

Peer Review File

Article information: <https://dx.doi.org/10.21037/cco-22-87>

**Reviewer A**

*Comment 1:*

Timely observations on impact of ER/PR negative breast CA histology on breast cancer specific survival as a function of surgical therapy. Adds to the current literature supporting breast conserving surgery over mastectomy for early onset breast cancer.

It has long been known that the absence of PR expression in ER positive breast cancer is associated with poorer prognosis particularly at 10 years. However, the putative negative impact of PR negative status on ER positive patients undergoing bilateral mastectomy, lumpectomy with whole breast radiation therapy or BCS, unilateral mastectomy or lumpectomy without radiation has not been examined previously. This report adds another potential explanation to the increasing understanding in the literature that bilateral mastectomy and unilateral mastectomy are inferior surgical procedures to BCS in women eligible for BCS at the time of their diagnosis.<sup>1</sup> This rich worldwide literature suggests that BCS is associated with increased overall survival in women with unilateral breast cancer. This information has led some to question whether a mastectomy should be offered to women who are candidates for BCS.<sup>2</sup> Universal fear of breast cancer recurrence remains the most common reason for women requesting bilateral mastectomy for a unilateral breast cancer. This misinformation is even more alarming among women with the highest risk of systemic failure due to their advanced stage at the time of diagnosis.<sup>3</sup> This erroneous perception of risk of breast cancer recurrence leads to poor outcomes when surgeons cannot clearly explain the relative significance of the risk of local recurrence, risk of a contralateral primary or the risk of metastatic disease to such patients.<sup>4</sup>

The interesting findings reported here should assist surgeons in explaining to patients that in the setting of ER positive-PR negative disease yet more information suggests that BCS should be the best option when breast cancer specific survival is the most pressing concern in the mind of the patient.

References

1. Tan M, Silva E. Addressing the paradox of increasing mastectomy rates in an era of de-escalation of therapy. Communication strategies. *The Breast J.* 2018, 38, 1-8.
2. Johns N, Dixon JM. Should patients with early breast cancer still be offered the choice of BCS or mastectomy. *European J Surg Onc.* 2016, 42, 1636-1641.
3. Lim DW, Metcalfe KA, Narod SA. Bilateral Mastectomy in Women With Unilateral Breast Cancer: A Review. *JAMA Surgery.* 2021; 156:569–576. doi: 10.1001/jamasurg.2020.6664.
4. Silva E. Breast conserving surgery versus mastectomy for early stage breast cancer.

Could patient choice lead to inferior outcome. The Breast J. 2014. 20, 97-99.

*Reply 1: We thank Reviewer B for their thoughtful review of our manuscript and insightful commentary regarding how our manuscript contributes a more granular demonstration of the benefits of BCS for women with localized breast cancer and its importance for long term prognosis rather than a fixation on local recurrence.*

**Reviewer B**

*Comment 1:*

Really interesting

The objective is post hoc

There is no justification for the question proposed

*Reply 1: We thank Reviewer C for their thoughtful review of our manuscript and helpful feedback.*

*Regarding this first comment, we tried to explain the justification for the question proposed in the second paragraph of the introduction:*

*“The study of ER and PR statuses on surgical outcomes is of interest because the breast is an endocrine gland with 10-30% of cells in the luminal epithelium of normal healthy breast tissue expressing estrogen receptor, and a smaller proportion expressing PR (14,15). It is possible that the removal of an entire breast or both breasts may lead to alterations in hormone levels or any associated feedback pathways which could affect proliferation of disease in the contralateral breast or circulating or disseminated tumor cells at distant locations. If such endocrine changes were induced by mastectomy in breast cancer patients, it may be reflected in their long-term outcomes relative to patients undergoing lumpectomy. If such a phenomenon existed, it could help shed light on the curious finding that most retrospective analyses since the previously-mentioned pioneering randomized controlled trials have found improved overall survival or disease-specific survival with lumpectomy and radiation relative to mastectomy (13,16–23). A 2013 retrospective analysis from the California Cancer Registry suggested that the discrepancy in overall survival may be related to a higher burden of non-fatal comorbidities among patients undergoing mastectomy relative to lumpectomy with radiation (13). However, an explanation for the discrepancy in disease-specific survival has remained elusive.”*

*Comment 2:*

Should be more general

Well written

Just say er-positive patients. Among er+  
How many groups were there sloppy

The study group is er+ patients

The covariate is pr status. Just say so!!

*Reply 2:*

*Reviewer C makes an excellent point that since ER+ is part of our inclusion criteria, we can refer to patients as simply PR+ or PR- instead of ER+PR+ or ER+PR-. The reason we did not initially do this is that we were concerned that someone not reading the manuscript in its entirety may misinterpret the content. However given that Reviewer C thinks that this will be clear to readers, we will switch to PR+ and PR-.*

*Changes in the text:*

*Throughout the manuscript, we have changed “ER+PR+” to “PR+” and “ER+PR-” to “PR-”.*

*Comment 3:*

There are four variables, pr status, radiation, mastectomy versus lumpectomy, bilateral mastectomy, which predict survival? Add age.

*Reply 3: In Table 1, the covariates predictive of survival vary for PR+ and PR- disease. In both, treatment (surgical extent and radiation) are significant and tumor size is significant. In ER+PR+ disease, race, age, and tumor grade are also significant. Age is included and is significant in the ER+PR+ group for breast cancer specific survival (Table 1).*

*Comment 4:*

Give main effects then subgroups. Test for interactions

Radiation works as abscopal

Cite narod and giannakeas

Put back the patients with mastectomy and radiation

*Reply 4:*

*In this study we did not perform subgroup analysis, we instead performed cumulative incidence estimation and competing risks regressions for patients with PR+ and PR-*

*disease. These were not subgroups, they were separate groups we were assessing independently.*

*Regarding Narod and Giannakeas, they have published many articles on DCIS and invasive breast cancer using SEER. We have cited one of Narod's studies in our manuscript. We can cite another but if Reviewer C could mention which publication specifically they are referring to that would be helpful.*

*We did not include patients undergoing mastectomy with radiation because in the United States from which SEER data is collected, radiation would not be indicated for a patient undergoing mastectomy for T1-2N0M0 disease. So patients undergoing adjuvant radiation in this scenario would not be receiving standard of care and may therefore represent a distinct population, so their inclusion could introduce more confounding. For this reason we chose to exclude them.*