Removing the primary tumour in metastatic breast cancer

During the past 100 years, the underpinning philosophy of the treatment of breast cancer has changed from exclusive local therapy, to a disease conceived as likely to be systemic from the start, so that most patients presenting with potentially curable disease have both local (surgical, radiotherapeutic, or both) and systemic therapy. In many centres, the proportion of patients with metastatic disease at first presentation is less than 10%, and these patients are primarily given systemic therapy. However, uncertainty remains about whether these individuals should also have local therapy, usually surgical removal of the primary tumours. Retrospective studies have drawn mixed conclusions on this topic and data from animal studies by Fisher and colleagues suggested that surgical removal of a primary tumour could accelerate the growth of metastatic disease, suggesting that the intervention could even be detrimental.

In The Lancet Oncology, Badwe and colleagues report findings from a randomised trial from Tata Memorial Hospital in Mumbai addressing the question of whether there is a potential survival gain after surgery in women with de novo stage IV breast cancer, and conclude that routine surgery is of no benefit. The investigators acknowledge a few limitations. The median overall survival was about 20 months, which is lower than that expected for patients in developed countries, and most patients were randomly assigned after responding to chemotherapy, so this is essentially a study investigating surgery to the primary tumour after chemotherapy. Contemporary therapeutic philosophy is to use targeted therapy where appropriate, and only 7% of patients with hormone receptor-positive disease were given endocrine therapy, and only 2% of those with HER2-positive disease received anti-HER2 treatment. As newer agents, such as CDK4/6 inhibitors, reach the clinic, the expectation is that disease control will be better and last longer, so could patients treated with these drugs in fact benefit from surgery in view of their overall better prognosis? Might this also be true for patients with HER2-positive breast cancer, in which prolonged overall survival can now be achieved with the combination of two anti-HER2 drugs (trastuzumab and pertuzumab) and chemotherapy? It is also interesting to note that women randomly assigned to have surgery had a significantly poorer distant disease-free survival than those who were not assigned to surgery; this is perhaps a confirmation of results from preclinical models, although ascertainment bias due to earlier local progression in the non-operated patients could also be an explanation.

So is this the definitive answer? All reported trials are historic, and all of medicine is the art and science of applying previous data to today’s patients, so one cannot simply dismiss the reported absence of a benefit of surgery. However, one additional change in clinical management does challenge some of the applicability of these data. Modern CT scanning, particularly of the lungs, can detect lesions as small as 2 mm, which would not have been identified a few years ago. These patients often cannot be definitively classified as metastatic or not. An uncritical interpretation of the data from Badwe and colleagues’ study would suggest that none of these patients should have definitive surgery, but many such patients might well have been cured with surgery and adjuvant therapy in the past when pre-operative imaging would not have detected such small lesions.

The issue at the heart of the challenge posed by these data is: what extent of metastatic disease needs to be present for surgery to be of no survival benefit? All patients are potentially metastatic at presentation, and the combination of local and systemic therapy is known to cure many of them. We do not know the volume or size of the metastatic disease in the patients in this study, although one presumes that most will have had unequivocal metastatic disease. But what about patients with 2 mm lesions identified on CT scanning, or those with distant disease found on bone marrow biopsy, or perhaps soon in circulating tumour DNA? Indeed, as systemic therapy becomes more effective, it could be that subsets of patients without any macroscopic evidence of metastases, perhaps those achieving high pathological complete response rates after very active regimens, such as combination chemotherapy plus dual anti-HER2 therapy, could also gain little from surgery to the primary tumour.

In conclusion, the study by Badwe and colleagues is important because it provides clear evidence that routine use of surgery to the primary lesion in patients with demonstrable metastatic disease does not result
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in prolonged survival. However, it leaves open two possibilities for future surgical practice changes for patients receiving very effective targeted therapy, if supported by additional, similarly high quality evidence: either additional surgery for those with detectable metastatic disease or perhaps even no surgery for those without.

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DC has been a consultant for Roche, Pfizer, and Novartis, and has a specific commitment to a Lilly research trial that is reimbursed to his institution.