VIEWPOINT

De-escalating Breast Cancer Surgery—Where Is the Tipping Point?

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Breast cancer survival in the United States has improved because of the increased uptake of screening mammography and improvements in systemic therapy. The cancers clinicians see today are smaller and have less nodal involvement than those seen in the 1990s, when many of the current treatment paradigms were developed. It is now recognized that subtype-specific systemic therapies reduce the incidence of locoregional as well as distant recurrences, and the neoadjuvant chemotherapy (NAC) paradigm has demonstrated that pathologic complete response, a powerful marker of favorable outcomes, can often be obtained in patients with human epidermal growth factor receptor 2 gene (*HER2*) overexpression and triple-negative cancers.

In recent years, rigorous research has resulted in a broad interest in de-escalation of breast cancer treatment. Clinicians can now avoid chemotherapy for many patients with hormone receptor–positive disease based on genomic profiling. Similarly, hypofractionated radiotherapy and partial-breast irradiation are strategies that have decreased the duration or extent of treatment for patients, although these have been variably adopted.[1] Despite data confirming excellent outcomes, there has been reluctance to back off from many treatments, sometimes despite considerable toxic effects, because of a reluctance to compromise survival end points.

There is currently a wave of enthusiasm for eliminating surgery entirely in patients with small amounts of ductal carcinoma in situ (DCIS) or those who appear to have had a complete response to NAC, but as with radiation and systemic therapy, caution needs to be exercised in de-escalation of surgery. If the oncology field were still in the era of the radical mastectomy (a deforming operation with substantial long-term sequelae), this enthusiasm would be easy to understand, but it is occurring in spite of the fact that the greatest progress in de-escalating breast cancer treatment has already occurred in surgery. Over the past 20 years, we have seen the widespread adoption of breast-conserving surgery and sentinel-node biopsy for axillary staging. More recently, the elimination of axillary dissection for patients with a limited nodal disease burden and a reduction in the use of margin re-excision after initial lumpectomy have occurred.[2] These advances have substantially decreased the burden of treatment for patients, and this means that patients with small amounts of DCIS or an excellent response to NAC are eligible for brief outpatient operations, which provide certainty as to the extent of their disease and allow a rapid return to normal activity.

So what is the impetus for the ultimate de-escalation of eliminating surgery as part of the initial treatment of breast cancer? At first glance, who would not want to skip a trip to the operating room? However, it is important to consider the alternatives. Avoiding a 1-hour lumpectomy means that the 7% to 20% of patients with DCIS who are thought to be at low risk, but are actually found to have invasive carcinoma when a core-needle biopsy shows DCIS, will have a potential delayed diagnosis of invasive disease.[3,4] The patient having NAC will require imaging and multiple needle biopsies to try and establish pathologic complete response in the breast, ignoring the well-documented observation that this is not an accurate way to identify axillary-nodal disease even prior to systemic therapy.[5] Additionally, an incorrect diagnosis of pathologic complete response because of a less complete histologic sampling with needle biopsy may result in the failure to receive additional systemic therapy, an approach shown in randomized clinical trials to improve disease-free survival and overall survival in those with residual tumor after NAC. In both DCIS and the post-NAC context, avoidance of surgery will mean more intensive imaging follow-up, a higher percentage of false-positive results, and more biopsies. For many patients, although admittedly not all, this is a recipe for increased anxiety. There is no expectation that elimination of surgery will improve survival outcomes. It can only decrease what is already minimal morbidity.

What has been absent to date in the enthusiasm surrounding the push for trials of no surgery is the voice of the patient. How much of a survival decrement or an anxiety increment is acceptable to patients with breast cancer to avoid a lumpectomy, with or without a sentinel node biopsy? Furthermore, the dialogue to date assumes that undergoing multiple vacuum-assisted biopsies in the radiology department while fully awake is a better option than surgery, but is that true? Additionally, is surgery the treatment patients would most like to avoid? Identifying those who could avoid radiotherapy would save more patient time, more adverse effects, and more health care costs. In addition, in the era when US women are increasingly choosing bilateral mastectomy for the treatment of small unilateral cancers to provide peace of mind, is there a reason to suppose that no surgery at all will be embraced by anyone other than a small minority of women?

The effectiveness of surgery alone in curing small breast cancers with a limited number of nodal metastases seems to have been forgotten.[6] Breast surgery is old-fashioned. It does not rely on molecular targets, high-tech equipment, or targeted therapies that cost thousands of dollars per course. Most patients will only accept the possibility of a decrease of 5% or less in survival to avoid chemotherapy,[7] a treatment with more toxic effects than lumpectomy and sentinel-node biopsy. Extremely large and costly noninferiority trials will

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be necessary to demonstrate that surgery can be safely avoided for the small number of patients eligible for the most limited surgical approaches. Locoregional recurrence, for many patients, is traumatic even when it does not decrease survival and needs to be considered as an end point in any trial. Patients who have a pathologic complete response (determined after surgery) to NAC and undergo surgery and radiation still can develop local recurrence. But how much of an increase in local recurrence would be ethically acceptable to avoid minor outpatient surgery?

All well-designed clinical trials are laudable if they have the potential to teach us something new, and this is true of the trials of no surgery as well. But they will be extremely costly, will alter management for a minority of patients, and, in our opinion, are not necessarily addressing the most pressing issues in breast cancer management. We do not want to stand in the way of thoughtful and rigorous clinical trials, but researchers need to be careful about how to invest precious research funding. While very limited trials of no surgery may be appropriate, this may be a question that has to wait until others are answered. When breast cancer is as easy to treat as a strep throat, surgery will no longer be necessary. At the moment, however, the desire to eliminate all breast cancer surgery in the patient with curable disease should not, in our view, be foremost among research priorities.

ARTICLE INFORMATION

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REFERENCES

1. Gillespie EF, Matsuno RK, Xu B, et al. Geographic disparity in the use of hypofractionated radiation therapy among elderly women undergoing breast conservation for invasive breast cancer. *Int J Radiat Oncol Biol Phys*. 2016;96(2):251-258. doi:10.1016/j.ijrobp.2016.05.006

2. Morrow M, Abrahamse P, Hofer TP, et al. Trends in reoperation after initial lumpectomy for breast cancer: addressing overtreatment in surgical management. *JAMA Oncol*. 2017;3(10):1352-1357. doi:10.1001/jamaoncol.2017.0774

3. Pilewskie M, Olcese C, Patil S, Van Zee KJ. Women with low-risk DCIS eligible for the LORIS trial after complete surgical excision: how low is their risk after standard therapy? *Ann Surg Oncol*. 2016;23(13):4253-4261. doi:10.1245/s10434-016-5595-3

4. Grimm LJ, Ryser MD, Partridge AH, et al. Surgical upstaging rates for vacuum assisted biopsy proven DCIS: implications for active surveillance trials. *Ann Surg Oncol*. 2017;24(12):3534-3540. doi:10.1245/s10434-017-6018-9

5. Schipper RJ, Moossdorff M, Beets-Tan RGH, Smidt ML, Lobbes MBI. Noninvasive nodal restaging in clinically node positive breast cancer patients after neoadjuvant systemic therapy: a systematic review. *Eur J Radiol*. 2015;84(1):41-47. doi:10.1016/j.ejrad.2014.09.020

6. Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. *J Clin Oncol*. 1989;7(3):355-366. doi:10.1200/JCO.1989.7.3.355

7. Vaz-Luis I, O'Neill A, Sepucha K, et al. Survival benefit needed to undergo chemotherapy: patient and physician preferences. *Cancer*. 2017;123(15):2821-2828. doi:10.1002/cncr.30671