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Controversies in Breast Cancer Surgery

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INTRODUCTION

Breast surgical oncology is a rapidly evolving field shaped by decades of practice-changing research and public health initiatives. Widespread dissemination of screening in the United States (US) enabled increased detection of early-stage disease and transformed breast cancer into a largely curable entity, although significant disparities in screening, stage at diagnosis, and survival persist.[1-3] For late-stage and biologically aggressive subtypes including HER2-enriched (HER2+) and triple-negative breast cancer (TNBC), increased use of neoadjuvant systemic therapy (NST) has enabled de-escalation of surgical treatment in the breast and axilla.[4,5] Nevertheless, women in the US continue to undergo contralateral prophylactic mastectomy (CPM) for unilateral disease at high rates compared to several other countries, with many average-risk women undergoing CPM even when breast-conserving therapy (BCT) is feasible.[6]

Ironically, higher rates of CPM are observed among recipients of neoadjuvant chemotherapy (NACT) than among recipients of adjuvant or no chemotherapy.[7] Thus, the benefit of NACT as a means of facilitating BCT in place of mastectomy is realized less often than it could be, prompting exploration of less toxic neoadjuvant systemic alternatives such as endocrine therapy (NET), which is less commonly used in the US. Notably, however, there is a strong trend towards using NACT to de-escalate locoregional treatment of the axilla given the morbidity associated with axillary lymph node dissection (ALND) with or without the addition of axillary radiation.

Here, we discuss the three important yet controversial topics described above, specifically: (1) high rates of CPM despite unclear benefit, (2) shifting indications for NST (i.e., NACT and/or NACT), and (3) evolving approaches to surgical management of the axilla.

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DISCUSSION

Contralateral Prophylactic Mastectomy

Breast cancer risk assessment is critical to surgical decision-making, particularly with regards to the appropriateness of CPM. Breast cancer risk factors can be divided into modifiable (i.e., alcohol use) and non-modifiable (i.e., age) factors. Several risk calculators are available to help counsel patients on their estimated lifetime breast cancer risk.[8] These tools help guide discussions on surgery choice in patients who may be considering prophylactic, also referred to as risk-reducing, mastectomy.

Improved radiographic technology and increased use of adjuvant endocrine therapy contributed to a decrease in contralateral breast cancer incidence among unilateral breast cancer patients since 1985, with the annual risk of contralateral breast cancer estimated to be only 0.2-0.5%.[9,10] CPM rates have been increasing over the last 20 years despite unclear and even contradictory evidence of survival benefit.[11-16] The most commonly cited reason for CPM is patient preference, often driven by fear and anxiety about future breast cancer diagnosis and cosmetic concerns such as asymmetry after unilateral mastectomy.[10,17] Women who are young, white, more educated, and have a family history of breast cancer are more likely to choose CPM.[18] While some studies have shown concomitant postoperative decrease in cancer-related anxiety after CPM, it is associated with increased risk of surgical complications and sometimes negative psychological outcomes including decision regret, compromised body image, and unsatisfactory sexual function.[10,11,15] The option for CPM is of greatest import for women deemed to have a high (>20%) lifetime risk of metachronous breast cancer. For these women, non-surgical options for breast cancer risk reduction include endocrine therapy chemoprevention and specialized radiographic surveillance protocols.

Evidence-based counseling, formal risk assessment, and, if needed, engagement of psychosocial support services should all be a part of shared decision-making (SDM) for CPM. Once the decision to pursue CPM has been made, the next steps in SDM involve type of mastectomy (nipple-sparing, skin-sparing, or simple), type of reconstruction (autologous, implant-based, or both), and indications for sentinel lymph node biopsy (SLNB). Nipple-sparing mastectomy (NSM) is oncologically safe, with no difference in survival compared to traditional mastectomy. Furthermore, it has a similar complication profile but improved aesthetic outcomes compared with other forms of mastectomy.[19] However, while promising, long-term data regarding future breast cancer risk and survival are relatively sparse.[20]

Increased access to reconstructive surgery has been linked to increased utilization of CPM.[21] Two important decisions must be made once a patient chooses reconstruction: the timing of reconstruction relative to mastectomy (immediate vs delayed) and type of reconstruction (autologous vs implant-based). Most CPM recipients undergo immediate, implant-based reconstruction.[22] Immediate reconstruction can be done in one stage (direct to implant or upfront autologous reconstruction) or two stages (tissue expander followed by later exchange for implant or autologous reconstruction). Immediate reconstruction is associated with improved psychosocial well-being, lower costs, and improved cosmesis but also with increased implant and flap failure rates compared to delayed reconstruction.[23-26] Data are

conflicting with regards to overall surgical and medical complication rates after delayed vs immediate reconstruction.[23,24]

Implant-based reconstruction is a less invasive procedure with quicker recovery compared with autologous reconstruction while still resulting in excellent cosmetic outcomes. However, risks include capsular contracture, implant failure, and a small risk of breast implant–associated anaplastic large cell lymphoma (BIA-ALCL), all of which may require additional future surgeries.[27,28] In contrast, autologous reconstruction uses a patient's own tissue, usually abdominal, to create a more natural appearance with good longevity and higher satisfaction on patient reported outcomes.[28,29] It is, however, a more invasive procedure with longer recovery, potentially catastrophic complications of flap loss, and additional donor site morbidity.[28]

Among mutation carriers, performing SLNB is rationalized by the concern for the difficulty of performing sentinel node mapping after mastectomy in the event of unexpected occult invasive cancer (1-3%). Thus, although the chance of a positive lymph node in such a scenario is estimated to be only 0.5%,[11] some advocate for SLNB in all mutation carriers undergoing CPM while others do not believe the risk of occult cancer justifies the risks – albeit low – of SLNB. MRI has been used to screen for breast cancer prior to surgery, thus lessening the risk of occult cancer that would require SLNB, but the high cost-benefit ratio of this approach has called this strategy into question.[11]

In conclusion, CPM has become increasingly common without clear evidence of survival benefit. Among women with clinically actionable genetic mutations, CPM is associated with decreased risk of a future breast cancer, but there are non-operative strategies that may confer similar levels of risk reduction. Both evidence-based risk assessment and an accurate capture of patient preferences are important components of the SDM process for CPM.

Neoadjuvant Systemic Therapy

NACT was first used in the 1970s in the treatment of locally advanced breast cancers.[30] In the 1980s and 1990s, two large randomized control trials (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-18 and B-27) demonstrated no survival difference between neoadjuvant and adjuvant chemotherapy.[31] Subsequent randomized trials confirmed substantial tumor response and increased rates of BCT after NACT but, likewise, no significant difference in mortality between neoadjuvant and adjuvant chemotherapy treatment groups.[32] Notably, pathological complete response (pCR) rates among NACT recipients varies by tumor subtype, with high pCR rates among hormone receptor-negative (HR−), high grade, and/or HER2+ tumors and low pCR rates among low-intermediate grade and hormone receptor-positive (HR+) tumors.[33] Furthermore, not only does pCR vary with tumor subtype, anatomic extent of pCR (i.e., whether it occurs in the breast, axilla, or both) also predicts survival for less chemosensitive (e.g., HR+/HER2−) and more aggressive (e.g., TNBC) subtypes.[34]

Over the past 30 years, NACT utilization has increased. Indications for NACT include the intention of downstaging large primary and/or node-positive tumors to enable less morbid operations and opportunities to preserve the breast. NACT also enables in

vivo demonstration of tumor chemosensitivity or chemoresistance, information that can subsequently guide treatment. However, in the event of chemoresistance, there is the theoretically increased risk of metastasis or local tumor enlargement from delay in surgery, with concomitantly worse prognosis or unavoidable mastectomy.[35,36] In fact, a meta-analysis of randomized trials evaluating neoadjuvant vs adjuvant chemotherapy found an increased risk of local recurrence in the NACT group, but there was no association with increased risk of distant recurrence or survival.[32] Furthermore, tumor progression during NACT, though relatively uncommon, is associated with decreased overall survival.[37]

Data regarding tumor response to NACT can help guide adjuvant therapy decision-making. For example, the KATHERINE trial demonstrated that in women with early-stage HER2+ breast cancer treated with NACT in combination with anti-HER2 targeted therapy but who still had residual disease on final post-NACT surgical pathology, treatment with adjuvant ado-trastuzumab emtansine (T-DM1, aka Kadcyla [Genentech]) decreased risk of recurrence or death by 50%.[38]

Unfortunately, NACT has proven less effective at breast and axillary downstage for HR+ tumors, which constitute nearly 75% of all invasive breast cancer.[39] Adjuvant endocrine therapy for HR+ breast cancer is known to improve survival, but less is known about the impact of neoadjuvant endocrine therapy (NET) as a single agent or in combination with chemotherapy. A recent analysis of US practice patterns showed a 20% utilization rate of NET.[40] Currently, it is most commonly utilized among elderly patients or those deemed unable to tolerate chemotherapy.[39] Notably, there is no significant difference in BCT rate between NET and NACT recipients, but NET is significantly less toxic.[39]

The optimal NET regimen with regards to composition and timing has been explored in several trials. The P024 trial compared four months of neoadjuvant tamoxifen with the aromatase inhibitor (AI) letrozole in postmenopausal women with HR+ breast cancers who were ineligible for BCT. The letrozole group had higher rates of BCT than the tamoxifen group.[41] The IMPACT trial compared neoadjuvant tamoxifen, anastrozole, and a combination of tamoxifen and anastrozole administered for three months in postmenopausal women with estrogen receptor-positive (ER+) invasive breast cancer. BCT rates were increased in in the anastrozole groups relative to the tamoxifen-only group, though all groups exhibited some response.[42] The American College of Surgeons Oncology Group (ACOSOG) Z1031 found all AIs (letrozole, anastrozole, and exemestane) used in the neoadjuvant setting among postmenopausal women with ER+ breast cancer facilitated increased BCT rates.[43] The PTEX46 trial found no difference in clinical response rate between neoadjuvant exemestane administered for four vs six months.[44] Several other studies evaluating optimal length of NET support 4-6 months, though longer times may be acceptable if patients show continued response.[45]

Most NET trials have been conducted among postmenopausal women, thus less is known about the safety and efficacy of NET in premenopausal women. The STAGE trial, focusing on premenopausal women, demonstrated that six months of ovarian suppression plus an AI in the neoadjuvant setting had more clinical response than neoadjuvant tamoxifen.[46] The ALTERNATE trial found no significant difference in the clinical response rate between

premenopausal women randomized to NET with either fulvestrant or fulvestrant plus anastrozole with stage II/III ER+, HER2− breast cancer.[47] In addition, little is known about the effect of NET on HR+ disease that is also HER2+, as most NET trials have been limited to individuals with ER+/HER2− disease. There were some women with this subtype included in both the aforementioned IMPACT and ASCOG Z1031 trials, and in both, AIs yielded slightly better response rates than tamoxifen among patients with HR+, HER2+ disease.[42,43]

During neoadjuvant therapy, patients should be followed with regular clinical breast exams to monitor response. Imaging may be obtained at the treating physicians' discretion and should be the same modality as baseline pre-treatment imaging.[48] The early months of the COVID-19 pandemic saw increased neoadjuvant therapy use, largely in response to the Society of Surgical Oncology (SSO) and the American Society of Breast Surgeons (ASBrS) recommending 3-6 months of NET in women with early-stage HR+/HER2− breast cancer and NACT in TNBC or HER2+ breast cancer instead of upfront surgery.[49,50] The rapid but heterogeneous adoption of these recommendations has provided an unprecedented opportunity to observe and analyze adherence, outcomes, and side effects for previously underutilized neoadjuvant care pathways. Between pandemic-related natural-history studies and upcoming trials aimed at risk-stratifying premenopausal women with HR+ disease, the next decade holds promise for expanding our understanding of how best to utilize NACT and NET among diverse women with breast cancer.

Management of the Axilla

Since the era of the Halstead radical mastectomy, surgery of the breast has been de-escalated to simple mastectomy and, for eligible patients, breast-conserving therapy. Similarly, there has been increased movement towards de-escalating locoregional treatment of the axilla.

Axillary surgery is performed to optimize control of regional disease and to stage the axilla, thereby providing information to guide adjuvant therapy and inform prognosis. In the 1990s and 2000s, significant progress was made in decreasing unnecessary axillary lymph node dissections and their associated morbidity. The NSABP B-32 trial randomized women with clinically node-negative invasive breast cancer to SLNB and ALND or SLNB alone. The SLNB false negative rate (FNR) was 9.8%. At eight-year follow-up, there was no significant difference in survival (91.8% ALND vs 90.3% SLNB) or regional recurrence (0.4% ALND vs 0.7% SLNB). However, ALND had nearly twice the rate of lymphedema (14%) as SLNB (8%).[51] This trial proved that SLNB is as safe and effective as ALND in staging the axilla in patients with clinically node-negative disease.

ACOSOG Z0011 built upon the findings of NSABP B-32 and examined whether women with one or two positive sentinel lymph nodes (SLNs) needed to undergo completion ALND. Women undergoing BCT with cT1-T2, cN0 invasive tumors but found to have one or two positive SLNs on final surgical pathological review were randomized to ALND or no further surgery.[52] At ten-year follow-up, neither the cumulative incidence of nodal recurrences (0.5% ALND vs 1.5% SLNB)[53] nor overall survival (83.6% ALND vs 86.3% SLNB) were significantly different.[54] Notably, a majority of patients in both groups received some form of systemic therapy and whole-breast radiation. Furthermore,

27% of patients in the ALND group had additional positive nodes in the final tissue sample. Given the randomized study design and presumed balance between the groups, this finding suggests that there were similar levels of unresected nodal disease among patients who underwent SLNB alone but this residual tumor did not adversely impact recurrence or survival.[52] Consistent with these findings, in ACOSOG Z0010, which included patients with cT1-2, cN0 invasive tumor, occult micrometastases were found in 10.5% of SLNB specimens, but this level of involvement had no impact on survival.[55] Similarly, the International Breast Cancer Study Group (IBCSG) 23-01 trial randomized patients with one or more micrometastatic (≤2 mm) SLNs to ALND or no ALND. Ten-year survival was not significantly different between the two arms (74.9% in ALND vs 76.8% in no ALND). As seen in prior studies, the lymphedema rate was higher (13%) among ALND recipients vs non-recipients (6%).[56]

While Z0011 examined whether additional axillary surgery is necessary when patients are found to have positive SLNs, the AMAROS trial sought to determine whether positive SLNs can be as effectively treated with radiation alone as opposed to ALND. Women with cT1-2, cN0 undergoing BCT or mastectomy who had a positive SLN were randomized to ALND or axillary radiation (ART). At five years post-treatment, there was no significant difference in axillary recurrence (0.43% ALND vs 1.19% ART) or overall survival (93.3% ALND vs 92.5% ART). However, clinical signs of lymphedema were more common after ALND (23%) than radiation (11%).[57] Thus, these trials support the current practice of performing SLNB in women with cN0 disease and of not routinely recommending further axillary surgery if they have <3 positive SLNs.

Axillary management in the context of neoadjuvant therapy is controversial. It remains unclear whether to treat patients based on clinical stage at presentation (cTN) or on their clinical (ycTN) and/or pathological (ypTN) stages following neoadjuvant treatment. There are three main groups of patients that warrant nuanced consideration with regards to surgical management of the axilla after neoadjuvant systemic therapy (NST): (1) those who are clinically node-negative (cN0) prior to and remain node-negative after NST, (2) those who are clinically node-positive with low burden of disease (cN1) who remain so after NST (i.e., ycN1), and (3) those who present with cN1 disease but become node-negative (i.e., ycN0) after NST. Significant axillary downstage is uncommon after NET, thus incorporating axillary response after NST into surgical decision-making is most relevant for those undergoing NACT. For patients who are cN0 before and after NACT, SLNB is appropriate. If SLNB is negative, then no further surgery is needed. If it is positive, ALND remains standard of care. Notably, these patients are NOT analogous to cN0 patients with positive SLNs in Z0011 and AMAROS because ypN1 disease in a cN0 patient suggests either previously undiagnosed, chemoresistant disease or new disease that developed while on treatment.[58] For patients that have nodal disease before NACT and remain node positive after, ALND is standard of care.[59]

The greatest controversy surrounds those who are cN1 at presentation but downstage by imaging and exam to ycN0. Several trials were developed to determine whether SLN mapping was possible and reliable after NACT for cN1 disease. The SENTINA trial in Europe examined the accuracy of SLNB in cN1 patients after NACT and had four study

arms, 2 for cN0 patients (arms A and B) and 2 for cN1 patients (arms C and D). After NACT, cN1 patients were clinically restaged as ycN0 (arm C) or ycN1 (arm D), with the former undergoing SLNB and ALND while the ycN1 patients went straight to ALND. In arm C, the SLN detection rate was 80% and overall false negative rate (FNR) of 14.2%, with rates decreasing to 8.6% with use of dual tracer (blue dye and radiocolloid) mapping and to 7.3% when at least 3 nodes were retrieved.[60] ACOSOG (Alliance) Z1071 trial exhibited a 90% detection rate and 12.6% FNR. The latter decreased to 10.8% with dual tracer mapping and 9.1% when 3 or more nodes were identified.[61] Finally, in the SN-FNAC (Sentinel Node Biopsy Following NeoAdjuvant Chemotherapy in Biopsy Proven Node Positive Breast Cancer) trial, the node detection rate was 87.6%, and the FNR was 8.4%.[62]

To assess whether the false negative rates from Z1071, SENTINA, and SN-FNAC could be improved, MD Anderson created a registry for targeted axillary dissection (TAD), which is the post-NACT identification and removal of both any SLNs identified via dual tracer mapping as well as any lymph node(s) clipped and biopsied prior to NACT. To facilitate TAD, the clipped node was localized with an I-125 impregnated seed immediately prior to surgery. They observed that the clipped node was not the sentinel node in 23% of patients. In patients undergoing SLNB alone, the FNR was 10.1% but adding the clipped node decreased the FNR to 1.4%.[63] If the SLNBs and/or previously clipped node are positive, ALND is recommended.[59] TAD is increasingly being used in practice, but long-term data on post-TAD outcomes are sparse.

There are two large ongoing clinical trials exploring the role of radiation in cN1 patients who had NACT and have a positive SLNB. The Alliance A11202 is randomizing women with positive SLNB after NACT to ALND or ART and measuring recurrence-free and overall survival. At the same time, NRG Oncology NSABP B-51 (aka Radiation Therapy Oncology Group [RTOG] 1304) is a companion trial in which cN1 patients found to be ypN0 on post-NACT SLNB are randomized to undergo or forego nodal radiation with the primary outcome being invasive breast cancer recurrence-free interval.[64]

There has also been a move towards de-escalating axillary treatment for elderly patients with early-stage, non-aggressive breast cancer, potentially omitting SLNB in some. IBCSG 10-93 randomized women > 60 years old with cN0, HR+ cancer to breast surgery and axillary clearance (SLNB and ALND) or breast surgery alone. At six-year follow-up, there were no significant differences in overall survival (75% axillary surgery vs 73% no axillary surgery) or axillary recurrences (two axillary recurrences in the axillary surgery group and three in the no axillary surgery group).[65] Another randomized trial of elderly patients >70 years old undergoing breast surgery with or without ALND found a 15-year recurrence rate of only 5.8% in the no axillary surgery group and no significant difference in mortality (14% in no ALND vs 13.6% in ALND), though more patients in the ALND group had received radiation.[66] It is also important to note that women in all these trials were taking adjuvant endocrine therapy. Nevertheless, despite these findings, and even Choosing Wisely recommendations that SLNB can be safely omitted in elderly women with early-stage cN0 breast cancer, a recent analysis demonstrated that 91% of early-stage breast cancer patients over age 65 have undergone some sort of axillary surgery.[67]

In summary, there is evidence to suggest that ALND may be omitted in select node-positive patients after NACT and safely omitted among elderly women with low-risk in-breast disease.

SUMMARY

In conclusion, use of CPM, indications for NST, and surgical management of the axilla represent areas of current debate and active research. Although much of breast surgical oncology is moving towards de-escalating surgical care both in the breast and the axilla, particularly with the use of NST, CPM represents an area of potential overuse despite unclear benefit for many recipients. Future research should focus on delineating the populations in whom CPM and de-escalation of locoregional are most appropriate and on exploring NET as a less toxic but potentially comparable alternative to NACT in some women with breast cancer.

Abbreviation/Glossary list:

ALND	axillary lymph node dissection
BCT	breast conserving therapy
CPM	contralateral prophylactic mastectomy
FNR	false negative rate
NACT	neoadjuvant chemotherapy
NET	neoadjuvant endocrine therapy
SLNB	sentinel lymph node biopsy

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Key points:

1. Contralateral prophylactic mastectomy (CPM) in women with unilateral breast cancer confers no survival advantage, can be associated with more complications, and represents a preference-sensitive decision.
2. Neoadjuvant chemotherapy (NACT) should be used in locally advanced, inflammatory, and higher-stage HER2+ and triple-negative breast cancers, when breast conservation is strongly desired, and to facilitate axillary downstage.
3. Neoadjuvant endocrine therapy (NET) in select postmenopausal women with hormone receptor-positive cancer is comparably effective to NACT.
4. Patients who are clinically node-positive and become clinically node-negative after NACT are eligible for sentinel lymph node biopsy, which should be done with dual tracer and ideally yields the retrieval of at least 3 nodes and the previously biopsied node. If these nodes are negative, then further axillary surgery can potentially be omitted.

Synopsis:

Breast surgical oncology is a rapidly evolving field with significant advances shaped by practice-changing research. Three areas of ongoing controversy are (1) high rates of contralateral prophylactic mastectomy (CPM) in the United States despite uncertain benefit, (2) indications for and utilization of neoadjuvant chemotherapy (NACT) and endocrine therapy (NET), and (3) staging and treatment of the axilla, particularly after neoadjuvant systemic therapy. We discuss the patient populations for whom CPM may or may not be beneficial, indications for NACT and NET, and the trend towards de-escalation of locoregional axillary treatment.

CLINICS CARE POINTS

1. CPM confers no survival advantage and has increased risk of complications but may be appropriate in some high-risk individuals. Appropriate counseling and SDM is encouraged.
2. NACT can be used to improve candidacy for BCT, downstage the axilla, and prevent distant metastases in locally advanced, inflammatory, HER2+, and triple negative breast cancers.
3. NET is an effective, less toxic but currently underutilized alternative to NACT for postmenopausal women with ER+ breast cancers who wish to improve candidacy for BCT.
4. Clinically node-positive patients who become clinically node-negative after NACT are eligible for SLNB. Use of dual tracer mapping, retrieval of at least 3 lymph nodes, and identification of the previously biopsied node significantly decrease the FNRs of post-NACT axillary staging. If SLNB – or, ideally, targeted axillary dissection (TAD) – is negative, ALND can be omitted. If SLNB is positive, proceed to ALND.