Reviewer’s report

Title: Neoadjuvant Trials in Early Breast Cancer: Pathological Response at Surgery and Correlation to Longer Term Outcomes - What does it all mean?

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Reviewer: Harry D Bear

Reviewer’s report:

This article presents a cogent and useful discussion of the role of neoadjuvant chemotherapy for breast cancer, focusing on the assessment and significance of pathologic response in clinical trials. Several points deserve comment, with some suggested corrections:

Minor Essential Revisions

1. In the abstract and at the end of the background section, the wording of their statement regarding the correlation of pCR with outcomes NOT being present in individual trials is not really accurate. Almost every neoadjuvant trial demonstrates that pCR is a predictor of patient outcomes. What I believe they mean to say is that in individual trials, increases in pCR with changes in NCT regimens do not necessarily translate or correlate with improvements in patient outcomes. This should be restated in both the abstract and background.

2. The last sentence in the abstract is difficult to understand. By the time I got to the end of the article, I was able to “get it,” but the statement in the abstract should be re-worked to make it clearer.

3. In the Background, it is certainly reasonable to cite a recent article demonstrating use of NCT to increase breast conservation on a population level, but the citations for individual trials showing this are somewhat unexpected, since the prospective randomized trials that really demonstrated this most convincingly and for the first time were published in the 1990’s and early 2000’s (e.g., NSABP B-18 and the ECTO trial from Europe).

4. Near the bottom of page 7, the association between pCR and outcomes should perhaps be described as “weaker” not “weak”. This association is variable in different studies. Although, for example, the German Breast Group has found that the association is weak, others have shown that there is a significant effect of pCR on outcomes for luminal cancers. In this regard, inclusion of E. Mittendorf’s paper (JCO, 2011) on combined pre and post NCT staging (termed CPS+EG) as a way to predict prognosis would be useful in this discussion.

5. Regarding RCB, I would certainly agree that this is an excellent system for analyzing residual disease after NCT and correlating this with prognosis, but it is arguably not “simple to apply” as suggested here. In fact, many feel that this is quite burdensome to pathologists, particularly in community settings, and difficult to reproduce reliably.

6. In the paragraph at the top of page 11, which refers to Figure 2, the second
line seems to have some garbled text that does not make sense. And in the last sentence, the word “and” before “as well as” should be deleted.

7. The section at the bottom of page 11 on “Adjuvant treatment” makes a number of very good points.

8. At the top of page 12, the alternative to excluding ER+ patients would be to define molecular markers that distinguish low vs. high risk and chemo-sensitive vs. chemo-resistant cancers in these trials.

9. In a similar vein, some mention of the alternative use of hormonal neoadjuvant therapy in low risk ER+ tumors should be made, since this may be less toxic with similar benefits to chemotherapy for these patients. However, it should also be mentioned that with overall clinical response rates in the range of 90%, NCT can be clinically beneficial in patients with ER+ tumors even if pCR is not achieved.

10. The paragraph on “Mechanism of action of investigational drug” really does not say anything useful and could be deleted with no loss.

11. In the middle of the paragraph on “length of followup”, the statement that KM curves would separate more widely with longer followup because of the steady rate of events is not necessarily true. If a change in NCT only affects early recurrences (e.g., for more aggressive cancers or clones), the KM curves might drop in parallel with longer followup rather than separating more widely over time.

12. Under the “possible effect of clonal heterogeneity,” consider referring to the seminal hypothesis of Goldie and Coldman, which predicted that response of a primary tumor to chemotherapy may NOT be predictive of the response in metastatic clones. In the last sentence of that section, suggest changing the first “prove” to “turn out” and “prove to be” to “is a”.

13. More discussion of using post-neoadjuvant trials of new or targeted therapies to improve outcomes for patients with residual disease, which is a marker for poor outcome, would be worthwhile.

Discretionary Revisions

14. In the 3rd line of the Discussion, “determining” should perhaps be replaced with something like “initial evaluation of”.

15. Also on page 7, it is not clear what is meant by quantification in the adjuvant setting; this makes sense for nodal metastasis, but NOT for DCIS.

16. The middle paragraph under “definition of pCR and review” seemed a bit repetitive of previous comments.

17. In the middle of the paragraph on “length of followup”, “Whereas” should be changed to something like “Conversely”.

18. In the section titled “What about novel agents…” where it says “no evidence of response,” are the authors referring to clinical response assessed during therapy? It is not clear.

19. The first sentence in the Summary is not clear.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.