Breast Cancer Tumor Size, Nodal Status, and Prognosis: Biology Trumps Anatomy

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In the articles that accompany this editorial, Wo et al and Hernandez-Aya et al present two provocative clinical findings with respect to the relationship of tumor size and lymph node status to clinical outcome. Together, these articles highlight the less than perfect connection between a tumor size and its ability to colonize lymph nodes and distant organs. The first article, by Wo et al, reports that in cases of extensive lymph node involvement, very small tumors may confer a more aggressive subtype than larger tumors with the same degree of lymph node involvement. The second article, by Hernandez-Aya et al, proposes that in triple-negative breast cancers, the worse prognosis associated with lymph node involvement may not be greatly affected by the absolute number of positive lymph nodes.

Wo et al were motivated to conduct their study because of their hypothesis that very small tumors that generate extensive lymph node involvement may represent a unique subset of highly malignant breast cancers. To evaluate this idea, they used the Surveillance, Epidemiology, and End Results registry to identify 50,949 women who were diagnosed with nonmetastatic T1 and T2 invasive breast cancers and were treated with surgery and axillary lymph node dissection. In support of their hypothesis, among women who had four or more involved lymph nodes (N2), those women with smaller tumors (T1a) had a higher breast cancer–specific mortality (BCSM) than those with larger tumors (T1b). This difference was not seen in patients with fewer or no lymph nodes involved. Notably, among patients with estrogen receptor–negative cancer and four or more involved lymph nodes, patients with T1b tumors experienced significantly lower BCSM relative to patients with T1a tumors. On the contrary, no significant difference was noted among patients with T1a tumors relative to patients with T1c or T2 tumors. That is, the authors demonstrate that for very small tumors with extensive lymph node involvement, there is a decreasing BCSM as the tumors get larger. After a set threshold (Figure 2 in the article by Wo et al), however, BCSM increases as one would expect, with increasing tumor size conferring increased mortality.

In another retrospective study, Hernandez-Aya et al investigated the prognostic relationship between tumor size and lymph node status in 1,711 women with triple-negative breast cancer. Their work indicates that in triple-negative breast cancers, any amount of nodal involvement denotes a worse relapse-free and overall survival. Essentially, once lymph nodes are involved, outcomes are not greatly affected by the absolute number of positive lymph nodes. In addition, when the authors compared node-negative to node-positive disease for all tumor sizes and all degrees of positive nodal involvement, there was a significant difference in outcomes. Unlike in the Wo et al study, Hernandez-Aya et al categorized patients according to T1, T2, and T3/T4, and did not additionally subcategorize the T1 tumors. Thus, it is not clear whether additional subset analysis would show that T1a tumors do particularly worse than T1b or T1c tumors.

Why are these results surprising or, at least, deserving of being reported in this journal? The obvious answer is that they do not jibe with accepted—and profoundly influential—notions of malignant progression. From the beginning of our understanding of cancer as a disease of abnormal cellular growth, we have thought of malignant cellular expansion and metastases as a sequential process. By this concept, the initial defect in carcinogenesis is derangement in mitosis (or, later, the mitosis-apoptosis ratio), such that cancer cells accumulate as an abnormally large mass. With increasing cell accumulation and resulting additional changes in cell biology—now accepted as the consequence of genomic aberrancies—cells would be expected to acquire the ability to migrate, via blood and/or lymphatic channels, infiltrate organs other than their organ of origin, and proliferate in these sites as microscopic and then gross metastases. The fact that large breast cancers are more likely to be associated with axillary nodal metastases, and consequently distant metastases as well, has always been advanced as consistent with and, in fact, proof of this fundamental concept. Indeed, the push to diagnose breast cancers as early as possible after spontaneous tumor initiation, such as with mammography and now magnetic resonance imaging in selected cases, has been motivated by the idea that if a tumor can be removed before it learns metastatic behavior, distant metastases might be avoided. Hence, the success of breast screening programs to reduce mortality from this disease was the expected result and additionally increased our confidence in the malignant progression dogma.

But nagging enigmas in breast cancer behavior have always added a tinge of uncertainty. One of the most disturbing is the fact that metastatic pathways seem to be predictable and unpredictable at the same time. Modern data on sentinel lymph node mapping seems to support the principle, popularized by Halsted in the nineteenth century, that the flow of cells from the breast tumor to the axilla is orderly: if the first nodes that receive lymphatic flow are free of cancer cells, it is almost certain that the rest of the axilla will be clean. However,
negative axillary contents do not guarantee freedom from distant metastases, nor do axillary metastases portend systemic spread with certainty, even in the most extreme cases of nodal involvement. Indeed, the knowledge that cancers could disseminate early and yet spare the axilla led to the suggestion by Fisher, Shapiro and Fugmann that the use of anticancer drugs in the perioperative period could improve cancer-specific outcomes, which has indeed been confirmed experimentally. Hellman recognized that Halsted’s view of an orderly anatomic route of spread and Fisher’s of the lack of an obligatory requirement for a strict route could both be true, but how could these divergent views be reconciled biologically?

We have recently learned from well-conducted, randomized trials that the finding of isolated tumor cells in axillary lymph nodes does not necessary convey dire implications. Furthermore, for patients who are undergoing breast-conserving surgery and radiotherapy to the breast and low axilla, those with fewer than three involved sentinel axillary lymph nodes do not suffer from not having had a complete axillary dissection, although more than a quarter of patients so treated have residual nodal metastases that are left behind.

Now, adding to the confusion, are the respective findings of Wo et al. and Hernandez-Aya et al. that indicate that a subset of small tumors may be highly aggressive, despite their size, and that among triple-negative breast cancers, once lymph nodes are positive, the absolute number of lymph nodes involved does not change the inherent worse prognosis. Certainly, these findings might be regarded as statistical flukes, although the large sample sizes and methodologic competencies involved would render this unlikely. So assuming that the results are reproducible and hence valid, what might they mean, and how do they relate to the clinical enigmas cited above?

Some solace may be found in emerging novel concepts of cancer that are centered on the relatively new science of cancer metastasis. New data is, in fact, challenging the notion that cancer cells that leave a primary tumor—often called circulating tumor cells or CTCs—unidirectionally seed metastases in regional (lymph nodes) or distant sites. In contrast, there is evidence in experimental animal systems that CTCs can return to colonize and promote growth in their tumors of origin. Moreover, the ability to seed is necessary but not sufficient to generate colonies in seeded sites; indeed, cells can lie dormant for decades in such sites without growing.

That these concepts are rational is consistent with well-established biologic principles that are grounded in metastasis research. Using human cancer cells, it has been shown that the genetic tool kit for generating successful metastases seems to be site specific, with different, barely overlapping signatures for lung, bone, and brain involvement.

Moreover, the many barriers that CTCs face in infiltrating and growing in regional and distant organs—including tight vascular capillary endothelial walls and unfamiliar microenvironments—are less daunting in the cancer of origin. Here the cells encounter a leaky neovasculature and a familiar microenvironment. The hypothesis of cancer self-seeding was recently validated in diverse experimental models that included breast and colon adenocarcinomas and melanomas. Tumor-derived inflammatory cytokines interleukin (IL) -6 and IL-8 act as CTC attractants. The self-seeding CTCs tend to express matrix metalloprotease-1/collagenase-1 and the actin cytoskeleton component fascin-1. These molecules, in addition to seed-derived chemokine ligand 1, promote accelerated tumor growth, angiogenesis, and the recruitment of myeloid cells into the stroma. Hence, a large tumor may not only be a cause of distant seeding (the conventional concept) but also a result of self-seeding. This concept certainly complicates the relationship between tumor size and distant metastatic potential.

The site-specific nature of metastases has been confirmed not only by in vivo experiments in mice using cell lines from human sources, but also by the analysis of recurrence-free survival curves in patients whose tumors have been classified by molecular signatures. Although formal proof of the existence of self-seeding in human cancer specimens will require advances in single-cell genomic sequencing and bioinformatics technology (comparing tumor cells from primary and secondary sites), there are no a priori reasons why the concept is not applicable to all mammalian malignancies. On the basis of these data, therefore, we could envision a case in which a primary cancer is excellent at seeding axillary lymph nodes but not distant organs or vice versa: hence, the imperfect connection between axillary involvement and the involvement of distant organs. Furthermore, a large primary cancer could be large because of its pronounced mitotic activity or because it is an excellent self-seeder: hence, the imperfect connection between tumor size and metastatic behavior. Because of the site-specific nature of metastases, the abilities to self-seed or to seed distant sites should be imperfectly correlated as well. Therefore, we could envision a case in which a primary cancer is excellent at seeding axillary lymph nodes (via the sentinel node route) and/or distant organs, but not itself. Moreover, a small cancer that has demonstrated the capacity to seed a given number of lymph nodes may express node-specific and distant-organ metastatic genes but not self-specific ones. Therefore, it might be more aggressive, in terms of ultimate outcomes, than a larger cancer that involves the same number of axillary nodes. The larger cancer, in this instance, is better at seeding itself but less proficient at seeding regional lymph nodes or distant sites, so it needed more cells in the primary mass to accomplish the comparable degree of nodal involvement.

The important aspect of this discussion, then, is that simple anatomic reasoning—which has led to many advances in clinical oncology but also the clinical enigmas described above—may not be the most productive way forward in understanding the clinical behavior of cancers and hence prognosis. Elucidating the molecular mechanisms that underlie the biology of individual cancers would seem to be a more useful focus of our attention. Fortunately for us and for our patients, both technical and conceptual improvements are now available and are resulting in headway. These, coupled with insightful clinical observations as illustrated by the two articles in this issue, herald a future of greater understanding and resulting clinical progress.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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