Commentary Putative growth characteristics of micrometastatic breast cancer

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Abstract

The fate of cells that disseminate from a primary breast tumour remains poorly understood. Studies of the kinetics of recurrence in breast cancer patients are raising important questions about the biology of the metastatic process. Where do tumour cells reside once they leave the primary tumour, and what factors influence their dormancy and recurrent growth? Clinical data analyses are leading to hypotheses about the biology of metastasis, dormancy and recurrence. A combined clinical and experimental approach to testing these hypotheses will help to clarify this important issue in breast cancer biology and patient care.

Much remains to be learned about the biology of breast cancer micrometastases, including their predeliction for late clinical recurrences. When tumour cells have been disseminated systemically, where do they reside and what governs their subsequent fate? In this issue of Breast Cancer Research, Demicheli and colleagues [1] report on their investigation into the kinetics of metastastases to distinct metastatic sites, as well as the kinetics of contralateral breast cancer and development of other primary tumours. The study used data from 1,526 patients from the National Cancer Institute of Milan, for whom data on the site of first recurrence (bone, viscera, or soft tissue) were available. This study reports that the kinetics of recurrence to different metastatic sites followed the same bimodal pattern for recurrence (to any site) described previously by these authors and others, with a first peak at around 2 years and a second, smaller peak at about 5 years [2-6]. In contrast, development of contralateral breast cancer or other new cancers did not follow this bimodal pattern, instead exhibiting a relatively constant, low rate of occurrence over time, with no early peak [1]. These findings suggest that the biology of metastasis development is distinct from that of developing new contralateral breast or other cancers. They also suggest that metastasis to different sites follows the same kinetics of recurrence, perhaps reflecting systemic biological similarities that affect metastases, at least for the sites studied.

Concepts from experimental models of metastasis suggest that cancer cells may be distributed from primary tumours via the blood or lymphatic circulation, and arrested efficiently in the first capillary bed encountered [7]. Once in new sites, some cells may remain dormant but viable, resist cytotoxic therapies and produce late-developing metastases [8,9]. Clinical support for these concepts comes from studies in which carcinoma cells were identified in bone marrow of cancer patients, and these cells appear to portend poor outcome [10]. Although disseminated tumour cells have been identified in bone marrow (because this tissue has been examined), it is possible that they reside in many other organs (which generally have not been examined), consistent with experimental studies [8].

In an analysis of older literature, Weiss [11] concluded that numbers of metastases detected at autopsy in a given organ were usually (two-thirds of the time) in proportion to blood flow to that organ from the site of the patient's primary tumour. In contrast, in the other third of tumour-secondary site pairs there were more or fewer metastases than would be expected based on blood flow alone [11]. (Interestingly, among the latter were metastases from breast and prostate cancer to bone, where more metastases were found at autopsy than would be expected based on blood flow alone, suggesting a favourable growth environment for these cells in bone.) Additional autopsy studies looking for the presence of disseminated micrometastases in multiple organs are needed.

It is unfortunate that the study by Demicheli and colleagues [1] did not divide patients by hormone receptor status, and this information was not available for this patient cohort. Saphner and colleagues [5] reported that patients with oestrogen receptor (ER)-positive versus ER-negative tumours have distinct recurrence kinetics, with ER-negative patients exhibiting a greater hazard of recurrence during the first 5 years, and a lower hazard of recurrence from years 5 to 12, as compared with ER-positive patients. This phenomenon was well illustrated by the rates of recurrence in the National Cancer Institute of Canada Clinical Trials Group MA17 trial [12,13]. It would be most interesting to determine in more recent patient series whether hormone receptor status is associated with distinct patterns of recurrences to individual metastatic sites.

The nature of the biology responsible for the bimodal peaks has not yet been elucidated. Some experimental evidence suggests that late-developing metastases, especially in the era of adjuvant therapy, may represent emergence of cells that had been in a dormant state at the time of administration of adjuvant therapy [9]. Furthermore, the potential role played by cancer stem cells in development of late metastases remains to be determined [14]. The study by Demicheli and coworkers [1] presents interesting and important concepts that should be further assessed in other clinical series in which data on sites of first recurrence are recorded, including the effects of hormone receptor and human epidermal growth factor receptor (HER)2 status as well as specific treatments. A trial is currently underway that will assess the anti-HER2 therapy lapatinib in response to the chronic high and ongoing relapse risk for this subtype of the disease [15]. In addition, it would be interesting to include data on the kinetics of metastases from breast cancer to brain, because these are uncommon as a first site of metastasis (although metastasis to brain is increasingly common in HER2-positive patients treated with trastuzumab). These analyses will generate hypotheses about the biology of metastasis and latedeveloping metastases, which can be taken to further clinical and experimental investigations to help identify the mechanisms responsible.

Competing interests

The authors declare that they have no competing interests.

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