Seminars in Diagnostic Pathology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Surviving at a distant site: The organotropism of metastatic breast cancer

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ARTICLE INFO

Keywords:
Breast cancer
Molecular subtypes
Metastasis
Organotropism

ABSTRACT

Many cancers demonstrate a non-random distribution of sites for distant relapse while others have the propensity to metastasize to multiple organ systems. One of the notable recent findings is that the breast cancer subtypes differ not only in their biological characteristics as primary tumors but also in their capacity for metastatic progression. This information could potentially be utilized in treatment decision making and surveillance strategies.

Introduction

Breast cancer remains the most common malignancy among American women, except for skin cancer, with an estimated 246,660 new cases of invasive disease in 2016.[1] Approximately one-eighth (12%) of women in the US will develop invasive breast cancer during their lifetime. Breast cancer is the second leading cause of cancer mortality in women, with an estimated 40,450 cancer deaths in 2016.[1] The vast majority of these deaths is due to metastatic disease that is resistant to systemic therapies. Recent advances have made promising improvements in early detection of breast cancer. Yet, approximately 5 to 10% of patients are still diagnosed with metastatic diseases at initial presentation. Moreover, there is a 20–30% likelihood of developing distant metastasis when diagnosed with early-staged breast cancer despite recent advances in wide application of systemic (neo)adjuvant therapies.[2,3]

Clinicopathologic factors influencing breast cancer progression largely include histologic grade, lymphovascular spread, pathologic tumor/node stages, and receptor status, namely estrogen receptor (ER), progesterone receptor (PR) and HER2.[4–6] On the other hand, it has long been known that cancer metastasis is a non-random process. Each tumor type manifests a distinct pattern of distant organ involvement, a phenomenon known as "metastatic organotropism." For example, the overwhelming majority of patients with advanced stage prostate cancer suffer from bone metastasis, whereas liver relapse is predominantly observed among patients with late stage colorectal carcinoma, who rarely develop bone metastasis. In contrast, some tumor types, such as breast cancer and renal cell carcinoma, commonly metastasize to multiple organs.[7,8] It is with no doubt that the distant sites to which breast cancer preferentially relapse, of which bone, liver, lung and brain are among the most common organs, are of clinical significance, and are closely related to the patients' prognostic outcome.[3,8,9] Herein we provide a review of the most recent findings and emerging concepts in metastatic organotropism of breast cancer as this information is crucial to constructing a clinical and translational framework to develop more effective strategies for prevention and treatment of this lethal disease.

Revisiting the 'seed and soil' hypothesis in cancer metastasis

In 1889, Dr. Stephen Paget, an English Surgeon and the son of the famed pathologist, Sir James Paget, published a milestone article on cancer metastasis by analyzing autopsy records of 735 women who had died of breast cancer.[10] He was deeply impressed by the striking discrepancy between the relative blood supply and the frequency of metastasis in some organs, and documented the non-random pattern of metastasis to certain organs. For example, the incidence of metastasis to the ovaries was found to be higher than to the spleen and kidneys combined, and he noted that "in a cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone." To that end, he proposed the 'seed and soil' hypothesis to explain the marked kinship of breast cancer cells and bone: "when a plant goes to seed, its seeds are carried in all directions; but they can only grow if they fall in congenial soil." Accordingly, circulating tumor cells (the 'seeds') can achieve distant localization only at the sites where the microenvironment (the 'soil') is permissive for their growth, i.e., osteotropic tumor cells possess certain bone-homing characteristics, and the bone marrow supplies a fertile soil for them to grow on. Ever since, this concept has remained a basic principle in the field of cancer metastasis. Although Stephen Paget has long been credited with proposing the 'seed and soil' theory of metastasis, he himself credited this concept to the Austrian ophthalmologist, Ernst Fuchs (1851–1930), who defined

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https://doi.org/10.1053/j.semdp.2017.11.008

it as a "predisposition" of an organ to be the recipient of specific 'growths,' as he clearly stated "…the chief advocate of this theory of the relation between the embolus and the tissues which receive it is Fuchs…"

In the early 20th century, the New York pathologist James Ewing challenged Paget's 'seed and soil' hypothesis. In his proposal, metastatic dissemination occurred by purely mechanical mechanisms as a result of the anatomical structure and hemodynamic factors of the angiolymphatic system: "cancer cells grew at a particular site because they were directed to that site by the direction of blood flow and lymphatics."[11] This concept certainly explains the organ-specific metastasis of certain tumor types, such as colon cancer, as drainage of the large intestine through the portal vein leads to high incidence of liver metastasis.

To further investigate whether metastatic tumor cells "home" to specific organs and whether mechanical arrest of circulating emboli can explain patterns of metastasis or whether tumor cell-organ affinities are responsible for the growth of metastatic foci, Hart and Fidler conducted a detailed experimental analysis using a metastatic melanoma mouse model in 1980.[12] By intravenous injection of B16 melanoma cells into syngeneic C57BL/6 mice, they found that tumor nodules developed in the in situ lungs and in grafts of pulmonary or ovarian tissue. In contrast, neoplastic lesions failed to develop in control grafts of similarly implanted renal tissue or at the site of a surgical trauma. Parabiosis experiments suggested that immediate arrest of circulating neoplastic cells could indeed occur, but the subsequent growth of tumors in the implanted organs was not due to an enhanced initial arrest of tumor cells. These findings illustrated that the outcome of metastasis indeed depends on the intimate interaction between tumor cells and their host, thus further supporting the 'seed and soil' hypothesis.

To further attest to the hypothesis in the clinical setting, Hess *et al.* analyzed the metastatic patterns of adenocarcinoma from 11 primary tumor sites on 15 metastatic sites from 4399 patients diagnosed between 1994 and 1996. To that end, three primary tumors were found to have single, dominant metastatic sites: ovarian carcinoma to the abdominal cavity (91%), prostate to bone (90%), and pancreas to liver (85%). Furthermore, the liver was the dominant metastatic site for gastrointestinal (GI) primary tumors in 71% of patients, whereas bone and lung metastases were noted most frequently in non-GI primaries (43% and 29%, respectively). In contrast, colorectal cancers were seen only rarely to develop bone metastasis (Fig. 1). The algorithms that the authors developed achieved an accuracy of 64% on an 1851-patient independent test set, compared with a 9% accuracy when a random classifier was used.[8] Thus, distinct metastatic patterns are indeed discernable for the main sites of primary carcinomas.

A study based on a rich set of autopsy data consisting of 3827 patients between 1914 and 1943 also demonstrated a markedly organotropic pattern of cancer metastases (Fig. 1).[13] Interestingly, the proportion of some distant organs involved by a given advanced carcinoma was significantly different from the aforementioned clinical study (i.e., liver and lung in breast cancer; bone in prostate cancer; liver in colorectal cancer). However, this was a uniquely broad study of actual postmortem tissues on patients who died before the advent of contemporary therapies. Thus, the findings likely represent a close approximation of the progression of untreated malignancies in humans, although it is difficult to envision similar future studies of this scale in the era of modern medicine.

Moreover, review of early clinical data on site preferences of metastases from various tumor types suggested that locoregional metastases could indeed be attributed to anatomical or mechanical factors (through for example lymphatic drainage to regional lymph nodes), whereas distant relapse was site-specific for many cancer types.[14,15] Thus, both Paget's and Ewing's theories seemingly are 'correct,' but may reflect different stages of the multi-stage process of tumor metastasis: Ewing concentrated on the initial process of cancer cell migration into the surrounding tissue and lymphovascular spaces while Paget stressed that of tumor cell migration and secondary growth at a distance.

More recently, Fidler defined the modern "seed and soil" hypothesis as consisting of the following three principles.[16] Firstly, primary tumors (and their metastatic deposits) are biologically heterogeneous and consist of subpopulations of cells with diverse angiogenic, invasive and metastatic properties. This principle has been demonstrated by a large body of work showing that the expression of molecules associated with proliferation, angiogenesis, cohesion, motility and invasion vary among different cell populations within cancerous tissue. Secondly, the metastatic process is selective for neoplastic cells that have survived the long journey to the distant site, which includes angiolymphatic invasion, survival in the circulation, arrest in a distant capillary bed, and extravasation into, and multiplication within, the organ parenchyma. Thus, metastases can originate from a single cell but may also derive from multiple clones. Thirdly and most importantly, the outcome of metastasis depends on interactions of tumor cells with the biologically distinctive "soil" in the microenvironment of different organs. Therefore, development of anti-cancer drugs should be targeted at not only the tumor cells per se, but also the homeostatic factors controlling tumor cell proliferation, survival, invasion and metastasis.

Metastatic organotropism: an intrinsic property of breast cancer subtypes

As previously mentioned, adenocarcinomas originating from the ovary, prostate and pancreas tend to have a single, dominant metastatic site, whereas some other tumor types have a propensity to relapse in multiple distant sites. As an example of the latter, about half of advanced breast cancers metastasize to bone, and approximately 25% relapse in liver and lung, respectively.[8,9,17] Interestingly, the relative proportional distribution of metastatic breast cancer clones to these organs is fairly consistent across a number of large clinical studies,[8,9,18] whereas they are much higher in the aforementioned large autopsy

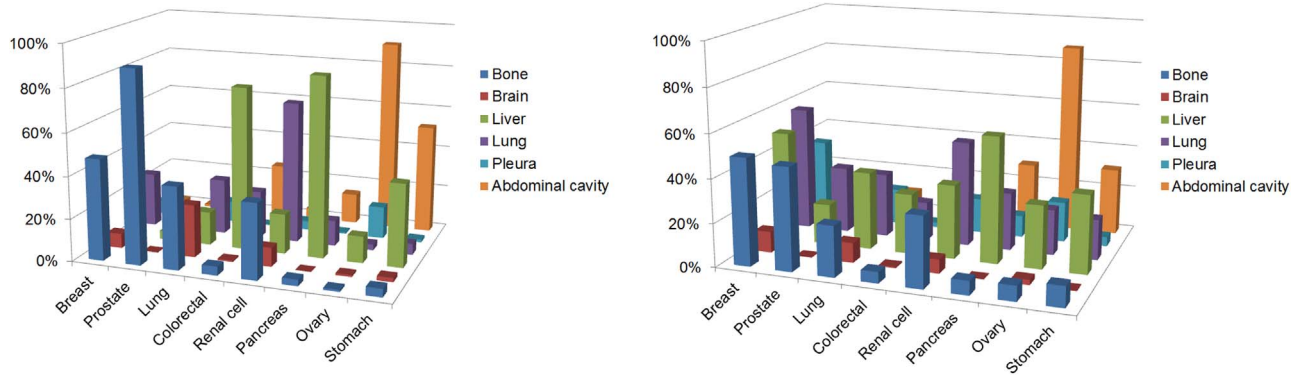

Fig. 1. Organ distribution patterns of metastases from common cancers in a large clinical series (left; based on the data presented in Hess, et al.[8]) and a large autopsy series (right; based on the data presented in Disibio, et al.[13]).