Size surprise? Tumour size, nodal status, and outcome after breast cancer

W.D. Foulkes MBBS PhD

When it comes to tumour size, axillary lymph node status, and outcome after invasive ductal breast carcinoma, several facts have been established. The first is that the larger the tumour in diameter, the greater the number of axillary lymph nodes that will be found to be affected by metastatic cancer. The second is that the larger the tumour size, the worse the outcome. The third is that the greater the number of lymph nodes involved by metastatic cancer, the worse the outcome.

Tumour size and axillary lymph node status are highly correlated, but they are independent measures of outcome. Even in very large tumours, the number of involved lymph nodes highly significantly influences outcome, and when 4 or more nodes contain metastatic tumour, a woman with a 10- to 20-mm primary tumour has a better 5-year survival than does a woman with the same number of lymph nodes involved by cancer, but a primary tumour size of 20–30 mm.

Those findings have been supported by numerous studies since the beginning of the 1990s. Nevertheless, they do not tell the whole story. Tumours that do not express the estrogen (ER) or progesterone receptor (PR) and that do not overexpress the human epidermal growth factor 2 (HER2)—the so-called triple-negative breast cancers (TNBCs)—show an attenuated relationship between tumour size, nodal status, and survival. That observation is especially true if those tumours also express either cytokeratin 5 or the epidermal growth factor receptor, or both ("core basal breast cancers"). Put simply, small core basal tumours are more likely to be associated with 1 or more positive axillary nodes than are non-basal breast cancers, and they have a worse-than-expected outcome at 10 years' follow-up. Conversely, large core basal breast cancers have a better-than-expected outcome at the same time point. Interestingly, the same relationship is not seen in TNBCs that do not express basal markers.

Why do core basal breast cancers break the size–nodes–survival rule, and what are the implications of the foregoing observations? One possible explanation is that core basal breast cancers have a fixed proportion of cells that have cancer stem-like properties, such that small tumours have a greater-than-expected propensity to metastasize early. The major implications of those observations are that attempts to cure breast cancer must focus on identifying and eradicating the stem-like tumour cells, and that early detection by mammography is unlikely to be able to deliver significant survival benefits to women who develop TNBC.

All of which take me to the superficially surprising results reported by Dr. Steven Narod in this issue of Current Oncology. Narod conducted a simple (but not simple-minded) analysis of breast cancers diagnosed between January 1987 and December 1999 at the Henrietta Banting Breast Centre at Women's College Hospital in Toronto. He studied the survival experience of 1894 patients with invasive breast cancers 5.0 cm or less in size, dichotomized based on whether the axillary lymph nodes were positive for metastatic breast tumour cells. The mean follow-up was nearly 10 years. He found that, for any given change in tumour size, the difference in mortality was greater for node-positive than for node-negative cancers. That observation might be seen as surprising if the assumption is that mammography is saving lives by detecting small tumours before they spread from the breast to the axillary lymph nodes and beyond. However, closer inspection of earlier data (for example, Figure 3 in Carter et al.) shows that when 5-year survival is plotted against tumour size, the steepest slope is seen in node-positive disease, and not when the axillary nodes are uninvolved by tumour. Thus, Narod helpfully places the data in a modern context, allowing earlier findings to be reinterpreted in the light of modern biology.

The most persuasive view regarding breast cancer progression holds that the die is cast early. In support of that opinion, the primary basal-like breast cancer from a woman who went on to develop a brain metastasis contained most of the critical mutations seen in the ultimately fatal metastasis—that
is, the mutations in the brain metastasis did not arise de novo. Similar features have been reported in a lobular breast cancer. Because small core basal and HER2-positive breast cancers are prone to metastasize early, those observations suggest that the intrinsic biology of many ER-negative tumours, especially those arising in younger women, will inevitably thwart efforts to reduce breast cancer mortality by detecting tumours at ever-decreasing sizes.

So, what of Narod’s idea that the better course would be to focus efforts on lowering tumour sizes from 5 cm to 2 cm—specifically, by encouraging breast examination and mammography in developing countries and in poor and underserved populations in the developed world?

On the face of the available data, such an effort would seem warranted. In their study, which included nearly 25,000 women diagnosed in the United States between 1977 and 1982 (that is, before chemotherapy was in widespread use), Carter et al. found that, as tumours decreased in size from less than 5 cm to 1–2 cm, the 5-year survival increased to approximately 68% from approximately 48% (a 20% difference) for patients with 4 or more positive axillary nodes, and to approximately 88% from approximately 72% (a 16% difference) for patients with 1–3 positive nodes. Those findings accord with Narod’s analysis.

One can thus imagine two women, one screened and one not, who are both destined to develop a 4-cm breast cancer with 5 positive nodes over the same time course. Narod’s data imply that if the first woman were to undergo screening and a 2-cm cancer with 5 positive nodes were to be detected, her 15-year outcome would be superior to that of the second woman, who was not screened and who presents with a 4-cm cancer with 5 positive nodes several years later (the longer follow-up should eradicate any lead-time bias). It is a matter for speculation whether that scenario would hold true for all subtypes of breast cancer and for all ages.

It is tempting to hypothesize that such an improvement in outcome will be limited to tumours that are ER-positive, because the relationship between tumour size, number of positive lymph nodes, and ultimate survival is fairly constant, except for TNBC and basal-like breast cancers in which the relationship is attenuated. Younger women (<50 years of age) with TNBC or basal-like breast cancer show a particularly attenuated size–nodes correlation (Foulkes WD. Unpublished data). Despite the hope for mammography and earlier detection implicit in the findings of Narod’s study, further limitations with respect to the benefit of mammography are suggested in a previous study by Narod and colleagues that used the same database and a 15-year follow-up. They found that, among 715 women with invasive breast cancer less than 5 cm in size, 79 lesions were detected by mammogram alone; the other 636 were palpable or lymph node–positive (or both). Among the 79 “mammography alone” patients, only 5% died, compared with 35% in the other group. Mammography is good at detecting “luminal A” cancers—that is, relatively slow-growing ER-positive, PR-positive, HER2-negative cancers. In Narod’s study, 54 of the 79 “mammography alone” cases fell into that subgroup, and at 15 years, 1 of those women had died. Interestingly, considering PR alone, the 15-year distant recurrence-free survival was 100% among 42 women with a nonpalpable mammographically detected PR-positive HER2-negative cancer 5.0 cm or less in size. Those findings do not offer much comfort to the advocates of mammography; the tumours that imaging can reliably detect are not often fatal, and the tumours that are often fatal cannot be reliably detected.

Uncomplicated, nongenomic studies such as those published here in Current Oncology force us to question how much we truly understand about the apparently simple relationship between tumour size, axillary lymph node status, and survival. Furthermore, they demand a re-examination of some of the assumptions underlying attempts to diagnose breast cancers at ever diminishing sizes. Indeed, such studies may lead to a rethink of the overall rationale for mammography as a screening tool. As many researchers and clinicians turn their attention to personalizing medicine, it is worth remembering that the generalities remain frustratingly obscure.

REFERENCES


**Correspondence to:** William D. Foulkes, Departments of Oncology and Human Genetics, McGill University, Montreal, Quebec H2W 1S6.  
**E-mail:** william.foulkes@mcgill.ca