

Understanding the factors associated with the surgical management of early breast cancer

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Breast cancer is the most common cancer affecting women and the second common cause of cancer-related mortality (1). Recent advances in the field of breast cancer biology have revealed that breast cancer is a complex disease composed of at least four main subtypes at the molecular level (2-4). Each has distinct prognosis, and unique molecular portrait that governs tumor progression. Nevertheless, surgery continues to play a pivotal role in managing patients in the early setting.

Over the past 3-4 decades, there have been continuous efforts in reducing the role of mutilating surgeries, which considerably comprise the quality of life of breast cancer patients. Based on the results of several randomized trials, breast conserving surgery (BCS) followed by radiotherapy have shown similar local control and survival outcomes compared to mastectomy (5-7), and hence become the standard treatment for patients with early breast cancer. The introduction of sentinel lymph node biopsy and breast reconstruction have further refined the surgical management of breast cancer patients and resulted in improvement in quality of life measures for these patients (8).

In the article published in *Annals of Surgical Oncology* by Showalter *et al.* (9), the authors reviewed the factors that influenced surgical and adjuvant radiotherapy in patients diagnosed with stage I breast cancer, based on an analysis of the SEER database. The study included 194,860 patients diagnosed over a 20-year period [1988-2007]. The main analysis indicated that higher mastectomy rates were independently associated with single/divorced women, white race, estrogen receptor (ER) negativity, earlier year of

diagnosis, smaller tumor size, and region. Further analysis showed that 20% of patients did not receive adjuvant radiotherapy following BCS, which was mainly observed in patients with smaller tumors, older women, single/divorced patients, African American and patients with ER-negative tumors. The authors went on to show that those who were offered radiotherapy after BCS survived better compared to those who were only subjected to BCS.

This study provides a good and important overview on practice behaviors and trends in surgical managements over time. However, similar to other SEER analysis, it does not provide in depth information, which could explain such findings and associations.

The study showed that mastectomy trends decreased over time in such patients, who should classically be subjected to BCS. The incidence of BCS increased from 40% in 1988-1992 to 68% in 2003-2007. This is also consistent with decreasing trends of mastectomy in the UK (10). Such change of surgical management confirms that guidelines have evolved and both oncologists and patients became aware and convinced of the efficacy of BCS in the early setting. However, the results also point out that some 30% of patients were subjected to mastectomy in recent years. Several reasons could explain that like increasing rates of prophylactic mastectomy as a function of time, and the need for re-surgery due to the presence of positive margins after BCS. In a recent study in the UK, one in five women who had BCS had a reoperation. Reoperation was nearly twice as likely when the tumor had an in situ component recorded. Unfortunately, such information is not available in the SEER database, hindering the authors from addressing

their potential confounding effects on the surgical decision.

The association between higher mastectomy rates and small tumor size and also ER-negative tumors, were hard to interpret. Classically, patients with smaller tumors are better candidates for BCS. While in this study only patients with tumors <2 cm were included, patients with micro-invasive tumors had 35-50% lower chance of performing BCS compared to patients with tumors measuring 1.1-2 cm and 0.1-1 cm respectively. It is plausible that these patients had more disseminated microcalcification, making BCS hard to be performed. Also, there has been a rising trend of performing prophylactic bilateral mastectomy in the US, particularly in patients presenting with early disease (11,12). However, the SEER database does not include information on these factors, to confirm such assumptions.

High mastectomy rates in patients with ER-negative have also been reported in the neoadjuvant setting (13). In the NeoALTO trial, patients with HER2-positive breast cancer were randomized to receive trastuzumab, lapatinib or their combination in the neoadjuvant setting together with paclitaxel (14). A multivariate logistic regression model have found that patients with ER-negative tumors had a 50% lower chance of receiving BCS independent of tumor size, treatment arm, clinical and radiological response to treatment. A similar observation was made in the current study as well, albeit in the adjuvant setting. This could potentially reflect that mastectomy is regarded as a superior option for patients with ER-negative tumor; who are known to have poorer prognosis compared to those with ER-positive tumors. Such conception is not supported by evidence and should be challenged. Another possibility in the Showalter study could be related to BRCA1 status. Patients with BRCA1 mutation are known to have a phenotype of triple negative breast cancer (15). Bilateral prophylactic mastectomy has been shown to reduce the risk of developing new primary tumors in these patients and hence is frequently offered to BRCA carriers (16-18). In this study, the authors did not report on the percentage of triple negative patients or BRCA status, which would have possibly explained such associations.

In the same study, the authors reported that 21% of patients treated with BCS did not receive adjuvant radiotherapy, and due to limitations of such population-based registries, authors couldn't explain the reasons not receiving radiotherapy in these patients. There was a survival difference between patients who underwent BCS followed by radiotherapy compared to those who didn't. This points out that even in very small tumors with

negative nodal involvement; adjuvant radiotherapy remains an important component of the treatment plan. However, it should be noted that the authors did not report whether this survival difference was maintained on adjusting for other confounding factors in a multivariate model. Indeed less "older" patients (>80 years; 6.3% vs. 22.7%, P<0.001) and more patients with ER-positive tumors (70% vs. 60%, P<0.001) were observed in the group receiving radiotherapy. This is particularly important as the difference in survival could be confounded by the presence of patients with poor prognosis in the "no radiotherapy" group.

In conclusion, this study provides an important snapshot on the evolution of surgical approach for patients with stage I breast cancer. It raises several interesting questions that require further studies to try to address them in a more detailed fashion.

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