EBioMedicine 57 (2020) 102852

Contents lists available at ScienceDirect

EBioMedicine

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

Commentary

Defining the role of lymph node metastasis in systemic breast cancer evolution

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ARTICLE INFO

Article History:
Received 5 June 2020
Accepted 6 June 2020
Available online xxx

Breast cancer research has always generated important, pioneering ideas about metastasis evolution which then shaped thinking in other solid tumor types as well. Based on the observation that spread to locoregional lymph nodes was associated with poor outcomes in breast cancer, William Halsted developed his hypothesis of orderly sequential progression in the late 19th century. It stated that distant metastases were seeded only after a primary tumor had successfully colonized the surrounding lymphatics and assigned a central causal role to lymph node metastases in the development of systemic disease. The radical mastectomy – a highly invasive surgery that dominated breast cancer therapy until the 1970s – was the result of Halsted's progression model.

In 1977, Bernard Fisher and colleagues showed that the radical mastectomy did not actually improve survival over simple mastectomy and radiation [1]. Moreover, in patients with no clinical evidence of lymph node involvement, axillary dissection did not further improve outcomes. Fisher formulated an "alternative" hypothesis of breast cancer metastasis evolution which posited that breast cancer is a systemic disease from the outset. In his view, lymph node metastases did not seed distant metastases; they simply reflected the general success rate of metastatic cells in a given patient [2]. Subsequent clinical trials that evaluated the benefit of lymphadenectomy in breast [3] and other cancers [4,5] have lent further support to Fisher's hypothesis. In many cancer types, removing lymph nodes without overt clinical signs of disease does not seem to improve outcomes, potentially indicating that they are not directly involved in seeding distant metastases. However, direct experimental evidence to support concrete metastasis evolution models in humans is still relatively rare. In this article of EBioMedicine, Venet et al. [6] present an interesting set of phylogenetic data suggesting that most distant metastases in breast cancer are not direct descendants of lymph node metastases.

To study the evolutionary relationships between lymph node and distant metastases, Venet *et al.* analyzed matched tumor samples from 16 estrogen-receptor positive breast cancer patients. They performed low coverage whole genome sequencing to identify somatic copy number alterations in primary tumors, locoregional lymph node metastases and distant metastases and reconstructed phylogenetic trees based on these data. Analyzing tree topologies, they found that lymph node and distant metastases shared a common subclonal origin in 25% of patients. In these cases, lymph node metastases could plausibly have seeded distant metastases - or at least they arose from the same subclone. In the remaining 75% of patients, at least one primary tumor area was more closely related to the distant lesions than any positive lymph node, making a direct descent from the primary tumor more likely. These percentages of metastasis-to-metastasis vs. primary-to-metastasis seeding instances are remarkably close to those observed in other cancer types [7,8]. Venet *et al.* also correlated patterns of metastasis origin with various clinicopathological variables and made some intriguing preliminary observations – for example, MYC amplifications appeared to be more frequent in patients with distinct lymph node and distant metastasis origins, and these patients also appeared to have better outcomes – but the small cohort size of 16 patients precluded definitive assessment of these associations.

Overall, Venet *et al.*'s results further challenge the idea of a causal connection between lymph node and distant metastases and are consistent with data from breast cancer clinical trials showing no survival benefit for axillary lymph node dissection [3]. In the future, it will be interesting to expand upon the preliminary correlation of clinical parameters with specific tumor evolutionary patterns performed in this study. To achieve this, large patient cohorts with high quality clinical annotation will be needed. This goal can probably only be reached through large multi-institutional collaborations, as the matched tumor samples that were used in this study are exceedingly rare and very difficult to find. However, efforts of this kind will be needed to establish whether a tumor's phylogeny is clinically relevant, that is, whether it contains information that is prognostically useful or can guide treatment. It is conceivable that in the future, clinicians will routinely assess a tumor's evolutionary history to learn

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https://doi.org/10.1016/j.ebiom.2020.102852

important insights about its biology (and hence expected behavior). Studies like this one are paving the way toward this goal.

Declaration of Competing Interest

The author declares no conflicting interests.

References

[1] Fisher B, Montague E, Redmond C, Barton B, Borland D, Fisher ER, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer. A first report of results from a prospective randomized clinical trial. Cancer 1977;39 (6 Suppl):2827–39 cited 2020 May 11Available from: http://www.ncbi.nlm.nih.gov/pubmed/326381.

[2] Fisher B. Laboratory and clinical research in breast cancer—a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res. 1980;40(11):3863–74.

[3] Giuliano AE, Hunt KK, Ballman K V, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA 2011;305 (6):569–75.

[4] Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 2017;376(23):2211–22 Available from: http://www.nejm.org/doi/10.1056/NEJMoa1613210.

[5] Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med 2019;380(9):822–32 [cited 2019 May 15]Available from: http://www.nejm.org/doi/10.1056/NEJMoa1808424.

[6] Venet D, et al. Phylogenetic reconstruction of breast cancer reveals two routes of metastatic dissemination associated with distinct clinical outcome. EBioMedicine 2020 https://doi.org/10.1016/j.ebiom.2020.102793.

[7] Naxerova K, Reiter JG, Brachtel E, Lennerz JK, van de Wetering M, Rowan A, et al. Origins of lymphatic and distant metastases in human colorectal cancer. Science 2017;357(6346):55–60 [cited 2018 Nov 4]Available from: http://www.ncbi.nlm.nih.gov/pubmed/28684519.

[8] Zhang C, Zhang L, Xu T, Xue R, Yu L, Zhu Y, et al. Mapping the spreading routes of lymphatic metastases in human colorectal cancer. Nat Commun 2020;11(1):1–11.