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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Changing Paradigms for Breast Cancer Surgery: Performing Fewer and Less-Invasive Operations

David W. Ollila, MD[1], E. Shelley Hwang, MD, MPH[2], David R. Brenin, MD[3], Henry M. Kuerer, MD, PhD[4], Katharine Yao, MD[5], and Sheldon Feldman, MD[6]

[1]Department of Surgery, The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Department of Surgery, Duke University, Durham, NC; [3]Department of Surgery, University of Virginia, Charlottesville, VA; [4]Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Department of Surgery, NorthShore University HealthSystem, Evanston, IL; [6]Department of Surgery, Montefiore Medical Center, The University Hospital for the Albert Einstein College of Medicine, New York, NY

ABSTRACT Historically, through the conduct of prospective clinical trials, breast cancer surgeons have performed less radical breast and axillary surgeries with no survival decrement to our patients. Currently, other opportunities exist for the treating breast surgeon to do less. Possibilities include active surveillance for ductal carcinoma in situ, ablative therapy for small primary breast cancers, selective omission of a sentinel node biopsy, and selective elimination of breast surgery after neoadjuvant systemic therapy. Breast surgeons must be leaders in the development and testing of effective therapy with the least intervention possible.

In the evolution of breast cancer surgery, the results of prospective, randomized trials have shown that less surgery is just as efficacious as more surgery. The Halstedian radical mastectomy gave way to the modified radical mastectomy, and eventually partial mastectomy.[1–3] Likewise, axillary management began as a complete axillary dissection and has subsequently been superseded by a sentinel node biopsy.[4–6]

The historical progression of breast cancer management demonstrates the breast surgeon can perform less surgery provided the extent of local therapy has no impact on overall survival. Current breast cancer researchers are continuing to seek less-invasive, less-morbid alternatives, while still achieving equivalent outcomes. This monograph will summarize the avenues and clinical trials where performing less surgery, or even no surgery, in the management of a breast cancer patient shows promise.

ACTIVE SURVEILLANCE FOR DUCTAL CARCINOMA IN SITU

Approximately 51,000 women in the US will be diagnosed with ductal carcinoma in situ (DCIS) this year alone, with almost all of these diagnoses being made in completely asymptomatic individuals.[7] Without treatment, it is estimated that only 20–30% of DCISs will progress to invasive cancer.[8,9] However, once diagnosed, over 97% of women are treated according to current guideline-concordant care (GCC),[10] with a combination of surgery, radiation and endocrine therapy—treatments similar to those recommended for patients with invasive cancer. The term ‘overdiagnosis’ has been used to define those conditions that look like early cancer but are not destined to cause symptoms or death during a patient’s lifetime. ‘Overdiagnosis’ then leads to ‘overtreatment’ since many of these cancers would have never caused any problems that would have required treatment. Overdiagnosis, and thus overtreatment, are inevitable consequences of cancer screening. Identifying ways to minimize the impact of overdiagnosis demands discrimination of clinically relevant lesions that require active treatment, from those that can be safely monitored with treatment only if progression occurs, similar to the approach commonly offered to men with early-stage prostate cancer.

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D. W. Ollila, MD
e-mail: david_ollila@med.unc.edu

To date, among the 97% of women with DCIS treated with GCC, neither randomized trials nor retrospective studies have shown a survival advantage of any one treatment option over another.[10–12] Moreover, none of the standard treatments have ever been compared in a rigorous fashion to active surveillance. Thus, there has been keen interest to address whether active surveillance in patients with low–intermediate grade DCIS would be safe for women at low risk of progression to invasive carcinoma, and whether the risks of active surveillance justify such an approach.

There are currently three international randomized controlled trials evaluating the risks and benefits of an active surveillance approach: the LORIS study (ISRCTN 27544579), the LORD study (EORTC; NCT02492607) and the COMET study (Alliance; NCT02926911). The patient populations, healthcare environments, and clinical trials organization of the three studies inevitably differ, but the objectives and many of the study endpoints are aligned. The evidence provided by the DCIS active surveillance studies will enable future patients with DCIS to make informed decisions about management options based on level I evidence. Collectively, the LORIS, LORD and COMET trials will provide an important opportunity to address a highly relevant healthcare issue with broad-reaching health, social, and economic implications, and help provide a framework for evidence development in other low-risk conditions where overtreatment is an emerging concern.

TUMOR ABLATION

Partial mastectomy is a low morbidity, ubiquitously available procedure providing excellent local control and cosmesis.[2,3] As such, it is appropriately considered the gold standard for the treatment of most early-stage breast cancers[13] and has set a high bar for comparison of new treatments. Tumor ablative therapy for the treatment of small breast cancers is attempting to meet or exceed the high bar. Tumor ablation can be accomplished in a single session in the ambulatory setting under minimal or no sedation, with extremely low morbidity and no scar, resulting in superior cosmesis when compared with a partial mastectomy.

Modalities for tumor ablation utilize various energy forms, including cryoablation,[14] interstitial laser ablation,[15] focused ultrasound ablation (FUSA),[16] and radiofrequency ablation.[17,18] Cryoablation, radiofrequency ablation, and laser ablation require the percutaneous insertion of a treatment probe into the tumor. FUSA is an entirely transcutaneous technique requiring no incision, probe, or needle placement into the breast.

Ablative therapy/partial mastectomy studies of cryoablation have demonstrated good efficacy, with total ablation of the targeted tissue in up to 92% of cases.[14] Multicenter treat and observe studies of cryoablation are currently enrolling in the US (FROST; Sanarus Technologies, Inc.; NCT0199225) and Ice3 (IceCure Medical Ltd; NCT02200705). Similar initial results have been achieved with interstitial laser therapy,[15] with a treat and observe study currently under development (Schwartzberg B, Personal communication, April 2018), and focused ultrasound,[16] with a trial studying the combination of FUSA with immunotherapy for the treatment of stage IV breast cancer also underway at the University of Virginia.[19]

Breast-conserving surgery combined with radiation therapy has been extensively studied and is the widely available ‘gold standard’ for the treatment of patients with small breast cancers.[3,20] In comparison, breast tumor ablation techniques are relatively new with minimal data, requiring complex technology with limited availability. Prospective studies of ablative therapies addressing local failure rates, cosmesis, cost effectiveness, the ability to detect residual untreated disease, and long-term patient satisfaction are ongoing. If a non-surgical ablative therapy is found to provide equivalent outcomes to surgical excision, patients will appropriately demand it and it will become the breast cancer treatment of choice. It is imperative that surgeons remain involved in the development and testing of these innovative and potentially disruptive ablative technologies. If they do not, others will eagerly step up to take their place.

SELECTIVE OMISSION OF A SENTINEL NODE BIOPSY

A patient with invasive breast cancer may only derive a therapeutic benefit from the sentinel node biopsy if the lymph node results actually change the therapy that the patient would have received. Older breast cancer patients tend to have more comorbidities[21] and die of causes unrelated to their breast cancer regardless of their axillary node status.[21] Previously published clinical trials give us insight into which older breast cancer patients may not need a sentinel node. The Cancer and Leukemia Group B (CALGB) 9343 trial[22,23] investigated patients who were $\geq$ 70 years of age with estrogen receptor (ER)-positive and predominantly progesterone receptor (PR)-positive breast cancers, randomizing them to whole-breast radiation therapy plus tamoxifen or tamoxifen alone. The primary endpoint, i.e. overall survival, demonstrated no difference between the two study arms.[22,23] Interestingly, two-thirds of these women had no axillary surgery at all, again with no breast cancer-specific mortality difference. Moreover,

patients who had no axillary surgery had very few axillary recurrences (6/204, 3%).[23] The explanation for omitting both radiation and sentinel node biopsy and having equivalent outcomes is understanding the biology of the patients enrolled on the trial. Hughes et al.[22,23] chose to investigate the two most favorable breast cancer phenotypes by gene expression patterns—Luminal A and Luminal B.[24] These are both richly ER+ with the most favorable prognosis of the known breast cancer phenotypes to date, and are exquisitely sensitive to anti-estrogen therapy.

Two additional studies, the International Breast Cancer Study Group (IBCSG)[25] and the Milano Group[26,27] randomized older ER+ breast cancer patients undergoing partial mastectomy to axillary clearance (IBCSG)/axillary dissection (Milan) plus tamoxifen versus no axillary surgery alone. In both trials, the no axillary surgery arms had a slightly higher locoregional recurrence rate (IBCSG: 1 vs. 3%; Milan 0 vs. 6%). However, this locoregional recurrence difference did not translate into a difference in breast cancer-specific mortality or overall survival between the two arms.[25–27] Both of these trials enrolled the most favorable phenotypes—older patients with richly ER+, Luminal A, and possibly some Luminal B, breast cancers. Thus, the fact that there is no difference in overall survival in a patient with ER+ breast cancer receiving tamoxifen should not be unexpected. Collectively, the three trials (CALGB 9343, IBCG, and the Milan trial) strongly suggest that no axillary surgery is necessary in Luminal A, and possibly some Luminal B, phenotypes. The Early Breast Cancer Trialist's Collaborative Group (EBCTCG) overview demonstrated that a recurrence did not influence survival in this subgroup of patients (Table 1).[28]

While we await the results of a prospective, randomized trial (Sentinel node vs. Observation after axillary UltrasouND [SOUND; ClinicalTrials.gov: NCT02167490]), older Luminal A, and some Luminal B, breast cancer patients may be spared a sentinel node procedure. Axillary surgery does not affect breast cancer-specific mortality in this subgroup of older ER+ early-stage breast cancer patients. This is congruent with National Comprehensive Cancer Network (NCCN) guidelines v.1.2018, which states "axillary staging may be considered optional in patients who have particularly favorable tumors and in patients for whom the selection of adjuvant systemic therapy and/or radiation is unlikely to be affected".[29]

SELECTIVE ELIMINATION OF BREAST CANCER SURGERY AFTER NEOADJUVANT SYSTEMIC THERAPY

The therapeutic value of surgery is questionable if the patient achieves a pathologic complete response (pCR) to neoadjuvant systemic therapy (NST).[30] NST can eliminate both invasive and in situ carcinoma in up to 50% of patients, particularly in triple-negative disease or HER2-positive cancers.[31,32] Determining which patients have achieved a pCR without surgical resection has been problematic because breast imaging alone lacks sufficient sensitivity and specificity to be effective.[33,34] Attempting to identify patients with a pCR without surgical intervention, Heil et al.[35,36] analyzed a multicenter pooled analysis comparing percutaneous core cut to percutaneous vacuum-assisted core biopsy (VACB) in patients with a clinical response to NST. Image-guided VACB and the existence of a marker clip improved the negative predictive value (NPV) and decreased the false-negative rate (FNR) when compared with the partial mastectomy specimen. Further investigation of image-guided VACB with a marker clip demonstrated an improved NPV of 94.4% and reduced FNR of 4.8%.[35]

Kuerer et al. conducted a feasibility trial in triple-negative breast cancer or HER2-positive patients comparing fine-needle aspiration (FNA) with VACB following NST. Individually, FNA and VACB had an NPV of 63 and 90%, respectively, and FNR of 52 and 10%, respectively. Combined FNA/VACB had an NPV of 95% and FNR of 5%.[37] The pathologic response in the VACB was concordant with the pathologic status of the partial mastectomy in approximately 98% of cases.[37,38] False-negative cases had < 12 cores taken and/or a very large initial tumor size. This feasibility study demonstrates that VACB is superior to FNA, and a follow-up study of image-guided VACB following NST requires a minimum of 12 cores of the original tumor bed and < 5 cm disease by initial breast imaging prior to NST (Fig. 1).[39]

This burgeoning new paradigm requires meticulous and precise image-guided biopsy of the tumor bed.[37,40,41] Patients with an excellent radiographic response to NST should still have a partial mastectomy unless they are on an institutional, prospective clinical trial or one of several international multicenter trials such as RESPONDER (ClinicalTrials.gov: NCT02948764), the MICRA trial (TrialRegister.NL: NTRA6120), or the NRG BR005 biopsy feasibility study (ClinicalTrials.gov: NCT03188393). The key in a multicenter clinical trial is the optimal, accurate, and safe selection of patients who are thought to have a pCR by breast imaging. The

TABLE 1 Prospective, randomized clinical trials of "older" ER+ patients

Study	Trial arms	Median follow-up (years)	Eligibility criteria	Locoregional recurrence	Survival
CALBG (2004, 2013)[22,23]	Tamoxifen + radiation/ lumpectomy versus Tamoxifen and lumpectomy alone (66% of patients did not have axillary node dissection)	10	> 70 years of age ER-positive BCS patients Node-negative 66% had ALND	0 versus 3% axillary recurrence	No difference in breast cancer-specific or OS
Martelli et al. (2012, 2005)[26,27]	Quadrantectomy and ALND versus quadrantectomy alone	15	> 65 years of age pT1N0 HR-positive	0 versus 6% axillary recurrence	No difference in breast cancer mortality or OS
IBCSG (2006)[25]	Surgery and axillary clearance versus surgery alone	6.6	≥ 60 years of age cN0 ER-positive	1 versus 3% axillary recurrence	No difference in DFS or OS

CALBG Cancer and Leukemia Group B; *IBCSG* International Breast Cancer Study Group; *ALND* axillary lymph node dissection; *ER* estrogen receptor; *BCS* breast-conserving surgery; *HR* hormone receptor; *OS* overall survival; *DFS* disease-free survival

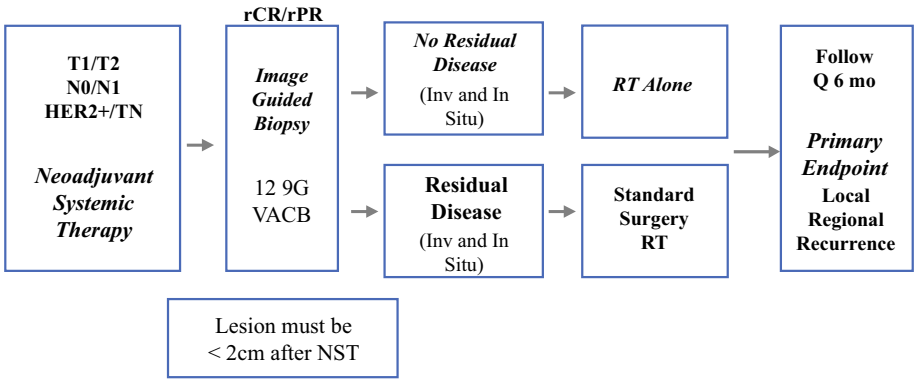

FIG. 1 MD Anderson Cancer Center multicenter protocol schema for eliminating breast cancer surgery in exceptional responders with neoadjuvant systemic therapy.[39] *TN* triple negative, *HER2* human epidermal growth factor receptor 2, *rCR* radiologic complete response, *rPR* radiologic partial response, *Inv* invasive, *RT* radiotherapy, *Bx* biopsy, *F/u* follow-up, *cDNA* circulating DNA, *VACB* vacuum-assisted core biopsy, *CTC* circulating tumor cell, *NST* neoadjuvant systemic therapy

methodology and parameters in whom percutaneous VACB can potentially supplant partial mastectomy after NST can only be answered by rigorously conducted clinical trials.

FINAL THOUGHTS ON THE FUTURE OF BREAST SURGERY

The role of surgery for breast cancer is rapidly evolving. Targeted systemic therapy and a deeper understanding of cancer biology will continue to inform our surgical approach. There is a growing awareness about overtreatment and the importance of quality of life for our patients.[42] In his keynote address to the American Society of Breast Surgeons (ASBrS) in 2013, Professor Umberto Veronesi emphasized a paradigm shift: "minimally effective, not maximally tolerated therapy". Multimodal therapy with surgery, systemic therapy, and radiation has been highly successful; however, the utility of surgery, and ultimately radiation, will diminish as medical therapy continues to improve. Previously described in this manuscript are the evolving shifts toward active surveillance of

DCIS, breast cancer tumor ablation, selective omission of sentinel node biopsy, and selective elimination of surgery after NST. The volume of breast cancer surgical cases will significantly diminish in the future, but less invasive percutaneous procedures will increase. This is great news for patients. Surgeons will need to expand their skills and clinical activities.

The ASBrS leadership has commenced the 2025 Working Group to provide education and mentorship to help equip surgeons with the requisite skills. Surgeons will have a prominent role due to our clinical expertise and being the point of entry for most patients. Defining an optimal surveillance approach, along with lifestyle-based risk reduction, are critical. Emphasis on breast cancer prevention and risk reduction will expand. Minimally invasive image-based resection technology, along with targeted tumor ablation, will rapidly progress. It is critical that surgeons have the imaging skills so they can perform these procedures. Most of our patients present with image-detected cancers and are asymptomatic, with a normal appearance. Visible scars and deformed breasts are no longer acceptable. Hidden scar techniques, nipple-sparing mastectomy, and oncoplastic surgical techniques are essential skills. Optimal patient preparation and more effective pain management techniques are essential to optimize patient-reported outcomes. All these skills must be incorporated into fellowship training and postgraduate courses. Less patients will require axillary surgery, however, when indicated, minimizing arm morbidity with axillary reverse mapping[43,44] and preventative lymphatic-venous bypass (LYMPHA procedure) is essential to minimize arm morbidity and lymphedema.[45]

We must continue to be the leaders of the breast cancer team. Patients identify us as the point person, and our knowledge in all aspects of screening, risk assessment, treatment and survivorship is critical. The landmark innovations, including breast conservation, sentinel node biopsy, skin- and nipple-sparing mastectomy, oncoplastic techniques, targeted tumor ablation, and intraoperative radiation have all been advanced by surgeons. We must continue to lead the way to develop and advance novel preventative and therapeutic approaches for the benefit or our patients.

In the coming decade, just as in the previous 4 decades, breast surgeons will continue to perform less surgeries. Our patients will not suffer needlessly and will in fact thank us for delivering the most minimally invasive effective care. Breast surgeons must take the lead in performing well thought-out trials that support performing less-invasive and potentially fewer therapies while maintaining low local recurrence rates and maximizing survival.

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