio observed in the high-risk group. Furthermore, factors defining this low-risk population are associated with a low risk of early relapse (6), and a median follow-up of 6.4 years is insufficient to properly assess prognostic factors within this group. This short-term follow-up might have contributed to the overlap of the hazard ratio confidence intervals (CIs) of the low-risk group (95% CI = 0.39 to 1.73) with the value for the whole group (HR = 1.33), erasing any potential statistical difference from the global effect.

In conclusion, we find that the results of Ejlertsen et al. are insufficient to overturn the widely accepted evidence of clinically useful independent prognostic value of LVI in invasive ductal carcinoma. Because breast cancer can be divided into distinct molecular subtypes with different outcomes, prognostic factors should no longer be assessed when subtypes of breast cancer are mixed. Genomic studies have shown that ER-positive invasive ductal carcinomas can be subdivided according to proliferation index (7). It would be useful to reanalyse the prognostic impact of LVI within this homogeneous low-risk subgroup.

References

Funding

L.M. receives funding for clinical and translational research from AstraZeneca, the maker of anastrozole, an aromatase inhibitor used to treat ER-positive breast cancer.

Notes

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DOI: 10.1093/jnci/djp490
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Advance Access publication on December 31, 2009.

molecular subtypes or histological subtypes. We have refrained from exploratory and data-driven subset analyses because of the inherent methodological issues.

We agree that quality control, external review, and use of technologically more advanced methods should be implemented whenever possible. In our large population-based study, lymphovascular invasion was, however, evaluated prospectively according to a well-defined protocol. Close adherence to a stringent protocol and sparse use of supplementary immunohistochemical analyses is a likely explanation of the somewhat lower frequency of lymphovascular invasion observed in our study.

The letter of Debled et al. implies that our conclusion was based on overlapping hazard ratios, whereas in fact we demonstrated statistically significant heterogeneity in the association between lymphovascular invasion and overall survival according to risk group ($P = .03$ in a Wald test of interaction). In a multivariable analysis that adjusted for other patient and tumor characteristics, the presence of lymphovascular invasion was for the whole group associated with an increased mortality (hazard ratio [HR] for death = 1.30, 95% confidence interval [CI] = 1.20 to 1.42), but this was not the case in the low-risk group (HR for death = 0.37, 95% CI = 0.12 to 1.16). The power of our study is expressed in these confidence intervals, and a post hoc power calculation would not add to this information (1).

Treatment decisions should whenever possible be evidence based, and lymphovascular invasion was not an independent high-risk criterion in this large, prospective, population-based study. Recently, Cheang et al. (2) reported a lower frequency of lymphovascular invasion in luminal A as compared with luminal B and luminal-HER2 positive breast cancer, and we agree that molecular subtyping of breast cancers holds promise for the future.

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References