

Which real indications remain for mastectomy?

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The study of He et al. compared outcomes after breast-conserving therapy including radiation therapy with mastectomy without radiation therapy, after preoperative systemic therapy for patients with early stage HER2-positive breast cancer.¹ After a median follow-up of 9.9 years, breast-conserving therapy was associated with significantly higher overall survival compared to mastectomy (86.0% vs 79.3%; $P = 0.02$). This difference was significant for patients who had a pathological complete response in axillary lymph nodes (91.3% vs 83.5%, $P = 0.02$) and for those with a pathological complete response in the breast (93.4% vs 87.0%, $P = 0.03$), although the latter result was not significant in multivariable analysis. The authors hypothesise that the better survival outcomes after breast-conserving therapy may be explained by the impact of radiation therapy on the microenvironment, and/or that more extensive surgery negatively impacted on the immune response or directly caused local, vascular or lymphatic seeding. We fully agree that the interactions between surgery, radiation therapy, systemic treatments, and the immune environment require further research.

More than 20 years ago, pivotal randomised trials unambiguously demonstrated the non-inferiority of breast-conserving therapy compared to mastectomy for women with early breast cancer. Modestly higher local recurrence rates after breast-conserving therapy were well-balanced by similar long-term overall survival and an improved quality of life. Over the last decades, multidisciplinary breast cancer management has

improved tremendously, and local recurrence rates after breast-conserving therapy have fallen markedly. Most observational studies since then reported improved outcomes following breast-conserving therapy compared to mastectomy.²⁻⁴

An EBCTCG meta-analysis comparing preoperative systemic therapy with postoperative systemic therapy suggested that patients receiving preoperative systemic therapy and breast-conserving therapy might have increased local recurrence rates compared to those receiving postoperative systemic therapy, although survival was identical.⁵ The randomized trials included were historic and current thinking is that there should be no concerns about higher local recurrence rates in contemporary care. Indeed, a more recent analysis of the SEER database using propensity score matching of 4890 patients treated with preoperative systemic therapy between 2010 and 2020 reported significantly worse overall survival and BCSS outcomes after mastectomy compared to breast-conserving therapy.⁶ However, despite increasing pathological complete response rates with modern treatments, this didn't translate into increasing use of breast-conserving therapy, even in HER2-positive disease with a likelihood of more than 60% of obtaining a pathological complete response.⁷

Opinions vary concerning how much statistical techniques, including propensity score matching or inverse probability treatment weighting, can mitigate the effects of the confounding that is inherent in observational research.^{8,9} Differences in outcomes between breast-conserving therapy and mastectomy after preoperative systemic therapy cannot be assessed by further randomized trials, due to ethical and practical reasons. Therefore, it is important to use available data from observational studies as well, while cautiously interpreting results as the risk of residual (unmeasured) confounding can never be eliminated. An important advantage of observational research is, moreover, that it is more reflective of the real-world population.

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Breast-conserving therapy has further advantages. It offers lower complication rates, shorter hospital stays, reduced need for pain medication and faster return to work and social life when compared with mastectomy. Importantly, it also avoids the need for breast reconstruction with its associated higher complication rates and high probability of additional symmetrizing and revisional procedures. If radiation therapy to the reconstructed breast is indicated, the risks of long-term complications and poorer cosmetic outcomes increase. Management strategies involving variation in timings, surgical methods, and treatment sequencing, are intensely debated without simple answers being available that would fit all individual patients and all clinical settings. The total burden on the individual patient (and in consequence, the health care system and society) is thus much lower when breast-conserving therapy can be offered, and the best strategy is, wherever possible, to avoid mastectomy and whole-breast reconstruction with its associated complexity.¹⁰ In the current era of shared decision-making with multiple treatment options, it is important to inform patients about all potential outcomes of therapy, including all these considerations.

In conclusion, this work adds to the growing scientific evidence supporting the use of breast-conserving therapy as the preferred standard treatment for the vast majority of patients with early-stage breast cancer. The introduction of breast-conserving therapy was a seismic improvement in care when introduced some 3–4 decades ago. Extending the scope of breast-conserving therapy is one of the major advantages of preoperative systemic therapy, which we should fully exploit.

Contributors

All authors contributed equally to the writing of the manuscript.

Declaration of interests

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