Antiangiogenic breast cancer treatment may benefit only patients with well-perfused tumors

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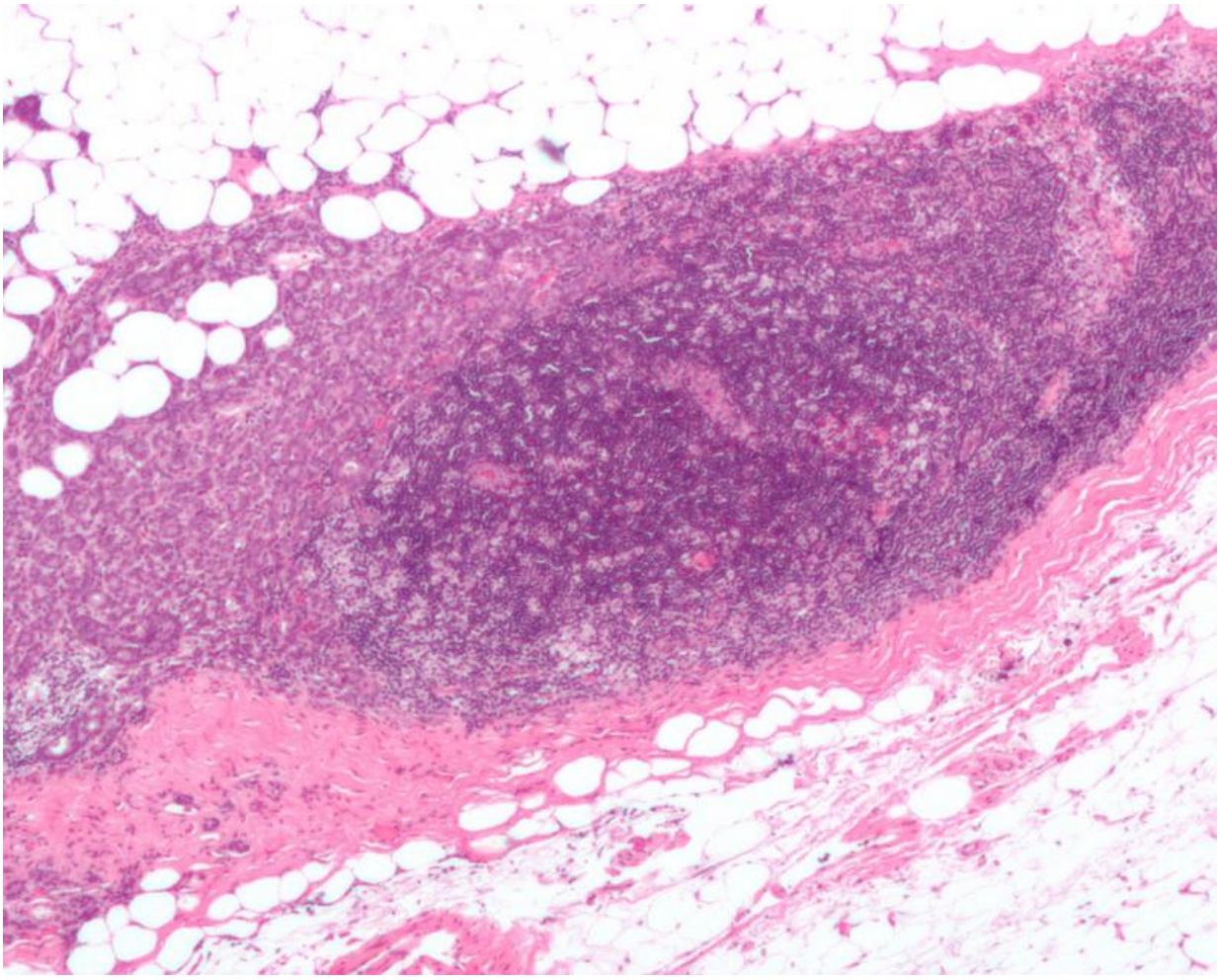

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

A Massachusetts General Hospital (MGH) research team, in collaboration with investigators at the Dana-Farber Cancer Institute, may have found a reason why the use of antiangiogenesis drugs - which has improved outcomes for patients with several types of cancer - fails to benefit some breast cancer patients. In their report published online in *PNAS* Early Edition, the investigators describe how preoperative treatment with the antiangiogenic drug bevacizumab primarily benefited patients whose tumors were highly perfused with blood vessels prior to treatment.

"As expected, bevacizumab treatment did reduce pressure within tumors and the density of tumor vasculature, but the pathologic response to therapy - whether or not it actually eradicated the tumor - appears to depend on the microvascular density of the tumor before treatment," says Rakesh K. Jain, PhD, director of the Steele Laboratory of Tumor Biology in the MGH Radiation Oncology Department and co-senior author of the current report. "In other words, our results indicate that a significant percentage of breast cancers do not have a blood supply sufficient to benefit from the vascular normalization provided by antiangiogenic drugs."

Antiangiogenesis drugs, which suppress the action of factors inducing the formation of blood vessels, have had beneficial results in treating several types of cancer; but studies of their use in breast cancer treatment have had inconsistent results. Exactly how antiangiogenesis drugs produce their effects is unclear, with one hypothesis proposing that they starve tumors of a blood supply and the other that they actually improve the delivery of oxygen to the tumor - which is required for the beneficial effects of radiation and chemotherapy - by "normalizing" the disorganized vessels that usually develop in and around tumors. Imaging studies have supported the latter theory, first proposed by Jain, but have not yet been conclusive.

To add to the understanding of the mechanism of antiangiogenic therapy - particularly in breast cancer - the investigators studied the effects of an initial dose of bevacizumab, followed by a standard chemotherapy in combination with bevacizumab prior to surgical removal of the tumor. This approach, called neoadjuvant therapy, is designed to reduce the size and suppress growth of the primary tumors. Of 91 patients with HER2-negative breast cancer who completed the protocol, only 16 were found to have no active cancer cells within their tumors at the time of surgery, what is called a pathologic complete response.

Examination of biopsy samples taken before and after bevacizumab administration revealed that achieving a pathologic complete response was more likely in patients whose tumors had a more dense blood supply prior to treatment. Participants with a greater number of mature, normalized blood tumor vessels - signified by the presence of cells called pericytes - after bevacizumab treatment had an even better pathologic response. These results suggest that, in breast cancer, the benefits of antiangiogenesis-induced vascular normalization - which include removal of immature vessels as well as improved function of mature vessels - require a sufficient pretreatment level of vascularization. Otherwise the pruning of immature blood vessels may counteract the increase in blood supply conferred by the normalization of mature blood vessels.

"Our findings provide the first direct evidence of a relationship between structural vascular normalization and the extent of tumor regression after neoadjuvant bevacizumab treatment in breast cancer," says Jain, the Cook Professor of Tumor Biology (Radiation Oncology) at Harvard Medical School (HMS). "We also identified several potential blood biomarkers of treatment response, which need to be validated in prospective, randomized trials."

Ian Krop, MD, PhD, co-senior author and director of Breast Cancer

Clinical Research for the Susan F. Smith Center for Women's Cancer at Dana-Farber, adds, "For years, breast cancer investigators have struggled to determine which cancers may respond to bevacizumab. Our results potentially identify the breast cancer patient population most likely to benefit from combined bevacizumab/chemotherapy treatment and suggest that new strategies to increase perfusion without pruning immature vessels, possibly by targeting alternative angiogenic pathways, should be explored to improve the outcome of patients with poorly perfused tumors." Krop is an assistant professor of Medicine at HMS.

More information: Role of vascular density and normalization in response to neoadjuvant bevacizumab and chemotherapy in breast cancer patients, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1518808112

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