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Trends and Controversies in Multi-Disciplinary Care of the Breast Cancer Patient

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Margins in Breast Conserving Surgery—Invasive Cancer and Ductal Carcinoma in Situ

Breast-conserving surgery (BCS) followed by whole breast irradiation (RT) has been a standard option for the management of early-stage breast cancer for more than 25 years. Over time, rates of local recurrence have declined steadily, and are now <10% at 10 years for women with invasive cancer(1, 2), and slightly higher for those with ductal carcinoma in situ (DCIS) (3). A fundamental part of BCS is removal of the tumor with a margin of surrounding normal breast tissue, so it is somewhat surprising that after a long clinical experience with BCS, what constitutes an adequate margin remains a matter of debate. In the prospective randomized trials that established the safety of BCS and RT for invasive breast cancer, the only microscopic margin definition used was no ink on tumor in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 trial. The other studies required only gross margins, so the actual microscopic margin widths are unknown. Three of the 4 original randomized trials examining the addition of RT to lumpectomy in DCIS also used

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no ink on tumor to define an adequate margin, while the SweDCIS study included patients with positive or unknown margins.

Over time, as surgeons and radiation oncologists sought to minimize rates of local recurrence (LR) after BCS, wide variations in what was considered an appropriate negative margin arose. In a study of 318 surgeons identified from a population-based patient sample, when asked what negative margin width precluded the need for re-excision in a 60 year old with a 0.8cm invasive carcinoma, no margin width was endorsed by more than 50% of respondents. Tumor not touching ink was selected by 11%, 1–2mm by 42%, and >5mm by the remainder (4). When asked about a 60 year old with a 1.4cm DCIS with RT planned, similar variation was seen. As a consequence of the lack of consensus on what constituted a negative margin, re-excision after initial lumpectomy became a common procedure. In a population-based sample of 1,468 patients attempting BCS in 2005–2007, Morrow et al reported that 38% underwent additional surgery after the first lumpectomy; re-excision in 26% and mastectomy in 12% (5). In a convenience sample of 2,206 patients treated in a similar time period, 23% had re-excision after initial lumpectomy(6), with half performed for a negative margin of no ink on tumor.

The surgical fixation on margin width reflects the long-held belief that disease burden is the primary determinant of local control. Changes in our understanding of the biology of invasive breast cancer, the recognition that adjuvant systemic therapy has a major impact upon the risk of LR, and improvements in breast imaging and pathologic evaluation of lumpectomy specimens led several national organizations to collaborate in the development of multidisciplinary, evidence-based consensus statements on margins in BCS for invasive carcinoma (2014) and DCIS (2016). This article will review relevant pathology issues in margin evaluation, discuss the current consensus guidelines for margins, and discuss what is known regarding their impact on patient outcomes.

Margin Evaluation

There is no standard technique of margin evaluation, nor are there a standard number of histologic sections which are examined from each margin surface. Margins can be evaluated using a radial (perpendicular) method, a shaved (en face) method, or by shaving the walls of the lumpectomy cavity after removal of the tumor (shaved cavity margins). The method of margin evaluation is not known to correlate with rates of local control. In general, higher rates of re-excision are seen with the shaved (en face) technique, and lower rates with separate shaved cavity margins (7). Variations in pathology protocols have considerable potential significance when surgeons assert that differences of 1–2mm in margin width distinguish an adequate from an inadequate excision. In addition to the method of margin assessment, other factors related to specimen processing, such as running of ink from the irregular fatty surface of the lumpectomy to the interior, may influence the measurement of margin width or rate of margin positivity. Removal of the fatty breast tissue from supporting stroma results in a loss of specimen height known as the “pancake phenomenon” which alters the measurement of anterior and posterior margins. Given the lack of standardization in pathology methods, it is not surprising that there is little consensus among studies regarding what constitutes an adequate negative margin.

Margins in Invasive Breast Cancer

When considering what constitutes an appropriate margin, it is useful to remember that a negative margin, regardless of how it is defined, does not indicate the absence of residual carcinoma in the breast. Holland et al used serial subgross sectioning to examine 264 mastectomy specimens containing clinically and mammographically unicentric tumors 4cm or less in size. In only 39% of cases was all the microscopic tumor confined to the clinically evident tumor, and in 41% of cases, residual carcinoma was present at a distance of >2cm (8). The presence of this residual tumor provides the rationale for the use of RT after BCS and suggests that a negative margin should be considered an indicator that the residual tumor burden in the breast is low enough that it is likely to be controlled with RT, rather than as evidence that all tumor has been removed from the breast. This shift in emphasis takes away much of the impetus to dichotomize resections as “adequate” or “inadequate” based on differences of 1–2mm.

Factors other than tumor burden are known to have a major impact on rates of LR. In a meta-analysis including 7,174 patients treated with BCS and RT, the relative risk of LR for patients with tumors expressing hormone receptors or HER2 was 0.49 (95% confidence interval [CI] 0.33–0.73) compared to those with triple-negative cancers. When patients with HER2 overexpressing cancers (treated prior to the use of adjuvant trastuzumab) were excluded, the relative risk fell to 0.33 for the non-triple-negative versus triple-negative patients. The same statistically significant differences in LR were seen in patients treated with mastectomy, indicating that this difference is not a function of tumor burden and margin status (9). The influence of tumor biology on LR is so profound that statistically significant differences in rates of LR are seen among cancers 1cm or less in size based on estrogen receptor (ER), progesterone receptor (PR), and HER2 status (10). Even within the subset of patients with node negative, ER positive, HER2 negative cancers treated with chemotherapy and tamoxifen in a clinical trial, Mamounas et al(11) found that rates of locoregional recurrence (LRR) at 10 years ranged from 1.6% in those with 21 gene recurrence scores (OncotypeDX; Genomic Health, Redwood City, CA) <18 to 7.8% in those with recurrence scores ≥31 (p=.028).

Another factor substantially impacting rates of LR is the widespread use of adjuvant systemic therapy. In the Early Breast Cancer Trialists' Group meta-analysis, 5 years of tamoxifen reduced the relative risk of LR to 0.47 compared to placebo, while cytotoxic chemotherapy in women younger than 50 years of age reduced the relative risk of LR to 0.63 compared to no therapy (12). Advances in systemic therapy that have improved survival outcomes have further reduced rates of LR. For example, the use of aromatase inhibitors or more prolonged durations of endocrine therapy reduce the relative risk of LR to 0.50 to 0.83 compared to 5 years of tamoxifen (13). The addition of trastuzumab to chemotherapy reduces the relative risk of LR to 0.47 compared to chemotherapy alone(13), resulting in a reduction of the 3-year rate of LRR after BCS and RT from 7% to 1% (p=0.01) in a single-institution study (14). The result of the more widespread use of better systemic therapies has been a steady decline in rates of LRR. In a study of 86,598 patients participating in 53 randomized trials between 1990 and 2011, LRR as a proportion of all recurrence decreased from 30% to 15% (p<0.001) (15).

Society of Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO) Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Stage I and II Breast Cancer

In view of the wide variation in re-excision rates and changes in our understanding of breast cancer biology, the SSO and ASTRO convened a multidisciplinary panel in 2013 to address the question of what margin width minimizes the risk of LR in patients with invasive cancer treated with BCS and whole breast RT. As part of the evidence base for the consensus, a meta-analysis of margin width including 33 studies with 28,162 patients and 1506 LRs and a median follow-up of 79.2 months was conducted. The crude rate of LR was 5.3%. The key findings of the meta-analysis were that positive or unknown margins increased the risk of the LR with an odds ratio of 2.44 versus negative margins, and that no relationship between increasing negative margin widths (1mm, 2mm, 5mm) and a reduced risk of LR was seen (16).

The main question addressed in the consensus was whether an “optimum” negative margin width could be identified. The meta-analysis examining margin widths of 1, 2, and 5mm included 19 studies and 13,081 patients with 753 LRs and a median follow-up of 8.7 years. A statistical association between increasing margin widths and a decreased rate of LR was not observed ($p=0.90$), nor was there statistical evidence for a trend ($p=0.58$). Adjusting for co-variables of age, endocrine therapy, radiation boost, use of re-excision, year of study recruitment, and first versus any LR did not alter these findings (16). The panel concluded that negative margins, defined as no ink on tumor, minimize the risk of LR, but that more widely clear margins do not significantly lower this risk. The routine practice of obtaining margins more widely clear than no ink on tumor was not felt to be indicated (17–19). This statement generated controversy because the meta-analysis(16) was unable to distinguish between margins of no ink on tumor and those up to 1mm in size since this information was rarely reported. In making the decision to endorse no ink on tumor, the panelists were heavily influenced by the long-term outcomes of the NSABP clinical trials which routinely used no ink on tumor as the definition of a negative margin and report excellent long term rates of local control (1, 2). Additionally, the variability in margin assessment discussed previously led the participants to believe that the totality of the evidence did not support distinguishing between margins of no ink on tumor and those of 1mm.

Margins and Tumor Histology—The consensus statement addressed specific clinical circumstances of interest to surgeons including the impact of histologic features of the tumor, such as infiltrating lobular carcinoma, or the presence of lobular carcinoma in situ (LCIS) or an extensive intraductal component (EIC) on recommended margin widths. Invasive lobular carcinoma grows as single files of tumor cells, which may make the extent of the lesion more difficult to determine clinically and radiographically. The risk of LR does not differ among [patients with invasive lobular and invasive ductal cancer (20), and in a study of 382 patients with lobular carcinoma comparing margins <1cm to those 1cm, no significant differences in LR were noted (21). Additionally, the majority of classic infiltrating lobular carcinomas are ER positive, endocrine sensitive tumors, and these patients will experience the previously discussed benefits of endocrine therapy on LR. Studies examining the impact of the presence of LCIS at the margins of resection have failed

to show an association between LCIS at the margin and LR (22). Thus, the margins consensus group concluded that wider negative margins than no ink on tumor are not indicated for invasive lobular carcinoma, and that classic LCIS at the margin is not an indication for re-excision. There was felt to be insufficient information regarding the significance of pleomorphic LCIS at the margin to draw a conclusion on the need for re-excision.

In contrast to the data on LCIS, it is clear that the presence of DCIS at a margin is associated with an increased risk of LR. Prior to the routine inking of margins, invasive cancers with EIC were noted to have an increased risk of LR compared to tumors lacking an EIC and a substantial number of patients with an EIC have additional foci of DCIS at a distance 2cm from the index cancer. However, based on studies demonstrating no increase in LR in patients with an EIC when clear margins were obtained(23), the margins panel did not feel that the routine use of margins more widely clear than no ink on tumor was supported. When calcifications are associated with the EIC, a post-excision mammogram to document their complete removal is a complementary method of ensuring complete excision, and consideration should also be given to the amount of DCIS in proximity to the margin when considering re-excision.

Margin and Tumor Biology—The consensus panel also reviewed data on biologic features, such as patient age and tumor subtype, which might affect margin recommendations. Young age, usually <40 years, was associated with an increased risk of LR in older studies(24), most likely due to the higher incidence of adverse pathologic features in younger patients. More recently, rates of LR in younger women have declined to levels comparable with those of their older counterparts, largely due to the increased use of chemotherapy and targeted therapies (25). Additionally, the large margins obtained with mastectomy do not improve LR or survival in young women (26). These observations led the margins consensus panel to conclude that young age is associated with a greater incidence of adverse pathologic and biologic features, but there was no evidence to suggest that increased margin width nullified the risk conveyed by these factors.

Similarly, the observation that patients with triple-negative breast cancer have a higher risk of LR than those with other subtypes(9) raised the possibility to some that more widely clear margins might reduce this risk. Studies comparing rates of LR after BCS and RT and mastectomy in patients with triple-negative cancer do not support this premise (27, 28). Pilewskie et al examined rates of LR in 535 patients with triple-negative cancer treated with BCS and RT and found that the 5-year risk of LR in those with margins 2mm was 4.7% compared 3.7% in patients with more widely clear negative margins (p=0.11) (29). This and the preceding discussion regarding young women emphasize the fact that bigger surgery does not overcome bad biology, and margins more widely clear than no ink on tumor are not indicated based solely upon patient age or receptor status.

Interpretation of the Consensus Statement—While the consensus statement indicates that margins more widely clear than no ink on tumor are not *routinely indicated*, it does not state that a minimal negative margin never requires re-excision. The extent of tumor in proximity to the margin is associated with the risk of residual tumor, and multiple margins

with large amounts of tumor within a few cells of the ink should prompt consideration of re-excision. The anterior and posterior margins are anatomically limited by the skin and the pectoralis fascia, and when all breast tissue in these areas has been removed, re-excision is not warranted for minimal negative margins. When residual breast tissue is present, the potential for a heavy residual tumor burden should be assessed based upon the amount of tumor in proximity to the margin and the tumor growth pattern. A key point of the margins consensus statement is that blanket rules that all margins must be 2mm, or any other arbitrary measurement, are not supported by the existing evidence. Clinicians should consider the multiple factors that affect LR when making a decision regarding the need for re-excision.

Impact of the Invasive Breast Cancer Margin Guideline on Practice

The invasive breast cancer guideline was published online in November 2013 and simultaneously published in the *Annals of Surgical Oncology*, *Journal of Clinical Oncology*, and the *International Journal of Radiation Oncology Biology and Physics* in May 2014 (17–19). A survey of members of the American Society of Breast Surgeons in October 2014 found that only 1.3% of 777 respondents would routinely re-excite a margin <2mm. Higher rates of re-excision were reported for more complex clinical scenarios such as multiple close margins or the presence of an EIC (30). Two single-institution studies compared rates of re-excision pre and post the SSO-ASTRO guideline (31, 32). In a retrospective study of 846 cases, Chung et al demonstrated a decrease in the re-excision rate from 19% to 13% ($p=0.03$) after the guideline. Similarly, Rosenberger et al reported a decrease in re-excision rate among a group of high-volume specialist breast surgeons from 21.4% prior to the guideline release ($n=504$) to 15.1% after guideline adoption ($n=701$; $p=0.006$), with re-excision rates declining continuously over time, from 20.6% in the first 3 months after guideline adoption to 13.5% in the final 3 months of the data set (32). In addition to reducing the burden of treatment for patients, avoidance of unnecessary re-excision was estimated to have saved \$30 million per year for the United States healthcare system using Medicare costs (33).

Circumstances in Which the Invasive Margin Guideline Does Not Apply

The evidence review for the invasive margin guideline was limited to patients treated with initial BCS and whole breast RT. It does not apply to those with pure DCIS, patients having partial breast irradiation, and, in particular, to those treated with neoadjuvant chemotherapy.

Breast cancer shrinkage in response to neoadjuvant therapy occurs in 2 different ways; concentrically and in a honeycomb or buckshot pattern. In patients with a pathologic complete response or concentric tumor shrinkage, consideration of margin width does not differ from that in the primary surgical setting. In patients with the honeycomb pattern, determination of the appropriate extent of resection is more problematic. Investigators from the University of Texas MD Anderson Cancer Center have shown that on multivariate analysis, a honeycomb pattern of response, residual disease >2cm, and clinical N2 or N3 disease were statistically significant predictors of LR after breast-conserving therapy (BCT) (34). However, whether the higher rate of LR observed with the honeycomb pattern shrinkage can be reduced with more widely clear margins is uncertain, as this pattern may

reflect biologic properties of the tumor. In the absence of definitive information on the benefit of more widely clear margins after neoadjuvant therapy, the author performs re-excision when less than the entire tumor bed was initially resected if viable residual tumor is scattered throughout the lumpectomy specimen and is within 1–2mm of the margin, even if it is not at the margin.

Margins in DCIS

All of the caveats regarding the lack of a standard approach to the pathologic evaluation of margins in invasive cancer apply to DCIS, and level I evidence from randomized trials on the effect of increasing margin width on LR is lacking. There are several reasons why the optimal margin width for DCIS might differ from invasive cancer. DCIS has been demonstrated to grow discontinuously in the ducts, particularly non-high-grade DCIS, raising concerns that minimal negative margins could be associated with a heavy residual tumor burden in the breast. Additionally, the use of adjuvant systemic therapy is much less common in DCIS than in invasive breast cancer, and the competing risk of death from metastatic disease is absent, potentially making local control more important. Retrospective single-institution studies suggesting that a negative margin of 1cm eliminates the reduction in LR seen with RT(35) led some to conclude that larger margins are also beneficial in those receiving RT. This, coupled with observations that re-excision is more frequent for DCIS than invasive cancer(5), led the SSO, ASTRO, and the American Society of Clinical Oncology (ASCO) to develop a multidisciplinary, evidence-based consensus guideline for margins in DCIS in 2015.

SSO-ASTRO-ASCO Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in DCIS

As was done for the invasive carcinoma guideline, a meta-analysis examining the relationship of margin width to LR in patients receiving whole breast RT was conducted. The meta-analysis included 7883 patients in 20 studies and 865 LRs. The median follow-up was 78.3 months, and the median incidence of LR was 8.3% (36). Due to heterogeneity among studies, both a frequentist analysis and a Bayesian network analysis were conducted and confirmed that negative margins compared to positive margins reduced the risk of LR by approximately 50%. The findings of both the Bayesian and the frequentist analysis regarding the optimal negative margin width are shown in Table 1. All negative margin widths significantly reduced the odds of LR compared to positive margins. The relative odds ratio (OR) for 2mm versus 1mm or no ink on tumor was 0.72 indicating a weak association between 2mm margins and a reduced risk of LR while the frequentist analysis demonstrated an OR of 0.51 ($p=0.01$) for 2mm compared to smaller clear margins. A benefit for margins wider than 2mm was not observed with either statistical methodology (Table 1). Based on these findings, the panel concluded that margins of 2mm reduced the risk of LR relative to more narrow negative margins and that the practice of obtaining negative margin widths wider than 2mm was not supported by the evidence. However, the panel cautioned that clinical judgment must be used in determining the need for re-excision in patients with clear margins <2mm (37–39). Factors felt to be important in determining the need for re-excision include overall life expectancy, residual calcifications on mammogram, the extent of DCIS in proximity to the margin, which margin is close, and the cosmetic impact of re-excision.

The panel strongly emphasized that a margin <2mm alone should not be considered an indication for mastectomy. The support for selective re-excision with margins <2mm was strongly influenced by the high long-term rates of local control in NSABP DCIS trials requiring a negative margin of no ink on tumor(40) and the large study of Van Zee et al which found no benefit for margins greater than no ink on tumor after adjusting for multiple covariates (3). The panel also considered the impact of tamoxifen use on margin recommendations and concluded that although tamoxifen reduces the incidence of LR, primarily in patients with positive margins(40), there was no evidence to suggest an association between negative margin width and the benefit of endocrine therapy.

Margins in Patients Treated with Excision Alone—The use of RT reduces LR even in predefined “low-risk” subgroups with DCIS excised to margins of 3 mm (41). Studies of patients treated with excision only were not included in the meta-analysis used for the DCIS margins consensus, and examination of individual published studies provided conflicting evidence. The Eastern Cooperative Oncology Group (ECOG) E5194 study included patients with high-grade DCIS 1cm in size and non-high-grade DCIS 2.5cm in size excised to margins of 3mm or more. After 12 years of follow-up, LR rates did not differ for margins <5mm, 5–9mm, or 10mm ($p=0.85$) (42). In contrast, Van Zee et al observed a strong statistical relationship ($p < 0.0001$) between LR and margin width, with 10-year LR rates of 16% for margins >10mm and 27% for negative margins 2mm (3). While the panel was comfortable endorsing margins of at least 2mm for patients treated with excision alone, the heterogeneity of the evidence did not allow for a definitive recommendation for more widely clear margins in patients foregoing RT.

Margins for DCIS with Microinvasion (DCIS-M) and DCIS Associated with Invasive Carcinoma—There are 2 areas of potential overlap between the DCIS margin guideline and the invasive guideline(17–19, 37–39), DCIS-M and invasive cancer with associated DCIS. Based on expert consensus, the panel felt that DCIS-M should be treated according to the DCIS guideline since the majority of the lesion is DCIS and small retrospective studies suggest that rates of LR are similar to those seen with pure DCIS, and since systemic therapy utilization more closely reflects that seen with pure DCIS.

The recommendations for patients with an EIC were addressed in the discussion of the invasive guideline and mirror the considerations for re-excision in pure DCIS with margins <2mm. The natural history and systemic treatment of these lesions is more similar to invasive cancer than DCIS, leading the committee to endorse the invasive cancer margin of no ink on tumor for patients with invasive cancer and an EIC or lesser amounts of DCIS.

Areas for Future Research

Changes in our understanding of tumor biology and the widespread use of systemic therapy in patients with invasive cancer have reduced rates of LR and excellent outcomes are seen with margins of no ink on tumor. Less is understood about the relationship between margin width and factors such as age, lesion size, histologic pattern, and gene profile scores in DCIS, and this is an appropriate area for further study. Greater clarity on the optimal margin for patients having a partial response to neoadjuvant therapy would also be welcome as

indications for neoadjuvant therapy continue to expand. The impact of partial breast irradiation on margin recommendations is unclear. While it is unlikely that margin width will be the primary endpoint of a clinical trial, prospectively collecting this information during studies in relevant populations would provide very useful information to address these questions.

Incorporation of ACOSOG Z0011 and AMAROS Trials into Local Therapy Decisions

Management of the axilla is an essential element of breast cancer care. As recently as the early 1990s, all breast cancer patients underwent axillary lymph node dissection (ALND) regardless of clinical nodal status. ALND accurately identifies lymph node metastases and stages the axilla, however the procedure is associated with possible morbidity including pain, paresthesias, shoulder dysfunction and lymphedema (43, 44). Importantly, only 20–35% of breast cancer patients presenting with clinically node-negative disease have nodal metastases suggesting the need for a more selective approach for axillary staging (45–47). Sentinel lymph node dissection (SLND) represents such an approach. SLND is predicated on the observation that the breast has an orderly pattern of lymphatic drainage with specific lymph nodes, the sentinel lymph nodes (SLNs), draining the breast first. The status of the SLNs, whether they contain metastases or not, reflects the status of the entire axilla. The SLND procedure has been validated in single-institution and multi-center studies as well as prospective randomized trials (47–52).

For clinically node-negative breast cancer patients, SLND is standard for axillary evaluation. Patients in whom the SLN(s) do not demonstrate metastases can forego ALND without diminishing disease-free survival (DFS), overall survival (OS), or local-regional control (50, 51). This was shown definitively in the NSABP B-32 trial; a study that randomized 5611 women to SLND and ALND or SLND and ALND only if the SLN was positive. The trial's 10-year follow-up data showed no difference in DFS (76.9% in both groups; $p=0.92$) or OS (88.7% for ALND versus 88.7% for SLND alone; $p=0.27$) between patients with SLN-negative disease who underwent ALND versus SLND alone (50). LRR were uncommon, occurring in less than 5% of patients in both arms of the study. Axillary recurrences as a first event were also uncommon, occurring in three (0.2%) patients in the ALND group and nine (0.4%) patients in the SLND group (50).

Although completion ALND for SLN negative patients was abandoned soon after adoption of the SLND procedure, for many years, ALND continued to be recommended for SLN positive patients. The need to perform ALND in all SLN positive patients was questioned for several reasons to include improvements in screening mammography leading to earlier cancer detection, thereby reducing axillary tumor burden (53). In addition, SLNs are often subjected to enhanced pathologic evaluation to include serial sectioning with or without immunohistochemical (IHC) staining for cytokeratin resulting in the identification of small-volume metastatic including isolated tumor cells and micrometastases (54). In the NSABP B-32 trial, patients who had disease identified in their SLN only by IHC who underwent ALND were found to have additional micrometastases in 4.4% of cases and macrometastases

in only 0.4% of cases (55). In addition, it is known that systemic therapy impacts local regional control. Several clinical trials were therefore conducted to address the utility of performing ALND in all SLN positive patients and data from these studies have suggested that select patients with a positive SLN can be spared ALND. Here we review these studies focusing on the American College of Surgeons Oncology Group (ACOSOG) Z0011 and AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trials (Table 2).

ACOSOG Z0011 Trial

Trial Results—The ACOSOG Z0011 trial was designed to determine whether clinically node negative breast cancer patients undergoing BCT and found to have low volume metastatic disease identified by SLND require ALND. The study was a prospective, randomized trial that enrolled clinical T1–2,N0,M0 breast cancer patients who were undergoing lumpectomy and whole breast RT and had 1 or 2 positive SLNs on standard pathological examination with hematoxylin and eosin (H&E) staining (56, 57). Patients were randomized to ALND or no further axillary treatment (i.e. SLND only). The study, conducted from 1999 to 2004, was designed to accrue 1900 patients but was closed early due to slow accrual and a lower-than-expected event rate. Ultimately, 891 patients were enrolled, 445 in the ALND group and 446 in the SLND-only group. Patient, tumor, and treatment characteristics were well matched between groups (57). The groups differed with respect to the SLN metastasis size. In the ALND group, 37.5% had micrometastases in their SLN, whereas in the SLND-only group, 44.8% had SLN micrometastases ($p=.05$). The median number of positive nodes in both groups was one, however the percentage of patients with at least two positive nodes was higher in the ALND group (40.8%) than in the SLND-only group (21.9%) ($p<.001$). Additional nodal metastases were found in 27.3% of the patients in the ALND arm.

The ACOSOG Z0011 trial's primary endpoint was 5-year OS. In the initial study report, at a median follow-up of 6.3 years, there was no significant difference in the OS rates in the ALND group (91.8%) versus the SLND-only group (92.5%) (56). DFS and LRR were secondary endpoints. The 5-year DFS rates did not differ significantly; 82.2% in the ALND group and 83.9% in the SLND-only group. LRRs were uncommon, occurring in only 16 patients (4.1%) in the ALND group and in 12 patients (2.8%) in the SLND-only group (57). Ipsilateral axillary recurrences occurred in less than 1% (57). On the basis of these data, the ACOSOG investigators concluded that ALND can be omitted in select breast cancer patients with clinically node-negative disease and a positive SLN. Results of the study after longer follow-up have recently been reported. After a median follow-up of 9.25 years, the 10-year OS rates were 83.6% in the ALND group versus 86.3% in the SLND-only group ($p=0.4$) (58). The 10-year DFS rates were 78.3% in the ALND group and 80.3% in the SLND-only group ($p=0.30$) (58). The 10-year cumulative incidence of LRR was 6.2% in the ALND group versus 5.3% in the SLND group ($p=0.36$) (59). The 10-year cumulative incidence of ipsilateral axillary nodal recurrences was 2 (0.5%) in the ALND group versus 5 (1.5%) in the SLND-only group (59). This represented a single ipsilateral axillary recurrence in the SLND arm of the trial since the initial study report. Factors associated with local regional failures on multivariable analyses adjusted for treatment arm included pathologic tumor size, hormone receptor status and modified Bloom-Richardson score (59).

Strategies for Implementation of the Trial Data—The results of the ACOSOG Z0011 trial were practice-changing. Shortly after publication of the trial data, the National Comprehensive Cancer Network guidelines were changed to reflect the study results. Several groups, including those from the Memorial Sloan Kettering Cancer Center and University of Texas MD Anderson Cancer Center published studies detailing how they were incorporating the trial results into clinical practice. At the Memorial Sloan-Kettering Cancer Center, a protocol was instituted whereby ALND is omitted in patients meeting trial entry criteria. The trial data was not extrapolated to patients not represented in the trial; therefore, patients with clinically positive nodes, patients receiving neoadjuvant chemotherapy, or patients undergoing mastectomy or receiving partial breast irradiation (APBI), are not eligible for the protocol, and ALND is performed in these patients if their SLN shows evidence of metastasis. An important aspect of the practice at Memorial Sloan Kettering is that patients' axilla are not screened with preoperative ultrasound. If patients are referred after undergoing imaging that shows possible nodal metastases, their disease is managed according to the number of abnormal nodes visualized. If three or more abnormal lymph nodes are seen, fine-needle aspiration biopsy is performed on the most suspicious, and if this confirms metastatic disease, ALND is performed. If fewer than three abnormal nodes are seen, SLND is performed.

A report detailing their institutional experience during the first 15 months after this protocol was initiated has been published (60). Between August 2010 and November 2012, 2157 patients underwent BCT, of whom 380 (18%) had a positive SLN. Of the SLN positive patients, 93 were ineligible for various indications, including neoadjuvant chemotherapy, detection of SLN metastasis by IHC only, and conversion to mastectomy. The clinicopathologic characteristics of the patients in this Memorial Sloan Kettering cohort generally resembled those enrolled on the Z0011 trial: the median age was 58 years, median tumor size was 1.7 cm, approximately 50% of the tumors were grade 2, and 90% of the tumors were estrogen receptor (ER)- or progesterone receptor (PR)-positive. The higher rate of hormone receptor positivity than in the Z0011 trial is likely due to the use of a 1% cutoff for positivity consistent with the 2010 change in the ASCO guidelines (61). These data demonstrate that the ACOSOG Z0011 population is representative of patients seen in clinical practice who undergo BCT for clinical T1-T2, N0 breast cancer. Of the 287 patients meeting Z0011 criteria, 84% met criteria for omission of ALND. ALND was performed in 45 patients, 29 with at least three positive SLNs, and 16 with extracapsular extension. ALND was performed in 39 of the patients for whom it was advised, and 28 (72%) had additional positive nodes. These results suggest that the presence of three or more positive SLNs and gross extracapsular extension are appropriate criteria for identifying patients at high risk of additional nodal disease.

At the MD Anderson Cancer Center, the data were discussed in a multidisciplinary forum and it was agreed that omission of ALND should be considered in patients meeting the trial's eligibility criteria (62). It was also agreed that ALND should not be omitted in patients not meeting the eligibility criteria, including patients with clinically node-positive disease, patients receiving neoadjuvant chemotherapy, and patients with three or more positive SLNs on H&E evaluation, and/or gross extranodal extension in the SLN(s). There

was agreement that the trial results are not applicable to patients undergoing mastectomy or those undergoing accelerated partial-breast irradiation. All patients on the ACOSOG Z0011 trial underwent BCT which was to include whole breast RT using a two-portal opposed tangential irradiation technique, without the addition of a third field. Although this is designed to treat the breast, it includes a portion of the low axilla, with 51% of level I and 26% of level II axillary nodes receiving 95% of the prescribed dose (63). Patients undergoing mastectomy or APBI will not routinely receive this radiation treatment of the axilla, hence the recommendation, at the time of publication of the ACOSOG Z0011 results that these patients require an ALND in the setting of a positive SLN.

For purposes of this discussion regarding multidisciplinary care of breast cancer patients, it is important to note that there has been considerable discussion regarding the radiation therapy administered to patients enrolled on the ACOSOG Z0011 trial. Quality assurance data regarding radiation field design were not captured in the trial, therefore early after publication of the study results, some questioned radiotherapy coverage of the regional nodes. To ascertain this, Jagsi and colleagues reviewed all available detailed radiotherapy records from patients enrolled on the study (64). Detailed records were obtained from 228, including 185 (81%) who received tangent-only treatment. For patients receiving tangent-only treatment in whom sufficient detail was available to assess tangent height, high tangents were used in approximately 50% of patients in both arms of the study. Approximately 20% of patients received directed nodal regional radiation; which was balanced between arms. And approximately 15% of patients did not receive any radiation at all. It should be remembered that Z0011 was a surgery trial, not a radiation trial, therefore the primary finding, that ALND is not required in patients with clinical T1-2N0 breast cancer undergoing BCT and found to have one or two positive SLN(s), stands.

The MD Anderson group evaluated their clinical practice in the year following publication of the ACOSOG Z0011 results and reported a significant decrease in the rate of performing ALND when compared to the year prior to publication of the trial data indicating incorporation of the data into practice. In that manuscript they also reported a significant decrease in performing intraoperative nodal evaluation since that information would not impact the operative strategy which led to a decrease in median operative times (65).

There are caveats to the recommendation to routinely perform ALND in patients undergoing mastectomy found to have a positive SLN. Specifically, there is data from the International Breast Cancer Study Group (IBCSG) 23-01 trial supporting the omission of ALND in mastectomy patients found to have a micrometastasis in their SLN(s). The IBCSG 23-01 trial randomized 931 patients with primary tumors less than 5 cm and SLN micrometastases to completion ALND or no further surgery (66). The study's primary endpoint was DFS and at a median follow-up of 5 years, the 5-year DFS rates of the ALND (84.4%) group and SLND-only group (87.8%) did not differ significantly ($p=0.16$). Importantly, the trial enrolled both mastectomy and BCT patients and in the SLND-only group, 9% of patients underwent mastectomy, suggesting that ALND can be omitted in mastectomy patients who have a SLN with micrometastasis. Additional data supporting axillary radiation in lieu of ALND in mastectomy patients comes from the AMAROS trial which will be discussed in detail below.

ACOSOG Z0011 – a Practice Changing Trial—In addition to reports from Memorial Sloan Kettering and MD Anderson, data from a survey conducted by the American Society of Breast Surgeons (ASBrS) as well as analysis of the National Cancer Data Base (NCDB) confirm the impact the ACOSOG Z0011 trial has had on clinical practice. The ASBrS survey was completed by approximately 850 members (67). When presented a scenario of a patient with 1 or 2 positive SLNs undergoing BCT, 60% indicated that they would rarely or never perform ALND, 23% indicated they would sometimes perform ALND, and 20% indicated that they would routinely perform ALND. It should be noted that this survey was conducted only about 18 months after publication of the trial data and it would be reasonable to hypothesize that as surgeons have become more comfortable with these data, the percentage who would rarely or never perform ALND will have increased and the percentage who would routinely perform ALND will have decreased in subsequent years. And while these data confirm that the majority of ASBrS members who completed the survey embraced the Z0011 findings, additional survey data suggest that many extrapolated the findings to patients not meeting the trial's eligibility criteria; 36% of respondents indicated that they would consider omission of ALND in patients undergoing accelerated partial breast irradiation and 27% would consider omission of ALND in patients for whom radiation therapy is not planned.

Review of the NCDB confirmed that surgeons have both incorporated the ACOSOG Z0011 data into practice and extrapolated the data to patients not meeting the study's eligibility criteria (68). Among patients meeting trial eligibility criteria, the rate of performing SLND alone increased from 6.1% in 1998 to 56.0% in 2011. The increased rate of ALND omission was observed regardless of facility type or location, tumor types and other patient factors. There was also an increase in the use of SLND alone in patients not meeting trial eligibility criteria: from 4.5% in 1998 to 25.8% in 2011 for patients undergoing mastectomy without radiotherapy, from 8.7% to 52.5% for patients undergoing accelerated partial breast irradiation or not planned for radiotherapy, from 13.7% to 35.9% for clinically node positive patients and from 2.3% to 12.9% for patients with 3 or more positive nodes.

AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery)

Trial Results—AMAROS is a second trial evaluating axillary management in patients with clinically node-negative breast cancer that supports omitting ALND in appropriately selected patients. Between 2001 and 2005, the trial enrolled patients with clinical T1b–2 tumors with no palpable axillary adenopathy but a positive SLN and randomized them to ALND (n=744) or axillary radiation therapy (AxRT) (n=681). ALND was defined as dissection of the level I and II axilla with removal of at least 10 nodes. AxRT targeted all three levels of the axilla and the medial supraclavicular fossa. The prescribed dose was 25 fractions of 2 Gy. For patients randomized to ALND, additional axillary radiotherapy was allowed when four or more positive lymph nodes were identified. The trial's primary endpoint was non-inferiority of 5-year axillary recurrence defined as not more than 4% for the AxRT group with an expected 2% in the ALND group. At a median follow-up of 6.1 years, an axillary recurrence had occurred in four patients in the ALND group and 7 patients in the AxRT group (69). The 5-year axillary recurrence rates were 0.43% in the ALND arm and 1.19% in the AxRT arm. There were no significant differences between the groups with

respect to DFS or OS. The 5-year DFS rates were 86.9% and 82.7% in the ALND and AxRT groups respectively (HR 1.18, 95% confidence interval [CI] 0.93–1.51; $p=0.18$) and the 5-year OS rates were 93.3% and 92.5% in the ALND and AxRT groups respectively (HR 1.17, 95% CI 0.85–1.62; $p=0.34$). Due to the very low event rate, the planned non-inferiority test was underpowered, however it was reasonably concluded that both ALND and AxRT provided excellent axillary control for clinically node negative patients found to have a positive SLN (69).

Quality of Life Studies in AMAROS—An important aspect of the AMAROS trial was the assessment of lymphedema, shoulder mobility and quality of life (QoL) assessed using the EORTC QoL questionnaire. Information regarding clinical signs of lymphedema and arm circumference was obtained at baseline, year one, year three, and year five. Clinical signs of lymphedema were significantly more common in the ALND group than the AxRT group at all time points. An increase in arm circumference of at least 10% was also more common in the ALND group compared to the AxRT group however the difference was only significant at 5 years (69). At that timepoint, 13% of patients in the ALND arm and 6% of patients in the AxRT group had an increase in arm circumference of at least 10%. A percentage of patients in the ALND group (6%) and the AxRT group (2%) received both surgery and radiation. While this subgroup had higher rates of lymphedema, the significant difference between the ALND and AxRT arms of the trial remained when these patients receiving both modalities were excluded from analyses. There were no significant differences between the treatment groups with respect to range of motion or other QoL measures including pain, arm symptoms or body image.

Implementation of AMAROS trial results into clinical practice—Less has been published regarding the incorporation of the AMAROS trial data into clinical practice. One important thing to note is that 82% of patients enrolled on the AMAROS study underwent breast conserving surgery (69). Based on the ACOSOG Z0011 data, these patients could have been spared both ALND and AxRT. With that said, the AMAROS trial data does provide evidence that patients with clinical T1-2N0 breast cancer undergoing mastectomy and found to have low volume SLN positive disease could receive AxRT in lieu of ALND, perhaps with lower morbidity. Importantly, the data suggest that mastectomy patients with low volume SLN positive disease do not require both ALND and AxRT.

Conclusion

SLND is standard practice for staging the axilla in patients with clinically node-negative breast cancer. Patients with a negative SLN, do not require any further axillary therapy. Based on the ACOSOG Z0011 data, patients with clinical T1-2 tumors and only 1 or 2 positive SLNs who are undergoing BCT with whole breast RT also do not require further axillary therapy. Based on the IBCSG 23-01 data, the same is true for patients undergoing mastectomy found to have micrometastases only in their SLN(s). For mastectomy patients found to have macrometastases in their SLN(s), available data suggests that those patients can undergo either ALND or AxRT. Additional data regarding axillary management in these patients will come from the POSitive Sentinel NODE: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy (POSNOC) trial which is currently being

conducted in Australia, New Zealand and the United Kingdom. POSNOC is enrolling patients with clinical T1-2N0 breast cancer undergoing either BCT or mastectomy and found to have one or two SLNs with macrometastases and randomizing them to adjuvant systemic therapy alone or adjuvant systemic therapy plus axillary therapy. Axillary therapy may be ALND or AxRT.

Current Perspectives on the Role of Radiation Therapy in Early Stage Breast Cancer—More vs. Less

Radiation therapy (RT) following breast-conserving surgery has been shown in multiple randomized trials, in generally unselected patients to lower the risk of recurrence within the breast (Table 3)(70–73). Moreover, a meta-analysis (24) confirmed that the addition of radiation not only conferred an improvement in any first recurrence, but also all-cause mortality. However, radiation is not without a price; both in terms of long-term side effects (74), as well as inconvenience and financial cost.

While it has long been recognized that there are substantial differences in the risk of distant disease across biologic subtypes, more recently, it has been observed that subtype is also prognostic for LR (9). Recognition of the heterogeneity of breast cancers, along with improvements in local control with the addition of effective systemic therapy, has prompted a repeat look at whether select patients can be safely spared radiation. In addition, parallel work is ongoing to learn whether patients with favorable disease can be treated with either an accelerated whole-breast regimen, or radiation limited to only a portion of the breast, both of which can minimize the burden of therapy. In contrast, in patients with node positive tumors and high-risk node negative disease, research has focused on whether there is added benefit from nodal treatment in addition to radiation to the breast. A related question, also unanswered, is the role of radiation following mastectomy in women with limited nodal disease. Ideally, an improved understanding of tumor biology as it relates to LR will permit more precise tailoring of treatment to each individual, allowing omission of radiation or more focused treatment in some, and more comprehensive treatment in those at higher risk.

Omission of Radiation Therapy

Interest in omitting radiation in low-risk patients is not new. The initial studies investigating breast-conserving surgery alone mainly relied on anatomic criteria (tumor size and nodal status) to identify presumed favorable patients. In 2006, the Joint Center for Radiation Therapy reported their updated results of a prospective single arm trial of observation following BCS in women with T1N0 tumors with widely negative margins (75). Patients with lymphovascular space invasion or an extensive intraductal component were excluded, but having ER positive disease was not required. No systemic therapy was permitted. Despite a median tumor size of 0.9 cm, the study was closed early due to an unexpectedly high rate of in-breast recurrence (23% at a median follow-up of 86 months). Similar results were seen in a prospective study from Finland (76) in which patients with T1N0 disease with PR positive tumors were randomized to radiation or observation after BCS. The NSABP also randomized patients with tumors less than 1.0 cm to radiation alone, tamoxifen alone, or radiation with tamoxifen (77). 57% of patients had ER positive disease. At 8 years,

LR was 9% for radiation alone, 17% for tamoxifen alone, and 3% for the two combined (all comparisons <0.05). The Princess Margaret Hospital also studied substituting tamoxifen for radiation in a prospective randomized trial of patients 50 and older with T1 or T2 disease (78); 81% of whom had either ER or PR positive disease. At 8 years, the patients who received tamoxifen alone had a significantly higher risk of LR than patients receiving tamoxifen with RT (17.6% vs 3.5%; $p<0.001$). Thus, despite inclusion of patients with favorable disease characteristics, these trials showed a consistent benefit to radiation.

Two other randomized trials have looked at omitting radiation in older women with ER positive breast cancer. Cancer and Leukemia Group B trial 9343 (79) randomized 636 women older than 70 with clinical stage I disease to radiation alone or radiation with tamoxifen. With a median follow-up of 12.6 years, the addition of radiation modestly lowered the risk of LRR (90% vs 98%, $p<0.001$), but had no impact on overall survival. Unfortunately, additional pathologic details such as tumor grade and lymphovascular space invasion, which could have potentially identified subsets of patients more likely to benefit from radiation, were not collected prospectively. A similar randomized trial from the United Kingdom (80) of tamoxifen alone or tamoxifen with RT in women over 65 with node negative tumors smaller than 3.0 cm showed a small but statistically significant local control benefit to RT (4.1% vs 1.3% at 5 years, $p=0.001$), but as expected, no difference in overall survival.

In the last decade, an improved understanding of the diversity of breast cancers has led to reevaluation of omission of radiation, but now focusing not simply on patients with small tumors with widely negative margins, but on favorable biologic subtypes. Patients with luminal A disease have been targeted for omission of radiation given the low risk of recurrence seen in retrospective series (81). In the absence of intrinsic genetic profiling, this has been approximated by ER, PR, HER2 and grade. Liu et al also retrospectively examined patients from the previously discussed Canadian randomized trial of tamoxifen alone or tamoxifen with radiation in whom receptor information was available (82). While the group as a whole showed a significant reduction in LR with radiation, patients with approximation of the luminal A subtype (ER+, PR+, Her2 negative, Ki 67 $< 14\%$ and grade I/II) were found to have a low risk of recurrence both with and without radiation, and no statistically significant advantage to RT.

Three single arm studies in the US and Canada are now prospectively studying hormonal therapy alone following BCS. Lumina from the Ontario Oncology Group (clinicaltrials.gov NCT01791829) approximates luminal A subtype similar to Liu et al, using ER, PR, grade and Ki67. The IDEA trial led by the University of Michigan (clinicaltrials.gov NCT02400190) requires an oncotype score < 18 , based on retrospective data from the NSABP showing that the recurrence score is highly predictive of LRR (11). The Dana-Farber (PRECISION; clinicaltrials.gov NCT02653755) utilizes the PAM50 assay to define a favorable Luminal A subgroup. The most precise method of defining a low risk subgroup remains to be determined.

Hypofractionation

In the absence of omitting radiation altogether, multiple investigators have looked at shortening the course of treatment. The concept of hypofractionation (or fraction size greater than 1.8 Gy-2.0 Gy) is predicated on an improved understanding of breast cancer radiosensitivity (83), coupled with an enhanced ability to deliver a uniform distribution of radiation throughout the breast (84). The Ontario Clinical Oncology Group randomized 1234 patients to a standard course of radiation (25 fractions to 50 Gy) compared with a shorter course of 16 fractions to 42.5 Gy (85). A lumpectomy site boost was not permitted in either arm. Eligible patients had T1 or T2 node negative tumors. Larger patients were excluded to avoid the compound effective of a higher total dose also delivered in a greater dose per fraction. At 12 years, there was no difference in LR or survival, and no compromise in long-term toxicity or cosmetic outcome. A similar study from the UK (83) randomized 2215 patients to 50 Gy in 2 Gy fractions or 39.9 Gy in 2.66 Gy fractions. In contrast to the Canadian study, a lumpectomy site boost was permitted, but not required. With a median follow-up of 9.9 years, there was no statistically significant difference in LR between arms (HR for LR 0.77, 95% CI 0.51–1.16, $p=0.21$). There were however fewer patients with a marked or moderate cosmetic defect in the short-course arm. Additional support for hypofractionation comes from a randomized trial at MD Anderson (86) also comparing conventional to hypofractionated radiation. A lumpectomy site cone down was required in both arms. In contrast to the Canadian study, 75% of patients were obese or overweight, and 25% had a separation greater than 25.0 cm, increasing the generalizability of this approach. Maximal physician-reported acute toxicity was less in patients receiving the short course, and at 6 months, physician reported fatigue, and patient reported lack of energy were all improved in the short-course arm.

Hypofractionation is rapidly becoming standard of care for most women with early-stage invasive breast cancer. Not only is long-term local control similar, but there is now convincing data that toxicity and quality of life is not compromised, and may even be improved. Several questions, however, remain regarding the safety of hypofractionation after mastectomy, or for nodal radiation, and whether hypofractionation is equally effective for DCIS.

Partial Breast Radiotherapy(APBI)

Recent research has also questioned whether treatment to the whole breast is necessary to provide optimal local control. APBI is predicated on the observation that the majority of local recurrences are at the site of initial disease (87) and that radiation can therefore be confined to this smaller volume, and therefore ‘accelerated,’ or completed in fewer days. Typical time courses are twice daily for 5 days. The largest trial in the United States comparing conventionally fractionated whole breast irradiation with APBI, (NSABP B-51 completed accrual in 2013 and awaits data maturation ([clinicaltrials.gov. NCT00103181](https://clinicaltrials.gov/ct2/show/study/NCT00103181))). This trial permitted investigators to choose either external beam (38.5 Gy in 10 treatments), intracavitary or an interstitial approach (both 34 Gy in 10 fractions). In the meantime, several smaller studies are starting to report early results. The Groupe Europeen de Curietherapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) randomized 1184 patients with axillary node negative tumors < 3.0 cm (micrometastasis permitted) to

APBI utilizing interstitial brachytherapy or conventional fractionation (88). The difference in ipsilateral breast recurrence at 5 years was 0.52% ($p=0.42$), well within the 3% non-inferiority margin. Given the technical expertise required to perform interstitial brachytherapy, however, this is unlikely to be widely adopted in the United States. Early efficacy results of APBI delivered with external beam radiation have been reported by Livi and colleagues (89). 520 patients were randomized to whole breast radiation or APBI. Eligible patients had tumors up to 2.5 cm and negative axillary lymph nodes. In contrast to the NSABP study, APBI was given in 5 fractions of 6 Gy per fraction. With a median follow-up of 5 years, ipsilateral breast recurrence was 1.5% in both arms. ($p=0.86$). The cosmetic result was improved, however, in the APBI group. This is in contrast to the RAPID trial from Canada which also utilized external beam whole breast irradiation in the APBI arm (90). In a preliminary report with 36 months median follow-up, patients randomized to APBI had worse cosmesis at 3 years (35% vs 17% of physician-reviewed photographs, $p<0.001$), and higher grade 1 and 2 acute toxicity when compared with whole breast RT ($p<0.001$).

Additional follow-up of these trials, as well as maturation of the, as yet unreported, NSABP study will help to clarify further the long-term toxicity, cosmesis and efficacy of this approach. In addition, the most appropriate patients for APBI, and the optimal technique, will need to be clarified with additional study. Preliminary studies have prompted caution in patients with triple negative disease (91), and those with an extensive intraductal component and lymphovascular space invasion (92). At the present time, the ASTRO consensus panel (93) recommends confining APBI to patients older than 60, with T1N0, ER+ invasive ductal carcinoma and no lymphovascular space invasion, unless patients are participating in a trial. Note the overlap in the most favorable category with patients who may be appropriate candidates for omitting radiation therapy.

Intraoperative radiation therapy

An even more compressed version of radiation delivers the entire course in one fraction directly to the tumor bed. Two recent randomized trials have addressed the efficacy of this approach. The TARGIT study (94) utilizes 50 KV x-rays intraoperatively, to deliver radiation directly to the lumpectomy cavity. High-risk patients (defined as those with invasive lobular carcinoma, an extensive intraductal component, or other criteria that could be specified by each participating center at the start of the trial) subsequently received conventional whole breast RT. When compared to whole breast RT, the risk of LR was not statistically different (3.3% vs 1.3%, HR 2.07; 95% CI 1.01–4.25), and the difference between the two arms fell within the pre-specified 2.5% non-inferiority margin. However, with a median follow-up of only 29 months, it's difficult to draw any meaningful conclusions about the efficacy of this technique.

An alternate form of intraoperative radiation, utilizing electrons, was compared with whole breast RT in the ELIOT trial (95). Of note, this distributes the radiation to a broader area surrounding the lumpectomy cavity than does intraoperative photons, used in the TARGIT trial. With 5.8 years median follow-up, in-breast recurrence was 4.4% in the intraoperative arm compared with 0.4% among those randomized to whole breast radiation (HR 9.3, 95%

CI 3.3–26.3). On subset analysis, high grade, tumor size greater than 2.0 cm and triple negative histology all predicted for a higher risk of in-breast recurrence, suggesting that more careful patient selection may improve their results. Nonetheless, at the present time, both intraoperative electrons and photons should not be used outside of a clinical trial.

Post-Mastectomy Radiation

Adjuvant RT following mastectomy in patients with 1–3 involved axillary nodes has long been controversial. Two randomized trials from Denmark published in the late 1990's demonstrated for the first time that post-mastectomy radiation (PMRT) not only lowered the risk of recurrence, but also improved overall survival. The Danish Breast Cancer Cooperative Group 82b trial (96) randomized 1708 premenopausal women with Stage II or III disease to 9 cycles of cyclophosphamide methotrexate, and fluoruracil (CMF) or 8 cycles of CMF and PMRT. Radiation consisted of the chest wall and regional nodes, including the supraclavicular, axillary and internal mammary (IM) nodes in the first 4 intercostal spaces. PMRT lowered the risk of LRR from 32% to 9% at 10 years ($p < 0.001$), and also resulted in a marked improvement in overall survival (45% vs 54%, $p < 0.001$). Similar results were also seen in the parallel Danish 82 C trial (97) of postmenopausal women with Stage II and III breast cancer who were randomized following mastectomy to PMRT and one year of tamoxifen, or tamoxifen alone. LRR improved from 35% to 8% with PMRT ($p < 0.001$), and overall survival from 36% to 45% ($p = 0.03$). A meta-analysis from the Early Breast Cancer Trialists Collaborative Group (EBCTCG) (98) corroborated these results. The most recent update in 2014 reported on 8135 women treated between 1964 and 1986 in 22 trials of PMRT. In all trials, radiation included the chest and comprehensive nodal radiation, including IM nodes. In women who had undergone an axillary dissection and had 1–3 positive nodes, radiation reduced LRR and improved breast cancer mortality (absolute gain at 20 years = 7.9%). Similar results were also seen in patients with a single involved node.

The extent to which the earlier PMRT trials should impact management today, however, is not clear. In recent years, LRR both with and without RT has decreased. Systemic therapy, which has been shown to lower the risk of LRR, has dramatically advanced since the Danish studies, and is likely the largest factor contributing to this improvement (99, 100). A recent retrospective analysis from MD Anderson of 1027 patients examined LRR following mastectomy (101). Patients were divided into two groups: 1978–1997, prior to the routine use of taxanes and aromatase inhibitors, and 2000–2007, reflecting an era with more effective systemic therapy. In the earlier cohort, radiation resulted in a statistically significant, but modest decrease in LRR (9.5% vs 3.4% at 5 years, $p = 0.028$). In contrast, among the more recently treated patients, the rate of LRR was low and not significantly different whether or not RT was used (2.8% without RT vs 4.2% with RT at 5 years). Retrospective data from the NSABP has suggested that the Oncotype DX recurrence score may be prognostic for LR as well (102), although whether it predicts benefit from RT remains to be seen. It is also not clear the extent to which molecular subtype should impact recommendations for radiation. Re-analysis of the Danish trials by receptor status suggested that patients with triple negative tumors may benefit less from PMRT (103), but clearly additional study is warranted. At present, all patients with involved axillary lymph nodes should be referred for discussion of the potential benefits and side effects of PMRT.

Regional Nodal Irradiation

Inclusion of the regional nodes in the breast conservation setting is also controversial. Several large series have demonstrated low rates of both supraclavicular (SCV) and internal mammary (IM) nodal recurrences in patients with 1–3 positive axillary nodes (104, 105), but as discussed above, these nodal stations were included in the randomized PMRT trials which showed a survival benefit (96, 97). However, additional radiation is not without cost; nodal radiation typically increases the volume of heart and lung receiving radiation, and also increases the risk of lymphedema (106).

More recently, the results of two large, mature randomized trials have refocused interest in nodal radiation. The MA.20 trial (107) randomized 1832 women to whole breast radiation or whole breast radiation and inclusion of the SCV and IM nodes. Eligible women were node positive (90%), or had high-risk node negative disease. Systemic therapy with chemotherapy and/or endocrine therapy was permitted. At 10 years, there was an improvement in LRR (6.8% vs 4.3%, $p=0.009$), as well as DFS (77.0% vs 82.0%, $p=0.01$) with nodal RT. As of yet there is no statistically significant difference in overall survival. Neither tumor location, nor number of positive nodes predicted for a greater benefit from extended radiation. As expected, nodal radiation modestly increased the risk of lymphedema and grade 2 pneumonitis. These results are strengthened by a very similar trial from the European Organization for Research and Treatment of Cancer (EORTC) (108). In this larger trial, 4004 patients were randomized to nodal radiation including the SCV and IM stations, or no nodal radiation. Unlike the Canadian study, 24% of patients underwent mastectomy, and a much greater proportion had negative axillary nodes (44%, all required to have medial or central primary tumors). Similar to MA.20, the addition of nodal radiation resulted in an improvement in distant DFS (78% vs 75%, $p=0.02$). While there was a trend towards an improvement in overall survival, this also did not reach statistical significance (82.3% vs 80.7%, $p=0.06$). There were no clear subsets that preferentially benefitted from nodal RT.

Whether nodal radiation should be given to all eligible patients based on these results is not known. Neither MA.20 nor the EORTC study showed an overall survival benefit to nodal RT. In addition, while the ACOSOG Z-11 study (57) did not ask a direct question of nodal RT, the excellent DFS, and low risk of nodal recurrence among patients purportedly treated with breast RT alone suggests that this may also be a viable option for select patients with node positive disease. Additional study is necessary to determine which patients benefit most from nodal RT.

Surgical Considerations in Patients Receiving Preoperative Chemotherapy

Early randomized trials of preoperative versus postoperative chemotherapy in patients with operable breast cancer demonstrated that the two approaches were equivalent with respect to both disease free and overall survival (109, 110). Yet important secondary outcomes from these studies included increased opportunities for breast conservation, downstaging the axillary lymph nodes, and enthusiasm regarding the potential to tailor systemic therapy based on the in-vivo tumor response (111–113). While tailoring postoperative therapy remains an important area of investigation, the increasing rates of pathological complete response (pCR) both in the breast and axilla following preoperative chemotherapy provide

important prognostic information (113) and have had a considerable impact on locoregional treatment considerations (114). As our understanding of breast cancer molecular subtypes has evolved it has also become increasingly clear that the effectiveness of preoperative chemotherapy varies by molecular subtype (115).

Patient Selection for Preoperative Therapy

Preoperative or neoadjuvant chemotherapy (NACT) reduces the need for mastectomy and axillary lymph-node dissection, thus decreasing the morbidity of surgery, without compromising outcomes. However, selection of the ideal candidates for preoperative chemotherapy remains critical. Patients with high-grade ER-negative and/or HER2-positive breast cancers are more likely to experience pathological complete response to NACT than those with low-grade, ER-positive tumors (116, 117). In a meta-analysis of 30 studies including over 11,600 patients, the overall pooled pCR rate was 18.9% (16.6–21.5%); when examined by subtype, patients with HER2+/HR- breast cancer were 7 times more likely to experience a pCR and patients with triple negative breast cancer were 5 times more likely to experience a pCR, when compared to those with HR+/Her2- disease (115). Yet achieving a pCR is not absolutely necessary to facilitate BCS. For patients interested in downstaging to achieve BCS, the goal of NACT is to achieve sufficient tumor shrinkage to allow resection of the tumor with clear margins and an acceptable cosmetic result.

A meta-analysis of 14 early prospective randomized trials of preoperative versus postoperative therapy, including 5,500 patients, demonstrated that preoperative therapy decreased the mastectomy rate by 16.6% (95% CI 15.1–18.1%) (110). This modest reduction in the mastectomy rate does not reflect the true potential of NACT to impact rates of BCS however, as many of the patients were candidates for BCS at presentation. In the NSABP B 18 trial (111), patients initially presenting with T3 disease were more likely to achieve BCS after NACT than those who underwent primary surgery (22 vs 3%). More recently, preoperative trials in patients with HER2-overexpressing tumors such as the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) trial (118), which compared chemotherapy plus trastuzumab and lapatinib with chemotherapy plus either lapatinib or trastuzumab, continue to report only modest rates of conversion from mastectomy to BCS (26.4% in the trastuzumab–lapatinib combination group, 27.7% in the trastuzumab group, and 26.4% in the lapatinib group) despite the fact that rates of pCR in the arm with dual HER2 blockade exceeded of 50% (118). Similarly, in the CALGB 40603 randomized trial of the addition of carboplatin and/or bevacizumab to paclitaxel in triple-negative breast cancer (TNBC) patients, pCR rates approached 60% (119). In this study 42% of patients originally felt to require mastectomy achieved sufficient tumor shrinkage to become eligible for BCS; increasing the overall percentage of BCS eligible patients to 68%, yet over one-third of these women still opted for mastectomy (120). In aggregate, these studies demonstrate that while rates of in-breast pCR suggest that an increasing number of patients could benefit from downstaging the primary tumor with NACT; surgical decision making after NACT remains complex and frequently patients who are candidates for BCS will opt for mastectomy (121).

For some patients the opportunity to avoid ALND may be an equally if not more attractive rationale to pursue NACT. Rates of pCR in the axillary lymph nodes are generally reported to be as high as 40% (111) and complete pathologic response in the axillary nodes is similarly associated with breast cancer molecular subtypes. In a study of 195 patients with biopsy proven N1 disease undergoing NACT and surgical therapy at Memorial Sloan Kettering Cancer Center nodal pCR rates ranged from 21% in patients with ER+/HER2 – tumors to 97% for patients with ER-/HER2 positive disease (122). The increased recognition of the potential to eradicate known or suspected nodal disease in patients with HER2+ and/or TNBC and the opportunity to avoid the morbidity of ALND has led some to recommend NACT in patients who would otherwise be suitable candidates for BCS and thus do not require downstaging of the primary tumor. Conversely NACT may be recommended in patients who have contraindications to BCS simply to reduce the likely of requiring an ALND. Clinical management of the axilla in patients with clinical N1 disease who convert cN0 after NACT is also the subject of two ongoing prospective trials; discussed in more detail below.

The use of preoperative therapy to downstage infiltrating lobular carcinoma (ILC) remains clinically challenging due to the fact that classic infiltrating lobular carcinomas are typically strongly ER+ and of low-intermediate nuclear grade. As such, reported rates of pCR with NACT in ILC remain low. A meta-analysis of data from 1,764 patients with ILC reported a pooled pCR rate of 5.9% (95% CI 3.6–9.4%) (123). In the 13 studies included in this meta-analysis that reported rates of BCS, a higher rate was observed in patients with ductal versus lobular cancers (54.8% versus 35.4%; pooled OR 2.1; $P < 0.00001$). However, in two prospective NACT trials that adjusted for hormone-receptor status, HER2 status, histological grade, and p53 expression, rates of pCR did not differ between ductal and lobular cancers, indicating that these features could potentially be used to select the subset of patients with lobular carcinoma most likely to benefit from NACT (124). Neoadjuvant endocrine therapy is also an option for patients with invasive lobular cancer.

Surgical Considerations for BCS

In patients undergoing preoperative chemotherapy with the potential to downstage to BCS, the tumor site should be marked with a clip prior to initiating NACT. The goal of surgical resection should be to remove any remaining palpable and/or radiographic findings; however removal of the entire volume of breast tissue originally occupied by tumor is not necessary (125). If there has been a complete radiographic response, surgical resection is still indicated to provide an appropriate sample of the tumor bed for pathologic analysis. There is no absolute guideline for the size of the resection in such cases and this will generally vary depending on the size of the original tumor and the size of the breast. A multidisciplinary discussion between the breast surgeon and the breast imager is often useful for planning the extent of resection in such cases.

Evaluating the presence and radiographic extent of residual disease after NACT for surgical treatment planning remains a challenge. In a study of 189 patients treated with NACT at a single institution, the accuracy of physical examination, ultrasound and mammography in predicting residual pathologic tumor size within 1 cm was 66%, 75% and 70% respectively

(126). Ultrasound was most likely to overestimate and physical exam was most likely underestimate the size of the residual disease. In more recent years, several studies have compared these conventional imaging modalities with breast MRI (127–131). A meta-analysis of 44 studies, including 2,050 patients (128), reported a median sensitivity and specificity of 0.92 and 0.60 respectively for MRI for the detection of residual cancer after NACT. Not surprisingly, the accuracy of MRI differed depending on the definition of pCR used (lower in studies that permitted residual DCIS) (128) and others have also shown that the accuracy of MRI after NACT varies with ER, PR, and HER2 status, and is greatest in patients with HER2-positive disease or TNBC, likely owing to the higher rates of pCR in these patients as compared to other tumor types (132, 133). While the meta-analysis also demonstrated that mammography had lower accuracy for detection of residual disease than MRI ($P = 0.02$) (128), in patients with malignant calcifications, a post-NACT mammogram is also indicated. Although calcifications do not always indicate residual malignancy(134), the presence of residual disease cannot be reliably excluded unless all radiographic abnormalities are removed.

The pattern of response to NACT also warrants consideration and it should be remembered that all currently available imaging modalities are limited in their ability to detect scattered microscopic foci of viable carcinoma. In addition, there is no consensus on what constitutes an adequate surgical margin when BCS is pursued after NACT. The NSABP B 18 trial (135) used the standard NSABP margin definition of no ink on tumor and, after controlling for age and tumor size, found no statistically significant differences in LR between patients who required NACT for downstaging to BCS, those who were candidates for BCS without NACT. Similarly, the meta-analysis by Mieog et al. (110) reported no significant differences in LR for patients who received NACT versus those who received adjuvant therapy, including the subset of patients who required NACT to downstage to BCS. In a large population of breast cancer patients treated with NACT at the University of Texas MD Anderson Cancer Center (MDACC) (34), the ‘Swiss cheese’ pattern of response, characterized by scattered microscopic foci of residual viable tumor, did however predict for an increased risk of LR. This has led many to advocate for consideration of re-excision when multiple scattered foci of viable tumor are close to the surgical margin in patients who required downstaging for BCS or when less than the original tumor volume was excised. In the absence of this pattern of tumor response, a margin of no ink on tumor is generally considered to be adequate.

Management of the axilla after NACT

NSABP B-18 (111), a randomized trial of preoperative versus postoperative chemotherapy in early stage breast cancer, demonstrated that patients who received preoperative chemotherapy were more likely to have pathologically negative lymph nodes compared with those who underwent surgery first (58% versus 42%; $P < 0.0001$), leading to the question of whether sentinel lymph node biopsy (SLNB) could be used to accurately stage the axilla in this population. Initial concerns regarding the feasibility and accuracy of SLNB following chemotherapy were centered on the potential for altered lymphatic drainage and the possibility that the effects of chemotherapy might not be uniform throughout the nodal

basin. Some also argued that knowledge of the axillary-node status before NACT was necessary to identify optimal candidates for adjuvant radiotherapy.

For women presenting with clinically node-negative disease, numerous studies have established that SLN identification rates and false-negative rates after NACT are comparable to those reported in patients with breast cancer who undergo upfront surgery (47, 136–144). Among 3746 pts with cN0 disease treated at MDACC (137), SLN identification rates were 97.4% for women who underwent SNLB after NACT (n=575) and 98.7% for patients treated with upfront surgery (n=3171), and false-negative rates were similar: 5.9% versus 4.1% ($P=0.39$). Importantly, after a median follow-up of 47 months, there was no difference in LRR between the two groups, 1.2% vs 0.9% for those with SLNB after NAC and those with upfront surgery respectively (137).

Consistent with NSABP B18, this study also demonstrated that NACT could be used to downstage axillary nodal disease in patients presenting with larger clinically node-negative breast tumors; rates of positive SLN after NAC were 20.5% and 30.4% for T2 and T3 tumors respectively as compared to 36.5% and 51.4% with upfront surgery; resulting in fewer axillary-node dissections without compromising locoregional control (137).

SLNB after NACT in patients presenting with cN0 disease is now accepted as standard care (145) yet the current recommendation that all clinically node negative patients receiving NACT should undergo axillary ultrasound remains a matter of debate. Advocates of this approach argue that pretreatment nodal status is necessary to identify optimal candidates for adjuvant radiotherapy yet outcome data supporting this recommendation for women presenting with cN0 disease are lacking. Axillary ultrasound was not a requirement in NSABP B-18 or B-27 (111, 136) trials of NACT in patients with operable breast cancer, which did not allow regional nodal radiotherapy and/or post-mastectomy radiation therapy. Data from a combined analysis of these trials (146) demonstrated the relative importance of pretreatment nodal stage versus post-chemotherapy nodal stage in this setting and provide important information regarding predictors of LRR. At 10-years of follow up, LRR events occurred in 10.9% of 3088 patients who received NACT (146). On multivariate analysis, independent predictors of LRR included patient age, clinical tumor size, clinical nodal status before NACT, and pathological nodal status and/or pathological breast tumor response after NACT were independent predictors of LRR (146). Importantly, among patients treated with lumpectomy and breast radiotherapy, regional recurrences were low, ranging from 0.5–2.3%, and were not associated with pathological node status or breast tumor response. Among those treated with mastectomy, regional nodal recurrence rates were also low (2.3–6.2%); however, rates of chest-wall recurrence were greater in patients with pathologically positive nodes and in those with residual disease in the breast. These findings suggest that in patients presenting with clinically negative nodes, pathologic nodal status and in-breast tumor response can be used to identify patients with sufficient risk of chest wall and/or regional nodal recurrence to benefit from radiation therapy.

More recent controversy has centered around the use of SLNB after chemotherapy in patients who present with clinically positive biopsy-proven nodal metastases. This issue is particularly relevant for patients with ER-negative and/or HER2-positive disease treated with

preoperative anti-HER2 therapy, in whom pCR rates in the axilla may exceed 50% (147, 148). As such, the reliable identification of patients who achieve a nodal pCR with SLNB would result in the opportunity to avoid ALND and the subsequent morbidity for an increasing number of patients. For patients who remain node positive following NACT, accurate detection of residual disease is equally important, as these patients may benefit from more aggressive local-regional therapy. In the updated analysis of NSABP B-18 and B-27 trials (146), clinically node-positive patients who received NACT and remained pathologically node positive experienced the highest rates of LRR following ALND, ranging from 15–22% after lumpectomy and radiotherapy of the breast and from 17–22% after mastectomy (146), implying that both groups should be considered for adjuvant radiotherapy: regional nodal radiotherapy in addition to breast radiotherapy for those who undergo BCS, and chest-wall radiotherapy for those treated with mastectomy.

Three multicenter studies have addressed the feasibility of SLN after NACT in patients with clinically node-positive disease with remarkably consistent findings; specifically the false negative rate (FNR) of the procedure is unacceptably high unless 3 or more SLN are removed (Table 4) (149–151). The Sentinel Neoadjuvant (SENTINA) trial (151), a four-arm prospective multicenter trial by the German Breast Group, included 1,737 patients who all received at least six cycles of anthracycline-based NACT. Arm C included 592 clinically node positive who converted to clinically node negative status and underwent SLNB and ALND. The SLN identification rate in this group was only 80.1% and the overall FNR was 14.2%. The FNR decreased to 7.3% when three or more SLNs were removed and both end points were improved with the dual mapping technique (radioisotope and blue dye) (149–151). Similarly, in the ACOSOG Z1071 trial (150), a phase II study that enrolled 663 patients with biopsy proven clinical N1 disease, 649 of whom completed NACT followed by SLNB and ALND (150). The pre-specified endpoint was a FNR of 10%. Surgeons were encouraged to use the dual-mapping technique and to remove at least two SLNs. The SLN identification rate was 92.9% and the overall FNR was 12.6%; decreasing to 9.1% when three or more SLNs were removed (150). Finally, in the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) study (149), removal of one SLN was associated with a FNR of 18.2% and removal of more than two SLNs was associated with a FNR of 4.9% (149). The importance of the SLN mapping technique and the relationship between the number of SLNs removed and the FNR of the procedure is not a new finding as this was clearly documented in the early prospective trials of SLNB in patients undergoing upfront surgery (46, 140, 143, 152). However, in patients who undergo upfront surgery, and in clinically node negative patients who receive NACT, the FNR is acceptable when fewer than 3 nodes are removed (47, 136–144); thus until now there has not been a discussion of a minimum number of nodes that must be identified and removed.

The consistency of the data from the 3 trials discussed above combined with an increasing desire to safely avoid ALND in women who achieve a nodal pCR have led many groups to consider how to implement these findings in clinical practice, with a focus on minimizing the FNR of the procedure. In ACOSOG Z1071, 57% of 641 clinically N1 patients who converted to clinically node-negative disease had 3 or more SLNs removed and in Arm C of the SENTINA trial this number was only 34% (150, 151); suggesting that a substantial numbers of patients will not have three or more SLNs identified after NACT in this setting.

In contrast, among 132 patients who converted from cN1 to cN0 status after NACT at MSKCC, 128 underwent SLN biopsy with the dual tracer technique and ≥ 3 SLN were identified and retrieved in 110 (86%) patients (122). Others have adopted the practice of placing a clip in the biopsied axillary node prior to NACT and then ensuring removal of the clipped node at the time of the SLN procedure. This was first reported for a subset of 170 patients in the ACOSOG Z1071 trial, where among the 107 patients in whom the clip was retrieved as a SLN, the FNR was 6.8% (153). The MDACC group has since expanded upon this practice and reported a FNR of 4.2% when the clipped node was analyzed independently in a cohort of 120 patients who remained pathologically node positive after NACT. When the clipped node and the SLN were analyzed together ($n=74$), the FNR decreased to 1.4% (154). However, similar to the ACOSOG Z1071 experience, the clipped node was in the axillary contents but not identified as a SLN in approximately 20% of patients (153). As a result, they implemented a practice of localizing the clipped nodes preoperatively with iodine-125 seeds and have termed this procedure TAD (Targeted Axillary Dissection) (154). A similar technique called the MARI procedure (marking the axillary node with radioactive seed) has been reported in the Netherlands (155) and others are investigating the utility of tattooing the positive node with a sterile black carbon suspension (156). Importantly, if biopsied nodes are not marked and localized at the time of the SLN procedure, there are no data to support random sampling of nearby axillary nodes to replace SLN mapping and identification of at least 3 nodes following NACT; thus until outcomes data are available documenting the clinical significance of leaving axillary lymph-node disease behind after NACT, surgeons should make every effort to minimize their FNRs and patients should be informed that ALND could be indicated if SLN mapping is unsatisfactory.

Pathologic evaluation of the SLN and the relevance of the distinction between post-NACT isolated tumor cells (ypN0i+, $<0.2\text{mm}$), micrometastatic disease (ypN1mi, $0.2\text{mm}-2.0\text{mm}$), and macrometastatic disease (ypN+, $>2.0\text{mm}$) in SLN after NACT is another factor that remains unclear. In a retrospective pathology study of 80 patients with biopsy proven N1 disease who received NACT followed by ALND, patients with a nodal pCR had improved DFS ($p=0.007$) and OS ($p=0.004$) when compared to those with micrometastatic disease; yet there was no difference in DFS or OS between those with residual micrometastatic vs macrometastatic disease (157). According to the 7th Edition of the American Joint Committee on Cancer (AJCC) staging system (158), patients treated with NACT who are ypN0i+ or ypN1mi at SLNB are considered to have residual nodal disease, and ALND remains the standard of care. In the SN FNAC study (149), SLN metastases of any size were considered positive, and in contrast to the body of literature in patients undergoing upfront surgery (51, 56, 57), there was no correlation between the size of the SLN metastases and the rate of positive non-SLNs. The authors also noted that if ypN0i+ SLN disease was considered SLN-negative, the FNR of the procedure would have increased from 8.4% to 13.3% (149). Similarly, when micrometastatic disease was included in the definition of residual nodal disease in a subset of 470 pts from the ACOSOG 1071, the FNR decreased from 11.3% to 8.7% (159). Again, until outcome data are available it should not be assumed that micrometastatic nodal disease in the SLN after NACT will be associated with the same favorable outcomes demonstrated in trials of upfront surgery (51, 66).

The careful incorporation of SLNB into the clinical management of patients who present with biopsy proven nodal disease and have a significant response to NACT, defined at the present time as conversion to clinically node negative status, represents a significant shift in clinical practice and an opportunity to further decrease surgical morbidity for our patients. For patients who remain pathologically SLN node positive after NACT, the question of whether completion ALND can be omitted in favor of axillary radiotherapy, which is associated with lower rates of lymphedema (69), is being addressed in the ongoing phase III A011202 trial, conducted by the Alliance for Clinical Trials in Oncology (Figure 1)(160). For patients who are pathologically node negative, either by SLNB or ALND after NACT, the NSABP B-51/Radiation Therapy Oncology Group (RTOG) 1304 (NRG 9353) is conducting a phase III randomized trial of more versus less radiotherapy (Figure 2)(161). If omitting regional nodal radiation and/or PMRT in patients who achieve a nodal pCR in this setting does not impact risk of LRR, NACT could become the new standard to facilitate a tailored approach to locoregional therapy in patients with operable node-positive breast cancer.

Expanding Indications for Nipple-Sparing Mastectomy

Historical Perspective

Contemporary breast surgery has come a long way from the guillotine mastectomy performed during the Renaissance period, during which most patients undergoing amputation of the breast perished from infection or exsanguination. Halstead introduced the radical mastectomy in the 1800s with the benefit of anesthesia and antisepsis, but this was a disfiguring operation associated with significant morbidity. Surgical technique continued to evolve, and the modified radical mastectomy was described by Patey in the mid-twentieth century. This procedure did involve primary skin closure and was compatible with some of the earliest breast reconstruction (162).

Subcutaneous mastectomy later came into favor as more patients underwent immediate reconstruction. This procedure was generally performed for patients with benign disease or significant family history of breast cancer. Many of these patients were later found to carry BRCA mutations. This procedure involved leaving the entire skin envelope intact with thick mastectomy flaps and a substantial pedicle of subareolar tissue to ensure viability of the nipple. Following this procedure, patients were observed over time to have a rate of cancer development of 1.9% at a median follow-up of 6.4 years, which was higher than anticipated (163). For this reason, subcutaneous mastectomy and its potential cosmetic benefits fell out of favor.

Soon after, the skin-sparing mastectomy technique was described, with the intent to improve upon cosmetic outcome and facilitate reconstruction as options and demand for this increased. A number of studies were published, demonstrating equivalent local regional control with skin sparing mastectomies versus non-skin sparing methods (164). It was also during this time period that breast-conserving therapy was shown to provide equivalent outcome to that of mastectomy. Over time, increasing numbers of women underwent BCS. However, in recent years, the pendulum has swung back, such that more women are electing

mastectomy, and often bilateral mastectomy, even if they are appropriate candidates for breast conservation (165).

Currently, significant numbers of women with early stage breast cancer and excellent prognosis choose to move forward with mastectomy. Because of this, there is an increased focus placed on cosmetic outcome and quality of life following surgery by both patients and physicians. Efforts to investigate this change in surgical preference have identified a number of factors, including use of MRI, increased patient involvement in decision-making and improved outcomes of reconstruction as contributing factors (165, 166).

In contrast to the significant improvements in facilitating reconstruction of the breast mound, similar improvements in cosmetic outcome have not been seen with reconstruction of the nipple areola complex. The nipple areolar complex is recognized as a defining feature of the appearance of the breast mound. Completion of this reconstruction increases patient satisfaction with their breast reconstruction, although patients are generally less satisfied with their nipple areolar reconstruction than their breast mound (167). Many patients require revision of the nipple areolar complex reconstruction, and all methods of nipple reconstruction are associated with decreased projection over time. The areola is often tattooed, and this can result in color variation and fading, requiring revision. Patients having unilateral mastectomy may have significant asymmetry (168).

Many methods have been tried over time to reconstruct the nipple including local or distant skin flaps, composite grafting and skate flaps. Early on, attempts were made to harvest the nipple areola complex as a full thickness skin graft and later reimplant it on the breast mound. Lack of pathologic evaluation of the nipple tissue, led to concern for risk of transplanting malignant cells, so this practice was discontinued (169). In this context, nipple-sparing mastectomy (NSM) again became of interest. The procedure however was altered from that of the subcutaneous mastectomy to a more oncologically sound procedure; involving preservation of the entire skin envelope and nipple areolar complex with removal of glandular tissue, including the nipple base.

Is it safe to spare the nipple?

Historical data describe a wide range of occult nipple involvement in mastectomy specimens. Studies done from 1976–1999 report nipple involvement in anywhere from 0 to 58% of cases (170, 171). These studies all have large variations in patient selection, sample size, tissue processing and pathologic analysis. More contemporary data suggest nipple involvement in only 6–7% of nipples from therapeutic mastectomies (172) and that occult involvement is usually ductal carcinoma in situ on histology. Multivariate analysis of factors predicting nipple involvement have demonstrated tumor size, distance from tumor to nipple and HER2 amplification to be significant (173). Brachtel et al. also described the separate pathologic examination of retroareolar tissue in 316 consecutive mastectomy specimens and found that nipple involvement correlates with presence of cancer in a nipple margin with sensitivity of 0.8 and a negative predictive value of 0.96.

In light of accumulating data suggesting a low likelihood of nipple involvement in the majority of cases, NSM began being offered to women with early stage breast cancer and to

those having risk reducing mastectomy. Conservative clinical parameters were initially used to determine which women might be appropriate candidates for this procedure, including (172, 174) patients undergoing risk reducing mastectomy or those with small, unifocal, peripheral, node-negative tumors. Physicians also recognized the importance of cosmetic considerations in patient selection, and in the early experience patients with fairly small, non-ptotic breasts were deemed appropriate candidates for the procedure.

What if the nipple is involved?

Care should be taken to select patients without obvious clinical or imaging involvement of the nipple. However, at present, there are no reliable factors that indicate likelihood of occult nipple involvement. Although the distance of tumor to nipple has been shown to correlate with likelihood of nipple involvement, some patients with tumors close to but not involving the nipple are now being offered this procedure (175). There is also controversy as to whether intraoperative evaluation can accurately identify nipple involvement for which further surgery is warranted, or whether permanent pathology is most accurate (176). Nipple involvement with malignancy (DCIS, invasive ductal cancer, invasive lobular cancer) should be treated with excision. Initial recommendations were for complete excision of the nipple areolar complex; however some authors suggest that this can be done with excision of the nipple itself and preservation of the areola (177). If the tumor is felt to be close to the nipple, a lateral or perioareolar incision can be used to minimize risk for skin necrosis if nipple excision is ultimately needed (178). Insufficient data exists to support use of radiation rather than excision for an involved nipple margin and nipple involvement alone is not an indication for PMRT (179). Observation of a positive nipple margin has been proposed for patients who appear to have small volume disease, but this has not been well studied. Additionally, re-excision of nipple margin has been proposed. However, the recommended technique of NSM would not be expected to yield enough residual tissue in the nipple such that re-excision would be technically possible (180, 181). The use of a single dose of intraoperative radiation with electrons, ELIOT, to the nipple areolar complex has been reported as standard practice and not only for positive nipple margin to reduce recurrence, but this has not been routinely incorporated into the care of patients in the US (182). As such, excision of a nipple demonstrating malignant involvement on pathology remains the standard of care.

Long term outcomes of NSM

Initial reports typically included patients carefully selected by conservative criteria to minimize the likelihood of occult nipple involvement and included descriptions of surgical technique and complications. A recent meta-analysis of 20 studies of NSM, 8 with comparison arms, including 5594 patients, most of whom had early stage disease, found no significant difference in DFS or OS for patients undergoing NSM as compared to modified radical or skin sparing mastectomy. Importantly, no significant difference was found in LRR (183). Information on LRR data from selected trials is summarized in Table 5 (181, 184–187). Despite various selection criteria, none appeared to show an increased risk for LRR with NSM.

Given that improving the aesthetic outcome of mastectomy with reconstruction prompted the evolution of this procedure, cosmesis and patient satisfaction outcomes are of significant interest; yet these data are limited. It should be noted that the nipple is not functional and is expected to be insensate after surgery. Small studies have shown return of some, albeit minimal, sensation to the nipple following the procedure; however the long-term implications of this, if any, are unknown (188, 189). Patients generally rate satisfaction with cosmetic outcome following NSM higher than that with skin-sparing mastectomy, but there does not appear to be a significant difference in other quality of life domains (190). One recent study suggested that patients having NSM might have improved scores in selected quality of life domains, namely sexual and psychosocial well-being (191). Patients report varying satisfaction with nipple location and appearance after this procedure, with one study reporting that only 56% of patients were satisfied with the appearance of the nipple (192). Patient selection factors and technical aspects of the mastectomy procedure heavily influence the outcome and nipple position. More data is needed on these outcomes, particularly in light of the expanding selection criteria for this procedure.

Expanding indications for NSM

Following publication of early data suggesting there was not an increased risk for LR associated with the nipple-sparing procedure, many physicians began expanding the criteria for whom NSM was considered to be a reasonable option. This included both oncologic considerations as well as cosmetic considerations; expanded criteria of an oncologic nature will be focused on here. Notably however, there has also been significant interest in exploring the feasibility and success of offering these procedures to women with larger, more ptotic breasts and for women with elevated risk for skin and nipple necrosis. Oncologic safety and technical feasibility of performing a complete mastectomy remain paramount as these indications expand.

Current accepted selection criteria generally include patients who are having risk reducing mastectomy or those with early stage node negative breast cancers. Patients with clinical or imaging involvement of the nipple should not be offered this procedure. It is acceptable to offer NSM to patients with central tumors, as long as there is not imaging involvement of the nipple, but there is not a discrete distance from tumor to the nipple that should be required to offer the procedure. Caution should be exercised in the setting of malignant calcifications behind the nipple. The nipple should not be spared in patients who present with clear nipple retraction or pathologic discharge. Plastic and reconstructive surgeons select patients to optimize cosmesis, using a variety of factors such as body mass index and ptosis, and these indications are evolving but are outside the scope of this discussion.

Patients with BRCA mutations

Historically, nipple-sparing or subcutaneous mastectomy was offered to women with benign breast findings who were having surgery for risk reduction. Many of these women, as mentioned previously, were later found to have hereditary cancer syndromes. Debate has existed as to whether it is appropriate to offer NSM to women with BRCA mutations due to the theoretical increased risk of developing a new primary malignancy in the retained ductal tissue of the nipple. Despite a paucity of data related to these risks, many surgeons began

offering this procedure to women with BRCA mutations to optimize cosmetic outcomes. Small studies do not appear to show increased risk for recurrence or new primary malignancy in the retained nipple in patients undergoing therapeutic mastectomy (193). A more recent retrospective review included 397 breasts of 201 BRCA1 or BRCA2 mutation carriers undergoing both therapeutic and prophylactic mastectomies. At a mean follow up of 32.6 months, the event rate was 2%, with a simultaneous local and distant recurrence (not in the nipple areolar complex), 2 axillary recurrences, and a new primary cancer (194). More recently, the largest retrospective study of patients undergoing risk reducing mastectomy was presented. This included 348 patients undergoing 551 NSMs at 9 institutions and at a relatively short mean follow-up of 34 months no new primary cancers were seen (195). Thus although data remain limited, it appears that high risk patients are frequently being offered NSM for risk reduction and there does not appear to be an increased risk of new primary malignancy.

Patients with locally advanced disease

Patients with Stage IIB and III disease have been offered NSM in select studies. In one study, the authors stated that the rationale for offering this procedure to patients with more advanced disease was that their risk of distant metastases outweighed their likelihood of LR (196). In this study, 77% of patients received preoperative systemic therapy, and 12% had a complete pathologic response. These findings have been reproduced in other small studies suggesting no increased risk for LR with NSM versus skin sparing mastectomy in patients with more advanced disease (197). However, these were highly selected patients, and as such that these results are not generalizable. Patients with locally advanced disease are candidates for both preoperative systemic therapy as well as PMRT; both of which should be taken into consideration during surgical treatment planning. An increased risk for complications with NSM following NACT has not been reported; yet data are limited (198). Patients with locally advanced disease do have a higher risk of LR and further prospective data are needed to determine if NSM can be safely recommended.

Patients with previous history of radiation

Patients with a previous history of radiation have typically been advised against undergoing NSM due to concerns about increased risk for postoperative complications. However, as interest in the procedure have broadened, the risks do not appear to be prohibitive for a patient highly motivated to try to retain her nipple areolar complex. It should be noted that risk of nipple necrosis is increased, 4.3% vs. 0.9% in one study comparing patients with and without history of radiation. Patients with a prior history of radiation also appear to have more unplanned surgeries over time, frequently related to early postoperative complications such as infection, skin and nipple necrosis, and hematoma (199). As with other clinical scenarios, patient selection is important. Tang et al. reported that age >55 years, breast volume > 800cm³, smoking and periareolar incision placement were significantly associated with increased risk for complications in this patient cohort (200).

Patients who will be undergoing postoperative radiation

As oncologic criteria for offering NSM have expanded, more of these patients are anticipated to undergo PMRT. Similar to patients with a history of previous radiation,

complication rates, including nipple necrosis and implant loss, are higher after NSM and PMRT. Nipple necrosis was reported in 4.1% pts receiving PMRT as compared to 0.9% in those without by Tang et al) and implant loss has been reported in up to 8.2% of patients with PMRT as compared to only 2.2% without (200). Spear et al. found even higher rates of explanation in this group, with rates of 11.1% (201). Rates of implant loss may be lower with use of single stage implant versus with use of tissue expander, which has also been reported for patients having PMRT following skin sparing mastectomy, yet data remain limited (202). Patients having NSM followed by PMRT also appear to have an increased risk for late complications requiring surgery such as capsular contraction, implant rupture and implant exposure (200), and there is a fairly high incidence of nipple malposition, but this does not appear to be significantly different from patients who undergo NSM without radiation (201).

Technical considerations of NSM

One of the most important considerations for ensuring technical success of the procedure is clear communication between the breast and reconstructive surgeon. As increasing numbers of patients become candidates for NSM from an oncologic standpoint, the selection of patients from a cosmetic standpoint is increasingly important. Although the reconstructive surgeon should address most of the factors that determine aesthetic appropriateness, some of these considerations do have an impact on oncologic outcome and technical performance of the procedure and will be addressed here.

Breast size and flap thickness

For the breast surgeon, achieving visualization and retraction to allow for a technically complete oncologic mastectomy is of paramount importance. As such, the majority of the data suggests that optimal candidates for NSM are those with small to moderate breast size and minimal ptosis. There are limited data to support using reduction, mastopexy or other techniques in order to offer these procedures to women with larger or more ptotic breasts yet the oncologic safety should remain the priority (203, 204). As with any mastectomy, patient body habitus should determine the appropriate thickness of skin flap; however given the frequent thin nature and longer length of the mastectomy and nipple areolar flaps with this approach, gentle tissue handling is critical (205). Magnetic resonance imaging (MRI) has been proposed as an aid to guide flap thickness, but at present the data are not sufficient to recommend this practice (206). Additional technical considerations such as minimizing use of methylene blue dye for the sentinel node procedure (207) and minimizing use of cautery, particularly in the area of the nipple areolar complex may also decrease rate of nipple necrosis. Although some advocate for the use of commercially available devices to assess flap viability intraoperatively, there is insufficient data to support their routine use.

Incision placement

Incision placement must be planned with the primary concern related to the breast surgeon's ability to do an adequate mastectomy, again with optimal access and visualization of the area of the tumor. With that said, optimal incision placement will also minimize risks for postoperative complication including skin and nipple necrosis. The inframmary fold incision is felt to be superior for limiting nipple necrosis but may prove to be challenging for

visualization, particularly with a malignancy in the superior breast. Donovan et al suggested that this approach was associated with higher incidence of positive or close anterior margin, which may affect LR risk (208). A lateral incision also appears to have a low risk for nipple necrosis (209). Most data suggest a higher risk for necrosis with a periareolar incision, so this should be avoided when possible (210).

Conclusion

NSM may provide improved cosmetic outcomes for patients who are recommended to or choose to undergo mastectomy. The oncologic safety of this procedure has been demonstrated in patients with early stage breast cancers and risk reducing mastectomies with a pathologically negative nipple margin, yet at present, data remain limited for many of the expanded patient cohorts described above. Patients with BRCA mutations are being offered NSM for therapeutic or risk reducing indications. There is not sufficient data to support routine consideration of NSM in women with locally advanced disease or known indications for PMRT. For reconstructive surgeons, patient selection is also expanding, but ensuring oncologic completeness of the mastectomy must remain of paramount importance. Multidisciplinary collaboration between breast surgeons, reconstructive surgeons and radiation oncologists is essential for minimizing complications and optimizing patient safety and outcomes as indications for NSM continue to expand.

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References

1. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. *J Clin Oncol.* 2009; 27(15):2466–73. [PubMed: 19349544]
2. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol.* 2006; 24(13): 2028–37. [PubMed: 16648502]
3. Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. *Ann Surg.* 2015; 262(4):623–31. [PubMed: 26366541]
4. Azu M, Abrahamse P, Katz SJ, Jagsi R, Morrow M. What is an adequate margin for breast-conserving surgery? Surgeon attitudes and correlates. *Ann Surg Oncol.* 2010; 17(2):558–63. [PubMed: 19847566]
5. Morrow M, Jagsi R, Alderman AK, Griggs JJ, Hawley ST, Hamilton AS, et al. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. *JAMA.* 2009; 302(14): 1551–6. [PubMed: 19826024]
6. McCahill LE, Single RM, Aiello Bowles EJ, Feigelson HS, James TA, Barney T, et al. Variability in reexcision following breast conservation surgery. *JAMA.* 2012; 307(5):467–75. [PubMed: 22298678]

7. Chagpar AB, Killelea BK, Tsangaris TN, Butler M, Stavris K, Li F, et al. A Randomized, Controlled Trial of Cavity Shave Margins in Breast Cancer. *N Engl J Med*. 2015; 373(6):503–10. [PubMed: 26028131]
8. Holland R, Velting SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1–2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer*. 1985; 56(5):979–90. [PubMed: 2990668]
9. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat*. 2012; 133(3): 831–41. [PubMed: 22147079]
10. Cancellaro G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, et al. Prognosis in women with small (T1mic,T1a,T1b) node-negative operable breast cancer by immunohistochemically selected subtypes. *Breast Cancer Res Treat*. 2011; 127(3):713–20. [PubMed: 21452022]
11. Mamounas EP, Tang G, Fisher B, Paik S, Shak S, Costantino JP, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol*. 2010; 28(10):1677–83. [PubMed: 20065188]
12. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, et al. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005; 366(9503):2087–106. [PubMed: 16360786]
13. Mannino M, Yarnold J. Accelerated partial breast irradiation trials: diversity in rationale and design. *Radiother Oncol*. 2009; 91(1):16–22. [PubMed: 19178972]
14. Kiess AP, McArthur HL, Mahoney K, Patil S, Morris PG, Ho A, et al. Adjuvant trastuzumab reduces locoregional recurrence in women who receive breast-conservation therapy for lymph node-negative, human epidermal growth factor receptor 2-positive breast cancer. *Cancer*. 2012; 118(8):1982–8. [PubMed: 21887681]
15. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Res Treat*. 2013; 139(2):603–6. [PubMed: 23681402]
16. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. 2014; 21(3):717–30. [PubMed: 24473640]
17. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Int J Radiat Oncol Biol Phys*. 2014; 88(3):553–64. [PubMed: 24521674]
18. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Ann Surg Oncol*. 2014; 21(3):704–16. [PubMed: 24515565]
19. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol*. 2014; 32(14):1507–15. [PubMed: 24516019]
20. Biglia N, Maggiorotto F, Liberale V, Bounous VE, Sgro LG, Pecchio S, et al. Clinical-pathologic features, long term-outcome and surgical treatment in a large series of patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). *Eur J Surg Oncol*. 2013; 39(5):455–60. [PubMed: 23490334]
21. Galimberti V, Maisonneuve P, Rotmensz N, Viale G, Sangalli C, Sargenti M, et al. Influence of margin status on outcomes in lobular carcinoma: experience of the European Institute of Oncology. *Ann Surg*. 2011; 253(3):580–4. [PubMed: 21248632]
22. Ciocca RM, Li T, Freedman GM, Morrow M. Presence of lobular carcinoma in situ does not increase local recurrence in patients treated with breast-conserving therapy. *Ann Surg Oncol*. 2008; 15(8):2263–71. [PubMed: 18506537]

23. Schnitt SJ, Abner A, Gelman R, Connolly JL, Recht A, Duda RB, et al. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer*. 1994; 74(6):1746–51. [PubMed: 8082077]
24. Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Early Breast Cancer Trialists' Collaborative G. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011; 378(9804):1707–16. [PubMed: 22019144]
25. van Laar C, van der Sangen MJ, Poortmans PM, Nieuwenhuijzen GA, Roukema JA, Roumen RM, et al. Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients. *Eur J Cancer*. 2013; 49(15):3093–101. [PubMed: 23800672]
26. Cao JQ, Truong PT, Olivetto IA, Olson R, Coulombe G, Keyes M, et al. Should women younger than 40 years of age with invasive breast cancer have a mastectomy? 15-year outcomes in a population-based cohort. *Int J Radiat Oncol Biol Phys*. 2014; 90(3):509–17. [PubMed: 25194665]
27. Abdulkarim BS, Cuartero J, Hanson J, Deschenes J, Lesniak D, Sabri S. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. *J Clin Oncol*. 2011; 29(21):2852–8. [PubMed: 21670451]
28. Zumsteg ZS, Morrow M, Arnold B, Zheng J, Zhang Z, Robson M, et al. Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1-2N0 triple-negative breast cancer. *Ann Surg Oncol*. 2013; 20(11):3469–76. [PubMed: 23686101]
29. Pilewskie M, Ho A, Orell E, Stempel M, Chen Y, Eaton A, et al. Effect of margin width on local recurrence in triple-negative breast cancer patients treated with breast-conserving therapy. *Ann Surg Oncol*. 2014; 21(4):1209–14. [PubMed: 24327132]
30. DeSnyder SM, Hunt KK, Smith BD, Moran MS, Klimberg S, Lucci A. Assessment of Practice Patterns Following Publication of the SSO-ASTRO Consensus Guideline on Margins for Breast-Conserving Therapy in Stage I and II Invasive Breast Cancer. *Ann Surg Oncol*. 2015; 22(10):3250–6. [PubMed: 26202554]
31. Chung A, Gangi A, Amersi F, Bose S, Zhang X, Giuliano A. Impact of Consensus Guidelines by the Society of Surgical Oncology and the American Society for Radiation Oncology on Margins for Breast-Conserving Surgery in Stages 1 and 2 Invasive Breast Cancer. *Ann Surg Oncol*. 2015; 22(Suppl 3):S422–7. [PubMed: 26310280]
32. Rosenberger LH, Mamtani A, Fuzesi S, Stempel M, Eaton A, Morrow M, et al. Early Adoption of the SSO-ASTRO Consensus Guidelines on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: Initial Experience from Memorial Sloan Kettering Cancer Center. *Ann Surg Oncol*. 2016; 23(10):3239–46. [PubMed: 27411549]
33. Greenup RA, Peppercorn J, Worni M, Hwang ES. Cost implications of the SSO-ASTRO consensus guideline on margins for breast-conserving surgery with whole breast irradiation in stage I and II invasive breast cancer. *Ann Surg Oncol*. 2014; 21(5):1512–4. [PubMed: 24577813]
34. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. *J Clin Oncol*. 2004; 22(12):2303–12. [PubMed: 15197191]
35. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med*. 1999; 340(19):1455–61. [PubMed: 10320383]
36. Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, et al. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. *Ann Surg Oncol*. 2016; 23(12):3811–21. [PubMed: 27527715]
37. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Ductal Carcinoma In Situ. *Ann Surg Oncol*. 2016 (In Press).

38. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Ductal Carcinoma In Situ. *Pract Rad Oncol*. 2016 (In Press).
39. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Ductal Carcinoma In Situ. *J Clin Oncol*. 2016 (In Press).
40. Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst*. 2011; 103(6):478–88. [PubMed: 21398619]
41. McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol*. 2015; 33(7):709–15. [PubMed: 25605856]
42. Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, et al. Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study. *J Clin Oncol*. 2015; 33(33):3938–44. [PubMed: 26371148]
43. Fleissig A, Fallowfield LJ, Langridge CI, Johnson L, Newcombe RG, Dixon JM, et al. Postoperative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat*. 2006; 95(3):279–93. [PubMed: 16163445]
44. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007; 25(24):3657–63. [PubMed: 17485711]
45. Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA*. 2011; 306(4):385–93. [PubMed: 21791687]
46. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol*. 2007; 8(10):881–8. [PubMed: 17851130]
47. Veronesi U, Paganelli G, Viale G, Luini A, Zurrada S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med*. 2003; 349(6):546–53. [PubMed: 12904519]
48. Bergkvist L, de Boniface J, Jonsson PE, Ingvar C, Liljegren G, Frisell J. Axillary recurrence rate after negative sentinel node biopsy in breast cancer: three-year follow-up of the Swedish Multicenter Cohort Study. *Ann Surg*. 2008; 247(1):150–6. [PubMed: 18156935]
49. Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *J Clin Oncol*. 2000; 18(13):2553–9. [PubMed: 10893286]
50. Julian TB, Anderson SJ, Krag DN, Harlow SP, Costantino JP, Ashikaga T, et al. 10-yr follow-up results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients. *J Clin Oncol (Meeting Abstracts)*. 2013
51. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010; 11(10):927–33. [PubMed: 20863759]
52. Veronesi U, Viale G, Paganelli G, Zurrada S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg*. 2010; 251(4):595–600. [PubMed: 20195151]

53. Effect of mammographic service screening on stage at presentation of breast cancers in Sweden. *Cancer*. 2007; 109(11):2205–12. [PubMed: 17471486]
54. Mittendorf EA, Hunt KK. Significance and management of micrometastases in patients with breast cancer. *Expert Rev Anticancer Ther*. 2007; 7(10):1451–61. [PubMed: 17944569]
55. Weaver DL, Ashikaga T, Krag DN, Skelly JM, Anderson SJ, Harlow SP, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med*. 2011; 364(5):412–21. [PubMed: 21247310]
56. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011; 305(6):569–75. [PubMed: 21304082]
57. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg*. 2010; 252(3):426–32. discussion 32-3. [PubMed: 20739842]
58. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW. Ten-year survival results of ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1-2N0M0 breast cancer who have a positive sentinel node (Alliance). *J Clin Oncol*. 2016; 34(suppl) abstr 1007.
59. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. *Ann Surg*. 2016; 264(3):413–20. [PubMed: 27513155]
60. Dengel LT, Van Zee KJ, King TA, Stempel M, Cody HS, El-Tamer M, et al. Axillary dissection can be avoided in the majority of clinically node-negative patients undergoing breast-conserving therapy. *Ann Surg Oncol*. 2014; 21(1):22–7. [PubMed: 23975314]
61. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010; 28(16):2784–95. [PubMed: 20404251]
62. Caudle AS, Hunt KK, Kuerer HM, Meric-Bernstam F, Lucci A, Bedrosian I, et al. Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: a practice-changing trial. *Ann Surg Oncol*. 2011; 18(9):2407–12. [PubMed: 21327455]
63. Reznik J, Cicchetti MG, Degaspe B, Fitzgerald TJ. Analysis of axillary coverage during tangential radiation therapy to the breast. *Int J Radiat Oncol Biol Phys*. 2005; 61(1):163–8. [PubMed: 15629607]
64. Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol*. 2014; 32(32):3600–6. [PubMed: 25135994]
65. Caudle AS, Hunt KK, Tucker SL, Hoffman K, Gainer SM, Lucci A, et al. American College of Surgeons Oncology Group (ACOSOG) Z0011: impact on surgeon practice patterns. *Ann Surg Oncol*. 2012; 19(10):3144–51. [PubMed: 22847123]
66. Galimberti V, Cole BF, Zurrada S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013; 14(4):297–305. [PubMed: 23491275]
67. Gainer SM, Hunt KK, Beitsch P, Caudle AS, Mittendorf EA, Lucci A. Changing behavior in clinical practice in response to the ACOSOG Z0011 trial: a survey of the American Society of Breast Surgeons. *Ann Surg Oncol*. 2012; 19(10):3152–8. [PubMed: 22820938]
68. Yao K, Liederbach E, Pesce C, Wang CH, Winchester DJ. Impact of the American College of Surgeons Oncology Group Z0011 Randomized Trial on the Number of Axillary Nodes Removed for Patients with Early-Stage Breast Cancer. *J Am Coll Surg*. 2015; 221(1):71–81. [PubMed: 25899731]
69. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC

- 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol.* 2014; 15(12):1303–10. [PubMed: 25439688]
70. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002; 347(16):1233–41. [PubMed: 12393820]
 71. Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst.* 1996; 88(22):1659–64. [PubMed: 8931610]
 72. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol.* 2001; 12(7):997–1003. [PubMed: 11521809]
 73. Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol.* 1999; 17(8):2326–33. [PubMed: 10561294]
 74. Pierce SM, Recht A, Lingos TI, Abner A, Vicini F, Silver B, et al. Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer. *Int J Radiat Oncol Biol Phys.* 1992; 23(5):915–23. [PubMed: 1639653]
 75. Lim M, Bellon JR, Gelman R, Silver B, Recht A, Schnitt SJ, et al. A prospective study of conservative surgery without radiation therapy in select patients with Stage I breast cancer. *Int J Radiat Oncol Biol Phys.* 2006; 65(4):1149–54. [PubMed: 16750330]
 76. Holli K, Hietanen P, Saaristo R, Huhtala H, Hakama M, Joensuu H. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow-up results of a randomized trial. *J Clin Oncol.* 2009; 27(6):927–32. [PubMed: 19114687]
 77. Fisher B, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol.* 2002; 20(20):4141–9. [PubMed: 12377957]
 78. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med.* 2004; 351(10):963–70. [PubMed: 15342804]
 79. Hughes KS, Schnaper LA, Bellon JR, Cirincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013; 31(19):2382–7. [PubMed: 23690420]
 80. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. investigators PI. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol.* 2015; 16(3):266–73. [PubMed: 25637340]
 81. Arvold ND, Taghian AG, Niemierko A, Abi Raad RF, Sreedhara M, Nguyen PL, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol.* 2011; 29(29):3885–91. [PubMed: 21900114]
 82. Liu FF, Shi W, Done SJ, Miller N, Pintilie M, Voduc D, et al. Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy. *J Clin Oncol.* 2015; 33(18):2035–40. [PubMed: 25964246]
 83. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013; 14(11):1086–94. [PubMed: 24055415]
 84. Pignol JP, Olivetto I, Rakovitch E, Gardner S, Sixel K, Beckham W, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol.* 2008; 26(13):2085–92. [PubMed: 18285602]

85. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010; 362(6):513–20. [PubMed: 20147717]
86. Shaitelman SF, Schlembach PJ, Arzu I, Ballo M, Bloom ES, Buchholz D, et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. *JAMA Oncol.* 2015; 1(7):931–41. [PubMed: 26247543]
87. Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys.* 1990; 19(4): 833–42. [PubMed: 2170305]
88. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet.* 2016; 387(10015):229–38. [PubMed: 26494415]
89. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer.* 2015; 51(4):451–63. [PubMed: 25605582]
90. Olivetto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol.* 2013; 31(32):4038–45. [PubMed: 23835717]
91. Pashtan IM, Recht A, Ancukiewicz M, Brachtel E, Abi-Raad RF, D'Alessandro HA, et al. External beam accelerated partial-breast irradiation using 32 Gy in 8 twice-daily fractions: 5-year results of a prospective study. *Int J Radiat Oncol Biol Phys.* 2012; 84(3):e271–7. [PubMed: 22652104]
92. Cannon DM, McHaffie DR, Patel RR, Adkison JB, Das RK, Anderson BD, et al. Locoregional recurrence following accelerated partial breast irradiation for early-stage invasive breast cancer: significance of estrogen receptor status and other pathological variables. *Ann Surg Oncol.* 2013; 20(11):3446–52. [PubMed: 23709055]
93. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *J Am Coll Surg.* 2009; 209(2):269–77. [PubMed: 19632605]
94. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* 2014; 383(9917): 603–13. [PubMed: 24224997]
95. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* 2013; 14(13):1269–77. [PubMed: 24225155]
96. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med.* 1997; 337(14): 949–55. [PubMed: 9395428]
97. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet.* 1999; 353(9165):1641–8. [PubMed: 10335782]
98. Ebtctg, McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014; 383(9935):2127–35. [PubMed: 24656685]
99. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005; 353(16): 1673–84. [PubMed: 16236738]

100. Sartor CI, Peterson BL, Woolf S, Fitzgerald TJ, Laurie F, Turrisi AJ, et al. Effect of addition of adjuvant paclitaxel on radiotherapy delivery and locoregional control of node-positive breast cancer: cancer and leukemia group B 9344. *J Clin Oncol*. 2005; 23(1):30–40. [PubMed: 15545661]
101. McBride A, Allen P, Woodward W, Kim M, Kuerer HM, Drinka EK, et al. Locoregional recurrence risk for patients with T1,2 breast cancer with 1–3 positive lymph nodes treated with mastectomy and systemic treatment. *Int J Radiat Oncol Biol Phys*. 2014; 89(2):392–8. [PubMed: 24721590]
102. Mamounas, EP., Tang, G., Paik, S., Baehner, FL., Liu, Q., Jeong, J., et al. 21-gene Recurrence Score (RS) Predicts Risk of Loco-regional Recurrence (LRR) in Node (+), ER (+) Breast Cancer (BC) After Adjuvant Chemotherapy and Tamoxifen: Results from NSABP B-28. Society of Surgical Oncology Annual Meeting; 2013; National Harbor, Maryland. (abstract)
103. Kyndi M, Overgaard M, Nielsen HM, Sorensen FB, Knudsen H, Overgaard J. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. *Radiother Oncol*. 2009; 90(1): 74–9. [PubMed: 18471914]
104. Recht A, Gray R, Davidson NE, Fowble BL, Solin LJ, Cummings FJ, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 1999; 17(6): 1689–700. [PubMed: 10561205]
105. Taghian A, Jeong JH, Mamounas E, Anderson S, Bryant J, Deutsch M, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol*. 2004; 22(21):4247–54. [PubMed: 15452182]
106. Coen JJ, Taghian AG, Kachnic LA, Assaad SI, Powell SN. Risk of lymphedema after regional nodal irradiation with breast conservation therapy. *Int J Radiat Oncol Biol Phys*. 2003; 55(5): 1209–15. [PubMed: 12654429]
107. Whelan TJ, Olivetto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015; 373(4):307–16. [PubMed: 26200977]
108. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. *N Engl J Med*. 2015; 373(4): 317–27. [PubMed: 26200978]
109. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. 2005; 97(3):188–94. [PubMed: 15687361]
110. Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg*. 2007; 94(10):1189–200. [PubMed: 17701939]
111. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*. 1997; 15(7):2483–93. [PubMed: 9215816]
112. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol*. 2001; 19(22): 4224–37. [PubMed: 11709566]
113. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014; 384(9938):164–72. [PubMed: 24529560]
114. King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. *Nat Rev Clin Oncol*. 2015; 12(6):335–43. [PubMed: 25850554]
115. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer*. 2012; 48(18):3342–54. [PubMed: 22766518]

116. Ataseven B, Lederer B, Blohmer JU, Denkert C, Gerber B, Heil J, et al. Impact of multifocal or multicentric disease on surgery and locoregional, distant and overall survival of 6,134 breast cancer patients treated with neoadjuvant chemotherapy. *Ann Surg Oncol*. 2015; 22(4):1118–27. [PubMed: 25297900]
117. Boughey JC, McCall LM, Ballman KV, Mittendorf EA, Ahrendt GM, Wilke LG, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Ann Surg*. 2014; 260(4):608–14. discussion 14–6. [PubMed: 25203877]
118. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2012; 379(9816):633–40. [PubMed: 22257673]
119. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol*. 2015; 33(1):13–21.
120. Golshan M, Cirrincione CT, Sikov WM, Berry DA, Jasinski S, Weisberg TF, et al. Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: surgical results from CALGB 40603 (Alliance). *Ann Surg*. 2015; 262(3):434–9. discussion 8–9. [PubMed: 26222764]
121. Katz SJ, Lantz PM, Janz NK, Fagerlin A, Schwartz K, Liu L, et al. Patient involvement in surgery treatment decisions for breast cancer. *J Clin Oncol*. 2005; 23(24):5526–33. [PubMed: 16110013]
122. Mamtani A, Barrio AV, King TA, Van Zee KJ, Plitas G, Pilewskie M, et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. *Ann Surg Oncol*. 2016; 23(11):3467–74. [PubMed: 27160528]
123. Petrelli F, Barni S. Response to neoadjuvant chemotherapy in ductal compared to lobular carcinoma of the breast: a meta-analysis of published trials including 1,764 lobular breast cancer. *Breast Cancer Res Treat*. 2013; 142(2):227–35. [PubMed: 24177758]
124. Lips EH, Mukhtar RA, Yau C, de Ronde JJ, Livasy C, Carey LA, et al. Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. *Breast Cancer Res Treat*. 2012; 136(1):35–43. [PubMed: 22961065]
125. Boughey JC, Peintinger F, Meric-Bernstam F, Perry AC, Hunt KK, Babiera GV, et al. Impact of preoperative versus postoperative chemotherapy on the extent and number of surgical procedures in patients treated in randomized clinical trials for breast cancer. *Ann Surg*. 2006; 244(3):464–70. [PubMed: 16926572]
126. Chagpar AB, Middleton LP, Sahin AA, Dempsey P, Buzdar AU, Mirza AN, et al. Accuracy of physical examination, ultrasonography, and mammography in predicting residual pathologic tumor size in patients treated with neoadjuvant chemotherapy. *Ann Surg*. 2006; 243(2):257–64. [PubMed: 16432360]
127. Hylton NM, Blume JD, Bernreuter WK, Pisano ED, Rosen MA, Morris EA, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY TRIAL. *Radiology*. 2012; 263(3):663–72. [PubMed: 22623692]
128. Marinovich ML, Houssami N, Macaskill P, Sardanelli F, Irwig L, Mamounas EP, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J Natl Cancer Inst*. 2013; 105(5):321–33. [PubMed: 23297042]
129. Rosen EL, Blackwell KL, Baker JA, Soo MS, Bentley RC, Yu D, et al. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. *AJR Am J Roentgenol*. 2003; 181(5):1275–82. [PubMed: 14573420]
130. Turnbull LW. Dynamic contrast-enhanced MRI in the diagnosis and management of breast cancer. *NMR Biomed*. 2009; 22(1):28–39. [PubMed: 18654999]
131. Yeh E, Slanetz P, Kopans DB, Rafferty E, Georgian-Smith D, Moy L, et al. Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. *AJR Am J Roentgenol*. 2005; 184(3):868–77. [PubMed: 15728611]

132. Chen JH, Bahri S, Mehta RS, Kuzucan A, Yu HJ, Carpenter PM, et al. Breast cancer: evaluation of response to neoadjuvant chemotherapy with 3.0-T MR imaging. *Radiology*. 2011; 261(3):735–43. [PubMed: 21878615]
133. De Los Santos JF, Cantor A, Amos KD, Forero A, Golshan M, Horton JK, et al. Magnetic resonance imaging as a predictor of pathologic response in patients treated with neoadjuvant systemic treatment for operable breast cancer. Translational Breast Cancer Research Consortium trial 017. *Cancer*. 2013; 119(10):1776–83. [PubMed: 23436342]
134. Weiss A, Lee KC, Romero Y, Ward E, Kim Y, Ojeda-Fournier H, et al. Calcifications on mammogram do not correlate with tumor size after neoadjuvant chemotherapy. *Ann Surg Oncol*. 2014; 21(10):3310–6. [PubMed: 25056851]
135. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr*. 2001; (30):96–102. [PubMed: 11773300]
136. Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2005; 23(12):2694–702. [PubMed: 15837984]
137. Hunt KK, Yi M, Mittendorf EA, Guerrero C, Babiera GV, Bedrosian I, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. *Ann Surg*. 2009; 250(4):558–66. [PubMed: 19730235]
138. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg*. 2006; 93(5):539–46. [PubMed: 16329089]
139. Classe JM, Bordes V, Campion L, Mignotte H, Dravet F, Leveque J, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiothérapie Neoadjuvante, a French prospective multicentric study. *J Clin Oncol*. 2009; 27(5):726–32. [PubMed: 19114697]
140. Goyal A, Newcombe RG, Chhabra A, Mansel RE, Group AT. Factors affecting failed localisation and false-negative rates of sentinel node biopsy in breast cancer--results of the ALMANAC validation phase. *Breast Cancer Res Treat*. 2006; 99(2):203–8. [PubMed: 16541308]
141. Kelly AM, Dwamena B, Cronin P, Carlos RC. Breast cancer sentinel node identification and classification after neoadjuvant chemotherapy-systematic review and meta analysis. *Acad Radiol*. 2009; 16(5):551–63. [PubMed: 19345896]
142. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer*. 2006; 106(1):4–16. [PubMed: 16329134]
143. McMasters KM, Tuttle TM, Carlson DJ, Brown CM, Noyes RD, Glaser RL, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. *J Clin Oncol*. 2000; 18(13):2560–6. [PubMed: 10893287]
144. Tafral L, Verbanac KM, Lannin DR. Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. *Am J Surg*. 2001; 182(4):312–5. [PubMed: 11720661]
145. Gradishar WJ, Anderson BO, Blair SL, Burstein HJ, Cyr A, Elias AD, et al. Breast cancer version 3.2014. *J Natl Compr Canr Netw*. 2014; 12(4):542–90.
146. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol*. 2012; 30(32):3960–6. [PubMed: 23032615]
147. Dominici LS, Negron Gonzalez VM, Buzdar AU, Lucci A, Mittendorf EA, Le-Petross HT, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer*. 2010; 116(12):2884–9. [PubMed: 20564395]
148. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol*. 2005; 23(36):9304–11. [PubMed: 16361629]

149. Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol.* 2015; 33(3):258–64. [PubMed: 25452445]
150. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA.* 2013; 310(14):1455–61. [PubMed: 24101169]
151. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013; 14(7):609–18. [PubMed: 23683750]
152. Tafta L, Lannin DR, Swanson MS, Van Eyk JJ, Verbanac KM, Chua AN, et al. Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. *Ann Surg.* 2001; 233(1):51–9. [PubMed: 11141225]
153. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). *Ann Surg.* 2015; 261(3):547–52. [PubMed: 25664534]
154. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. *J Clin Oncol.* 2016; 34(10):1072–8. [PubMed: 26811528]
155. Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg.* 2015; 261(2):378–82. [PubMed: 24743607]
156. Choy N, Lipson J, Porter C, Ozawa M, Kierny A, Pal S, et al. Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. *Ann Surg Oncol.* 2015; 22(2):377–82. [PubMed: 25164040]
157. Sakakibara M, Nagashima T, Kadowaki M, Onai Y, Fujimori T, Yokomizo J, et al. Clinical significance of axillary microresiduals after neoadjuvant chemotherapy in breast cancer patients with cytologically proven metastases. *Ann Surg Oncol.* 2009; 16(9):2470–8. [PubMed: 19588201]
158. Edge, S., Byrd, DR., Compton, CC., Fritz, AG., Greene, FL., Trotti, A. *AJCC Cancer Staging Manual.* 7. New York: Springer; 2010.
159. Boughey, JC., Symmans, WF., McCall, L., Mittendorf, EA., Ahrendt, GM., Wilke, LG., et al. Methods impacting the false negative rate of sentinel lymph node surgery in patients presenting with node positive breast cancer (T0-T4, N1-2) who receive neoadjuvant chemotherapy - Results from a prospective trial - ACOSOG Z1071 (Alliance). *San Antonio Breast Cancer Symposium;* 2014. Poster No. P2-01-02
160. NCI Community Oncology Research Program - Kansas City. CTSU Alliance A011202: A Randomized Phase III Trial Evaluating the Role of Axillary Lymph Node Dissection in Breast Cancer Patients (CT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Neoadjuvant Chemotherapy. Available from: <http://www.kccop.org/cancer-trials/breast/index.cgi/summary?tid=110>
161. Mamounas E, White J, Bandos H, TBJ, Kahn AJ, Shaitelman SF, et al. NSABP B-51/RTOG 1304: Randomized phase III clinical trial evaluating the role of postmastectomy chest wall and regional nodal XRT (CWRNRT) and post-lumpectomy RNRT in patients (pts) with documented positive axillary (Ax) nodes before neoadjuvant chemotherapy (NC) who convert to pathologically negative Ax nodes after NC. *J Clin Oncol.* 2014; 32(5s suppl) abstr TPS1141.
162. Laronga C, Smith P. Nipple-sparing mastectomy: an oncologic and cosmetic perspective. *Surg Oncol Clin N Am.* 2014; 23(3):549–66. [PubMed: 24882350]
163. Rebbeck TR, Friebe T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2004; 22(6):1055–62. [PubMed: 14981104]
164. Singletary SE. Skin-sparing mastectomy with immediate breast reconstruction: the M. D. Anderson Cancer Center experience. *Ann Surg Oncol.* 1996; 3(4):411–6. [PubMed: 8790856]

165. McGuire KP, Santillan AA, Kaur P, Meade T, Parbhoo J, Mathias M, et al. Are mastectomies on the rise? A 13-year trend analysis of the selection of mastectomy versus breast conservation therapy in 5865 patients. *Ann Surg Oncol*. 2009; 16(10):2682–90. [PubMed: 19653046]
166. King TA, Sakr R, Patil S, Gurevich I, Stempel M, Sampson M, et al. Clinical management factors contribute to the decision for contralateral prophylactic mastectomy. *J Clin Oncol*. 2011; 29(16): 2158–64. [PubMed: 21464413]
167. Jabor MA, Shayani P, Collins DR Jr, Karas T, Cohen BE. Nipple-areola reconstruction: satisfaction and clinical determinants. *Plast Reconstr Surg*. 2002; 110(2):457–63. discussion 64–5. [PubMed: 12142660]
168. Momoh AO, Colakoglu S, de Blacam C, Yueh JH, Lin SJ, Tobias AM, et al. The impact of nipple reconstruction on patient satisfaction in breast reconstruction. *Ann Plast Surg*. 2012; 69(4):389–93. [PubMed: 22868326]
169. Allison AB, Howorth MG Jr. Carcinoma in a nipple preserved by heterotopic auto-implantation. *N Engl J Med*. 1978; 298(20):1132. [PubMed: 643032]
170. Verma GR, Kumar A, Joshi K. Nipple involvement in peripheral breast carcinoma: a prospective study. *Indian J Cancer*. 1997; 34(1):1–5. [PubMed: 9491654]
171. Menon RS, van Geel AN. Cancer of the breast with nipple involvement. *Br J Cancer*. 1989; 59(1): 81–4. [PubMed: 2547416]
172. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol*. 1999; 6(6):609–13. [PubMed: 10493632]
173. Brachtel EF, Rusby JE, Michaelson JS, Chen LL, Muzikansky A, Smith BL, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol*. 2009; 27(30):4948–54. [PubMed: 19720921]
174. Vljacic Z, Zic R, Stanec S, Lambasa S, Petroveckí M, Stanec Z. Nipple-areola complex preservation: predictive factors of neoplastic nipple-areola complex invasion. *Ann Plast Surg*. 2005; 55(3):240–4. [PubMed: 16106159]
175. Stoller A, Stone JC, Moroz K, Hanemann CW, McNabb L, Jones SD, et al. A comparison of clinical and pathologic assessments for the prediction of occult nipple involvement in nipple-sparing mastectomies. *Ann Surg Oncol*. 2013; 20(1):128–32. [PubMed: 23010730]
176. Morales Piatto JR, Aguiar FN, Mota BS, Ricci MD, Doria MT, Alves-Jales RD, et al. Improved frozen section examination of the retroareolar margin for prediction of nipple involvement in breast cancer. *Eur J Surg Oncol*. 2015; 41(8):986–90. [PubMed: 26002985]
177. Tang R, Coopey SB, Merrill AL, Rai U, Specht MC, Gadd MA, et al. Positive Nipple Margins in Nipple-Sparing Mastectomies: Rates, Management, and Oncologic Safety. *J Am Coll Surg*. 2016; 222(6):1149–55. [PubMed: 27118712]
178. Wong L, Wilson RM, Snapp WK, Bole R, Vyas KS. Nipple Pathology in Total Skin-Sparing Mastectomy: Implications for Immediate Reconstruction. *Ann Plast Surg*. 2016; 76(Suppl 4):S340–3. [PubMed: 26914349]
179. Gomez C, Shah C, McCloskey S, Foster N, Vicini F. The role of radiation therapy after nipple-sparing mastectomy. *Ann Surg Oncol*. 2014; 21(7):2237–44. [PubMed: 24687150]
180. Amara D, Peled AW, Wang F, Ewing CA, Alvarado M, Esserman LJ. Tumor Involvement of the Nipple in Total Skin-Sparing Mastectomy: Strategies for Management. *Ann Surg Oncol*. 2015; 22(12):3803–8. [PubMed: 26023040]
181. Warren Peled A, Foster RD, Stover AC, Itakura K, Ewing CA, Alvarado M, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. *Ann Surg Oncol*. 2012; 19(11):3402–9. [PubMed: 22526909]
182. Petit JY, Veronesi U, Orecchia R, Rey P, Martella S, Didier F, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). *Breast Cancer Res Treat*. 2009; 117(2):333–8. [PubMed: 19152026]
183. De La Cruz L, Moody AM, Tappy EE, Blankenship SA, Hecht EM. Overall Survival, Disease-Free Survival, Local Recurrence, and Nipple-Areolar Recurrence in the Setting of Nipple-

- Sparing Mastectomy: A Meta-Analysis and Systematic Review. *Ann Surg Oncol*. 2015; 22(10): 3241–9. [PubMed: 26242363]
184. Petit JY, Veronesi U, Orecchia R, Curigliano G, Rey PC, Botteri E, et al. Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. *Ann Oncol*. 2012; 23(8):2053–8. [PubMed: 22231025]
 185. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg*. 2009; 249(3):461–8. [PubMed: 19247035]
 186. Sakurai T, Zhang N, Suzuma T, Umemura T, Yoshimura G, Sakurai T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. *Med Oncol*. 2013; 30(1):481. [PubMed: 23377926]
 187. Jensen JA, Orringer JS, Giuliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. *Ann Surg Oncol*. 2011; 18(6):1665–70. [PubMed: 21174155]
 188. Dossett LA, Lowe J, Sun W, Lee MC, Smith PD, Jacobsen PB, et al. Prospective evaluation of skin and nipple-areola sensation and patient satisfaction after nipple-sparing mastectomy. *J Surg Oncol*. 2016; 114(1):11–6. [PubMed: 27087574]
 189. Wagner JL, Fearmonti R, Hunt KK, Hwang RF, Meric-Bernstam F, Kuerer HM, et al. Prospective evaluation of the nipple-areola complex sparing mastectomy for risk reduction and for early-stage breast cancer. *Ann Surg Oncol*. 2012; 19(4):1137–44. [PubMed: 21979111]
 190. Boneti C, Yuen J, Santiago C, Diaz Z, Robertson Y, Korourian S, et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. *J Am Coll Surg*. 2011; 212(4):686–93. discussion 93–5. [PubMed: 21463813]
 191. Wei CH, Scott AM, Price AN, Miller HC, Klassen AF, Jhanwar SM, et al. Psychosocial and Sexual Well-Being Following Nipple-Sparing Mastectomy and Reconstruction. *Breast J*. 2016; 22(1):10–7. [PubMed: 26782950]
 192. Peled AW, Duralde E, Foster RD, Fiscali AS, Esserman LJ, Hwang ES, et al. Patient-reported outcomes and satisfaction after total skin-sparing mastectomy and immediate expander-implant reconstruction. *Ann Plast Surg*. 2014; 72(Suppl 1):S48–52. [PubMed: 24317238]
 193. Peled AW, Irwin CS, Hwang ES, Ewing CA, Alvarado M, Esserman LJ. Total skin-sparing mastectomy in BRCA mutation carriers. *Ann Surg Oncol*. 2014; 21(1):37–41. [PubMed: 23982256]
 194. Yao K, Liederbach E, Tang R, Lei L, Czechura T, Sisco M, et al. Nipple-sparing mastectomy in BRCA1/2 mutation carriers: an interim analysis and review of the literature. *Ann Surg Oncol*. 2015; 22(2):370–6. [PubMed: 25023546]
 195. Jakub, J., Peled, A., Gray, R., Greenup, R., Kiluk, J., McLaughlin, S., et al. Multi-institutional Study of the Oncologic Safety of Prophylactic Nipple-Sparing Mastectomy in BRCA Population. American Society of Breast Surgeons; Dallas, Texas: 2016.
 196. Peled AW, Wang F, Foster RD, Alvarado M, Ewing CA, Sbitany H, et al. Expanding the Indications for Total Skin-Sparing Mastectomy: Is It Safe for Patients with Locally Advanced Disease? *Ann Surg Oncol*. 2016; 23(1):87–91. [PubMed: 26170194]
 197. Burdge EC, Yuen J, Hardee M, Gadgil PV, Das C, Henry-Tillman R, et al. Nipple skin-sparing mastectomy is feasible for advanced disease. *Ann Surg Oncol*. 2013; 20(10):3294–302. [PubMed: 23975304]
 198. Santoro S, Loreti A, Cavaliere F, Costarelli L, La Pinta M, Manna E, et al. Neoadjuvant chemotherapy is not a contraindication for nipple sparing mastectomy. *Breast*. 2015; 24(5):661–6. [PubMed: 26343944]
 199. Reish RG, Lin A, Phillips NA, Winograd J, Liao EC, Cetrulo CL Jr, et al. Breast reconstruction outcomes after nipple-sparing mastectomy and radiation therapy. *Plast Reconstr Surg*. 2015; 135(4):959–66. [PubMed: 25811561]
 200. Tang R, Coopey SB, Colwell AS, Specht MC, Gadd MA, Kansal K, et al. Nipple-Sparing Mastectomy in Irradiated Breasts: Selecting Patients to Minimize Complications. *Ann Surg Oncol*. 2015; 22(10):3331–7. [PubMed: 26202557]

201. Spear SL, Shuck J, Hannan L, Albino F, Patel KM. Evaluating long-term outcomes following nipple-sparing mastectomy and reconstruction in the irradiated breast. *Plast Reconstr Surg.* 2014; 133(5):605e–14e. [PubMed: 24572852]
202. Yan C, Fischer JP, Freedman GM, Basta MN, Kovach SJ, Serletti JM, et al. The Timing of Breast Irradiation in Two-Stage Expander/Implant Breast Reconstruction. *Breast J.* 2016; 22(3):322–9. [PubMed: 26864463]
203. Warren Peled, A., Foster, RD., Esserman, L. A comparison of oncoplastic reduction mammoplasty and mastectomy with immediate reconstruction in patients with locally advanced breast cancer. Pacific Coast Surgical Association Annual Meeting; 2012; Napa, California.
204. Rusby JE, Gui GP. Nipple-sparing mastectomy in women with large or ptotic breasts. *J Plast Reconstr Aesthet Surg.* 2010; 63(10):e754–5. [PubMed: 20598664]
205. Robertson SA, Rusby JE, Cutress RI. Determinants of optimal mastectomy skin flap thickness. *Br J Surg.* 2014; 101(8):899–911. [PubMed: 24664617]
206. Nasser, A., Huston, B., Kanth, A., Fourman, M., Palermo, R., Fisher, P., et al. Use of Pre-operative MRI to Predict Tissue Thickness of Mastectomy Skin Flaps. Northeastern Society of Plastic Surgeons; Washington, DC: 2013.
207. Lee JH, Chang CH, Park CH, Kim JK. Methylene blue dye-induced skin necrosis in immediate breast reconstruction: evaluation and management. *Arch Plast Surg.* 2014; 41(3):258–63. [PubMed: 24883277]
208. Donovan CA, Harit AP, Chung A, Bao J, Giuliano AE, Amersi F. Oncological and Surgical Outcomes After Nipple-Sparing Mastectomy: Do Incisions Matter? *Ann Surg Oncol.* 2016; 23(10):3226–31. [PubMed: 27352202]
209. Rawlani V, Fiuk J, Johnson SA, Buck DW 2nd, Hirsch E, Hansen N, et al. The effect of incision choice on outcomes of nipple-sparing mastectomy reconstruction. *Can J Plast Surg.* 2011; 19(4): 129–33. [PubMed: 23204883]
210. Carlson GW, Chu CK, Moyer HR, Duggal C, Losken A. Predictors of nipple ischemia after nipple sparing mastectomy. *Breast J.* 2014; 20(1):69–73. [PubMed: 24224902]

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Figure 1.

Alliance for Clinical Trials in Oncology A11202 trial schema (160). The Alliance A11202 study is a randomized phase III trial that is evaluating the role of ALND in patients with T1–T3 N1 M0 breast cancer who have SLN-positive disease after NACT. Specifically, XRT (to the breast or chest wall and nodes) plus ALND is being compared with XRT only in this patient population.

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; NACT, neoadjuvant chemotherapy; SLN, sentinel lymph node; XRT, radiotherapy

Modified from (114) with permission.

Figure 2.

NSABP B-51/RTOG 1304 (NRG 9353) trial schema (161). NRG 9353 is an ongoing randomized phase III clinical trial that is evaluating the role of XRT in patients with documented positive axillary nodes (T1–T3 N1 M0 breast cancer) who convert to pathologically node-negative disease after NACT. Specifically, the trial is designed to determine whether patients who undergo BCS can be treated with adjuvant breast XRT alone or require additional nodal XRT, and whether chest-wall and axillary XRT improves outcomes post-mastectomy (versus no XRT).

BCS, breast-conserving surgery; ER, estrogen receptor; FNA, fine-needle aspirate; NACT, neoadjuvant chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; pCR, pathological complete response; RTOG, Radiation Therapy Oncology Group; SLNB, sentinel lymph node biopsy; XRT, radiotherapy.

Modified from (114) with permission.

Table 1

Meta-analysis of Margin Width in DCIS Bayesian Analysis

	Margin Threshold Relative to Positive			
	0 or 1mm	2mm	3mm	10mm
No. of Patients	2230	2412	289	1963
Odds Ratio (95% CRI)	0.45 (0.32–0.61)	0.32 (0.21–0.48)	0.30 (0.12–0.76)	0.32 (0.19–0.49)
	Frequentist Analysis Margin Threshold Relative to >0 or 1mm			
	>0 or 1mm	2mm	3mm	10mm
No. of Patients	1533	4902	470	978
Odds Ratio (95% CI)	referent	0.51 (0.31–0.85)	0.42 (0.18–0.97)	0.60 (0.33–1.08)
p-value		0.01	0.04	0.09

DCIS, ductal carcinoma in situ; CRI, credible interval; CI, confidence interval Data from Marinovich ML(36)

Table 2

Summary of trials addressing management of the axilla in patients with a positive sentinel lymph node

Trial characteristic	ACOSOG Z0011 (1999–2004)	AMAROS (2001–2005)
Stages included	Clinical T1–2 N0 M0	Clinical T1b–2 N0 M0
Treatment arms	ALND (n=420) SLND-only (n=436)	ALND (n=744) AxRT (n=681)
Median patient age	ALND, 56 y SLND-only, 54 y	ALND, 56 y AxRT, 55 y
Median tumor size	ALND, 1.7 cm SLND-only, 1.6 cm	ALND, 1.7 cm AxRT, 1.8 cm
Median number of SLNs removed	2	2
Percentage of SLNs with macrometastases	50%	60%
Percentage of patients with additional lymph node metastases in ALND arm	27%	33%
Breast surgery type		
BCT	100%	82%
Mastectomy	0%	18%
Median follow-up time	6.3 years	6.1 years
5-year axillary recurrence rate	ALND, 0.5% SLND-only, 0.9%	ALND, 0.43% AxRT, 1.19%
5-year DFS	ALND, 82.2% SLND-only, 83.9%	ALND, 86.9% AxRT, 82.7%
5-year OS	ALND, 91.8% SLND-only, 92.5%	ALND, 93.3% AxRT-only, 92.5%

Abbreviations: ALND = axillary lymph node dissection; SLND = sentinel lymph node dissection; AxRT = axillary radiotherapy; NR = not reported; SLN = sentinel lymph node; BCT = breast conserving therapy; DFS = disease-free survival; OS = overall survival

Table 3

Local recurrence with and without radiation

Trial	n	Follow-up (years)	Eligibility	LR		P value
				BCS alone (%)	BCS + RT (%)	
NSABP B-06(70)	1851	20	Stage I or II, 4 < cm	39.2	14.3	<0.001
Ontario Clinical Oncology Group(71)	387	7.6	Node negative, < 4.0 cm	35	11	P<0.0001
Milan National Cancer Institute(72)	579	10	Primary < 2.5 cm	23.5	5.8	Not stated
Uppsala-Orebro Breast Cancer Study Group(73)	381	10	Primary < 2 cm, node negative	24.0	8.5	0.0001

BCS: breast conserving surgery; LR: local recurrence; RT: radiation therapy

Table 4

False-negative rates for SNLB after conversion to clinically node-negative disease following NACT.

Prospective trial	No. of patients	Biopsy proven N1 (%)	Pathological complete nodal response (%)	SLN identification rate (%)	Overall FNR (%)	FNR stratified by number of SNLs			FNR stratified by SNL-detection technique	
						1 (%)	2 (%)	3 (%)	Single agent (%)	Dual agent (%)
SENTINA (treatment arm C) (151)	592	25	52.3 [*]	80.1	14.2	24.3	18.5	7.3	16.0 [‡]	8.6
ACOSOG Z1071 (150)	649	100	41	92.9	12.6	31.5	21	9.1	20.3 [‡]	10.8
SN FNAC (149)	145	100	34.5	87.6	8.4	18.2	4.9 [§]	NR	16.0 [‡]	5.2

^{*} Pathological complete nodal response calculated for patients with successful SLN mapping.

[‡] With radioactive colloid only.

[‡] With either radioisotope alone or blue dye alone.

[§] Reported as two or more.

ACOSOG, American College of Surgeons Oncology Group; FNR, false-negative rate; NACT, neoadjuvant chemotherapy; NR, not reported; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

Table 5

Outcomes of nipple-sparing mastectomy

Study	Number patients	Median follow- up	Outcome
Petit et al (184)	1001	50 months	3.6% LR, all patients got single dose of intraoperative radiation to NAC
Gerber et al (185)	286	101 months	11.7% LR, same as skin sparing and total mastectomy
Sakurai et al (186)	788	78 months	7.2% LR
Jensen et al (187)	77	60 months	No LR in patients who retained nipple
Esserman et al (181)	657	28 months	2% LR

LR, local recurrence