The importance of early breast cancer treatment: delay can be deadly

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It is clear that extensive delays in treating breast cancer cannot be a good thing. But what constitutes "delay"? And what might be the consequences? Kou and colleagues aimed to answer these questions with their population-based analysis of recent Queensland data, reported in this issue of the *MJA*.[1]

Kou and colleagues identified women diagnosed with early breast cancer during 2010–2013, and, based on interviews with the women and other data sources, compiled timelines of their subsequent treatment, from diagnosis to neoadjuvant therapy (infrequent during the study period), surgery, chemotherapy, and radiotherapy. They derived six diagnosis- or treatment-to-treatment time intervals, and compared them with timelines recommended in Australian consensus-driven guidelines, and related these findings to the risk of breast cancer death to the end of 2020.

Their study yielded some concerning findings. Treatment for 1375 of 3044 women (45%) did not fully comply with the guidelines; that is, at least one treatment interval was longer than recommended. The risk of breast cancer death for these women was higher than for those whose treatment was fully consistent with the guidelines (adjusted hazard ratio [aHR], 1.43; 95% confidence interval [CI], 1.04–1.96), completely ablating any mortality benefit of adjuvant chemotherapy. Of the six treatment intervals, the differences for those from diagnosis to surgery (aHR, 1.76; 95% CI, 1.19–2.59), surgery to chemotherapy (aHR, 1.63; 95% CI, 1.13–2.36), and chemotherapy to radiotherapy (aHR, 1.83; 95% CI, 1.19–2.80) were each statistically significant.[1]

What should we make of this? My instinct was that one reason for delays along the treatment pathway was that these women were perhaps particularly unwell and consequently did less well than healthier patients. This may be part of the explanation, but it is unlikely to be the whole story. The authors adjusted for several relevant variables — age, cancer stage, tumour grade, and some demographic features — but some biases may persist. For example, it seems odd that a delay between the end of chemotherapy and the beginning of radiotherapy should have such a large effect on breast cancer mortality, given that the overall mortality benefits of radiotherapy itself are modest.[2]

Additionally, it is important to distinguish proportional effects (of biology and biases) and absolute effects (how much damage have we done?). The proportional effect for the entire cohort is large and statistically significant, and presumably reflects real biological effects as well as biases. However, given that (thankfully) only 5.4% of the women in the study by Kou and colleagues died of breast cancer,[1] the absolute differences were rather small.

This does not, of course, mean we can ignore the findings of Kou and colleagues, but we should put them in perspective. For some treatment intervals, the magnitude of the reported and statistically significant differences was about four percentage points, a difference that would make us sit up and take notice were they the results of treatment. Another disturbing but perhaps unsurprising finding was that delays were more frequent for women treated as public rather than as private patients, and also for those living in rural areas.[1]

Where to from here? First, we should determine whether other datasets could be suitable for assessing the influence of treatment delays on breast cancer mortality. Second, it would be interesting to examine whether the effect of delay is cancer subtype-specific. One might expect, for instance, that delays are more deleterious for women with more aggressive cancer phenotypes, such as triple negative breast cancer, and less so for those with hormone receptor-positive disease.

In the interim, the study by Kou and colleagues provides some real world support for the current Cancer Australia breast cancer treatment guidelines.[3] It would seem prudent to implement their recommendations as best practice: aiming to commence treatment within four weeks of diagnosis, chemotherapy within five weeks of surgery, and radiotherapy within four weeks of chemotherapy.

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1 Kou K, Aitken JF, Pyke C, et al. Treatment intervals and survival for women diagnosed with early breast cancer in Queensland: the Breast Cancer Outcomes Study, a population-based cohort study. *Med J Aust* 2023; 219: 409-416.

2 EBCTCG (Early Breast Cancer Trialists' Collaborative Group); McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; 383: 2127-2135.

3 Cancer Australia. Guidance for the management of early breast cancer: recommendations and practice points. Sept 2020. https://www.canceraustralia.gov.au/publications-and-resources/cancer-australia-publications/guidance-management-early-breast-cancer-recommendations-and-practice-points (viewed Sept 2023). ■

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