Changing Local Therapy in Breast Cancer: Who Needs What, and When?

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Abstract: The local therapy of breast cancer continues to evolve toward less surgery. Breast conservation is firmly in place, with recent trends toward decreased rates of re-excision. Axillary dissection is becoming a rare operation and is being replaced by sentinel node biopsy. The switch to sentinel node biopsy occurred first in patients with pathologically tumor-free nodes, and later in patients with limited nodal disease. Sentinel node biopsy is now also widely used in patients with pathologically positive nodes who receive neoadjuvant chemotherapy. Axillary surgery is being replaced with radiotherapy in some situations, and ongoing trials will further clarify the need for nodal radiotherapy in specific situations following neoadjuvant systemic therapy. Shorter radiotherapy regimens are widely accepted as the standard of care following breast conservation, and the omission of radiotherapy is recognized as appropriate for older patients. The appropriate sequencing of specific components of local therapy, particularly with regard to the timing of chemotherapy, requires thoughtful multidisciplinary planning and leveraging of the strengths of each component of therapy. Here, we review issues related to therapeutic sequencing and decision making in the local therapy of breast cancer.

Introduction

The treatment of primary breast cancer has undergone remarkable changes over the last 20 years, which have improved the lifespan and quality of life of patients with this disease. The changes in systemic therapy include the addition of new agents to the therapeutic armamentarium (aromatase inhibitors, human epidermal growth factor receptor 2 [HER2]–targeted agents, and platinum-based therapy) and the extended use of endocrine agents. On the other hand, local therapy options have in general shifted toward the use of surgical procedures associated with less morbidity and the increased use of radiotherapy. At the same time, the variety of radiotherapeutic options has increased, along with the indications for therapy. Local therapy recommendations have also been altered by the evolving understanding of the importance of tumor biology and the changing landscape of the timing of systemic therapy. We review the shifting paradigms witnessed over the last 25 years and the consequent changes in local therapy standards. The trajectory of a patient with

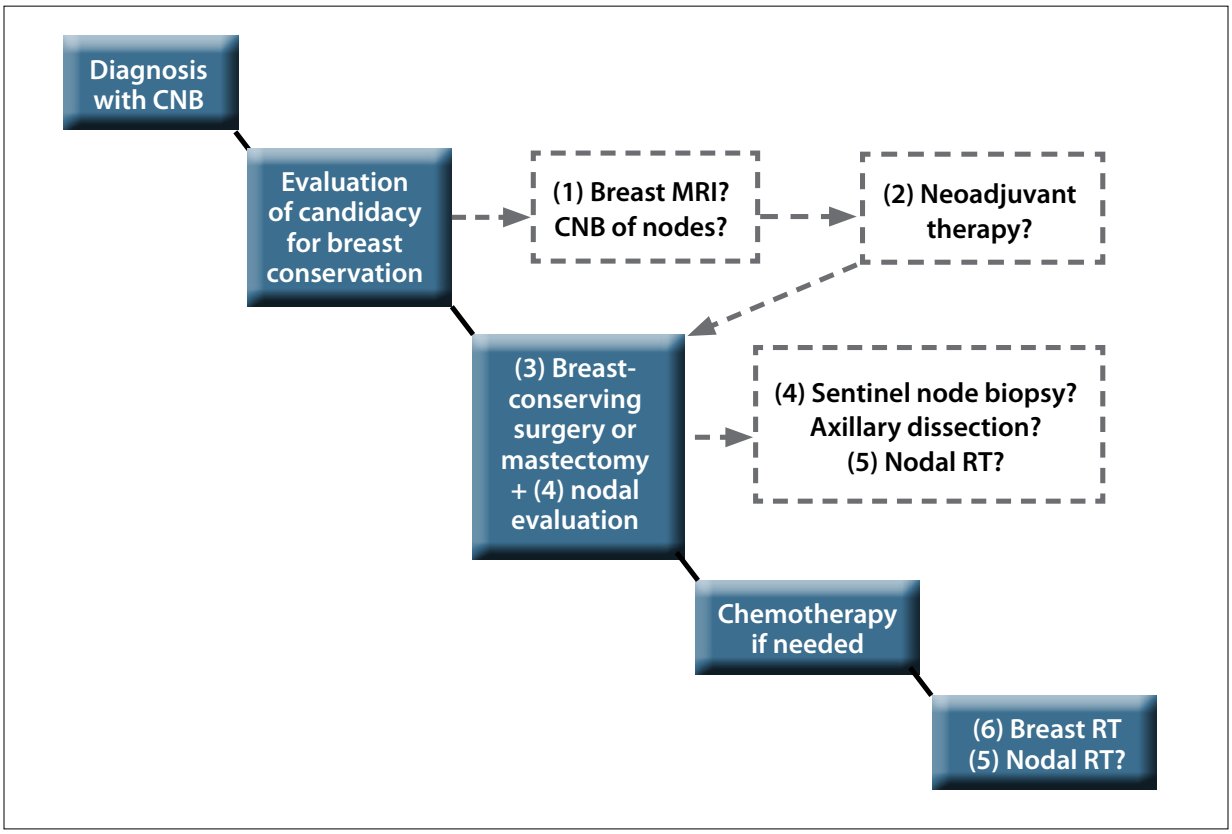

Figure 1. Components of local therapy: the blue boxes show surgery and radiotherapy recommendations in 1992, and the broken-line boxes show subsequent innovations and current questions in 2018.

CNB, core needle biopsy; MRI, magnetic resonance imaging; RT, radiation therapy.

early-stage breast cancer in the early 1990s is depicted in Figure 1, with the modifications that have occurred since then. The sequence and section numbering in our narrative correspond to the decision steps depicted in Figure 1. The indications for potential modifications in management are summarized in Figure 2 and discussed in each section below.

Extent of Preoperative Imaging

The surgical management of breast cancer continues to evolve toward an approach that spares more breast tissue, with breast-conserving therapy the standard of care in early-stage breast cancer.[1] After specific indications for mastectomy have been excluded (inflammatory breast cancer, prior irradiation to the ipsilateral breast, and in some situations concomitant pregnancy), the first question for patients with newly diagnosed breast cancer relates to the appropriateness of (and desire for) breast conservation. Appropriateness is largely determined by an evaluation of the extent of disease in the breast with mammography and ultrasonography. The use of preoperative magnetic resonance imaging (MRI) has been the subject of extensive discussion, given the exquisite sensitivity of MRI for breast cancer detection, although this has not translated into improved outcomes, at least in retrospective analyses.[2] Given its greater sensitivity, MRI examination does reveal multicentric disease that is not seen on conventional imaging, and its use therefore may lead to mastectomy not otherwise indicated. However, the current standard for mastectomy in multicentric disease is based on outdated and flawed data[3]; it is being re-evaluated in a clinical trial to test the safety of breast-conserving surgery (BCS) for women who have multicentric breast cancer with 2 or 3 foci if it appears that complete resection will result in acceptable cosmesis (NCT01556243).

A more accepted indication for MRI in patients with newly diagnosed breast cancer is evaluation of the response to neoadjuvant systemic therapy (NST); pathologic complete response (pCR) and residual disease are better delineated with MRI than with conventional imaging.[4] However, the value of MRI in allowing a more accurate resection of residual tumor is yet to be established outside the clinical trial setting.[5] The present use of breast MRI therefore varies widely, both across institutions in

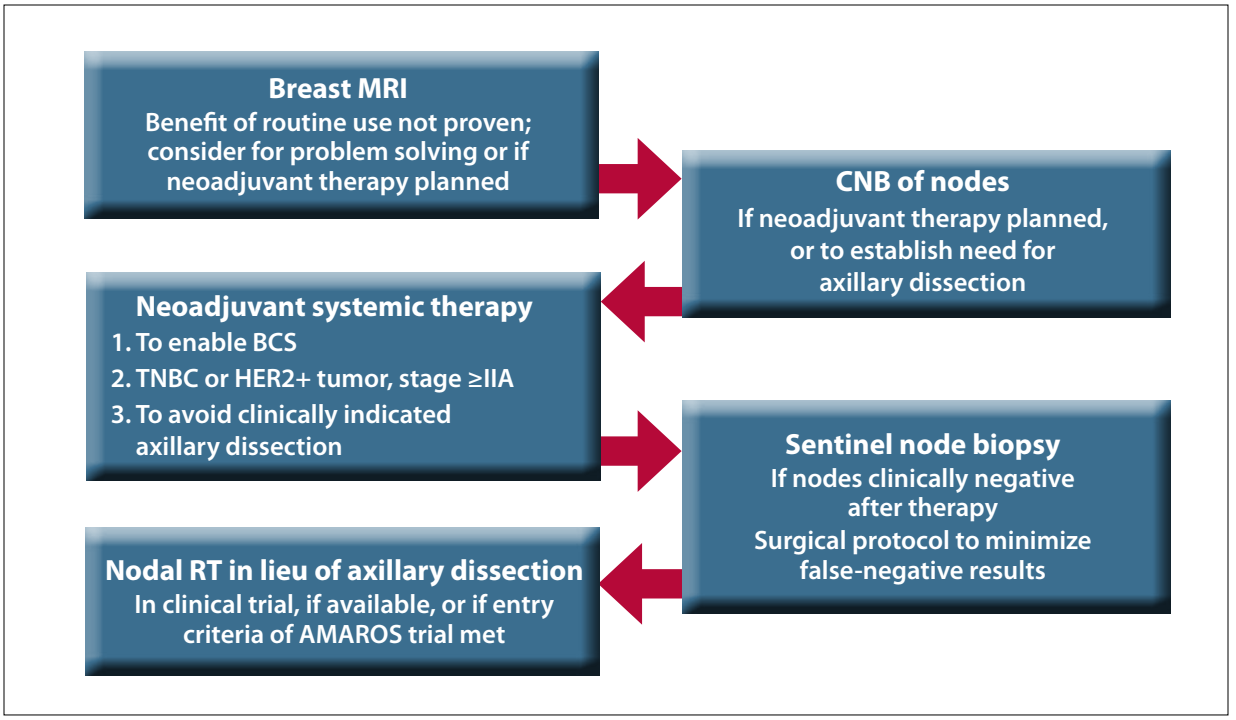

Figure 2. Indications for modifications of classic local therapy approach to breast cancer management.

BCS, breast-conserving therapy; CNB, core needle biopsy; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; RT, radiation therapy; TNBC, triple-negative breast cancer.

the United States and internationally. An ongoing clinical trial may help to resolve this conundrum but is limited to patients with hormone receptor–negative, HER2-positive disease (NCT01805076). This trial is examining the role of MRI in addition to mammography before surgery in determining the type of surgery for patients with stage I and II breast cancer. The aim of the study is to compare the rates of locoregional recurrence following BCS in patients randomly assigned to mammography plus MRI or to mammography alone. Patients with multicentric disease and those undergoing NST are excluded. The exclusion of patients with hormone receptor–positive disease means that large subsets of the current population of patients with breast cancer will not be addressed when the results of this trial become available. On the other hand, improvements in the performance of MRI and the possibility of decreased costs through abbreviated imaging may make this discussion moot over the next decade or so.

Imaging of the Axilla

Axillary lymph node imaging may identify suspicious nodes if NST is being considered.[6] If these are present, either core biopsy or fine-needle biopsy should be performed—not so much to predict the need for axillary dissection following neoadjuvant chemotherapy[7] but to determine the need for nodal radiotherapy following surgery (which remains standard for women with proven nodal involvement before NST). On ultrasonography, abnormal lymph nodes display cortical thickening, focal cortical lobulation, or increased blood flow to the hilum and cortex.[8] As the lymph node is replaced by metastatic tumor cells, it loses its fatty hilum and becomes hypoechoic.[9] A meta-analysis of ultrasound features in predicting nonpalpable axillary node involvement revealed that size and morphology were moderately sensitive and fairly specific in predicting malignancy (sensitivity of size, 48.8%-87.1%; sensitivity of morphology, 26.4%-75.9%).[10] The sensitivity of ultrasound-guided biopsy ranges from 31% to 63%, with a specificity of 100%. When NST is not required, imaging of the axilla can be useful in predicting lymph node involvement, but its utility is not agreed upon because not all women with involved sentinel nodes require axillary dissection.[11] Thus, the potential for a false-negative result of ultrasound-guided needle biopsy means that sentinel node biopsy is not avoided by a negative result of biopsy of a questionable node, and a positive biopsy result does not mean that a woman will require axillary dissection. Despite advances in sonographic imaging of the axilla, the false-negative rate remains at approximately 30% and can be higher with smaller metastases. However, nodal positivity, particularly when identified by ultrasound-guided

fine-needle aspiration, may imply a nodal burden that is not compatible with the criteria of the American College of Surgeons Oncology Group (ACOSOG) Z011 trial (Lymph Node Removal in Treating Women Who Have Stage I or Stage IIA Breast Cancer),[12] and these patients are likely to require axillary dissection.[13]

Indication for Neoadjuvant Systemic Therapy?

In patients with early-stage breast cancer, overall survival (OS) and clinical outcomes of breast-conserving therapy have been shown to be equivalent to those of mastectomy on long-term follow-up.[14-16] However, results from preclinical experiments in the 1980s generated data on mammary tumor biology,[17] which led Fisher and colleagues to hypothesize that preoperative chemotherapy would be advantageous to patients on several fronts, including improved OS. As a result, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial (A "Unified" Trial to Compare Short, Intensive Preoperative Systemic Adriamycin-Cyclophosphamide Therapy with Similar Therapy Administered in Conventional Postoperative Fashion)[18] was designed with the primary objective of evaluating the effect of preoperative (neoadjuvant) chemotherapy on disease-free survival (DFS) and OS, anticipating an improvement in these endpoints. So far, this improvement has not materialized. The second objective of NSABP B-18 was to relate primary tumor response to DFS and OS, with the hypothesis that the primary tumor response could be used to gauge the chemosensitivity of the tumor and the need for additional systemic therapy. After 20 years, pooled analyses of multiple subsequent studies have demonstrated that the occurrence of a pCR in women with HER2-positive or triple-negative breast cancer does identify a subgroup of patients with improved DFS.[19] A significant effect on OS remains to be demonstrated.[20,21] The practical value of NST as a test of chemosensitivity is presently being prospectively tested in ongoing trials in which additional non–cross-resistant postoperative regimens are used in women with residual locoregional disease in their surgical specimens. The third aim of NSABP B-18 was to determine if the use of preoperative chemotherapy resulted in higher rates of breast conservation. The NSABP B-06 trial (A Protocol to Compare Segmental Mastectomy and Axillary Dissection With and Without Radiation of the Breast and Total Mastectomy and Axillary Dissection) allowed the inclusion of women with tumors up to 4 cm in size,[22] but in practical terms, the use of primary BCS for women with A or B cup breasts is limited by the ratio of tumor to breast size. This third aim forms the basis of much NST use today.

Nonetheless, a recent meta-analysis of 10 randomized trials conducted from 1983 to 2005 that had a 9-year median follow-up included 4756 patients randomly assigned to NST vs adjuvant chemotherapy. The aim of this study was to investigate the long-term benefit of NST in terms of disease recurrence and OS.[23] However, it included several older trials wherein surgical resection was not always performed in the setting of a complete clinical/radiologic response. The results highlight the need for surgical resection of the tumor bed even in the presence of a clinical complete response because the absolute increase in locoregional recurrence was 13% when only radiotherapy was used, compared with 3.2% when surgery was used. The overall hazard ratio for locoregional recurrence across all trials was 1.28 (95% CI, 1.22-1.34). No significant differences in distant recurrence, breast cancer–specific mortality, or OS were found on the basis of use of neoadjuvant vs postoperative adjuvant therapy.

More recently, the tumor biological subtype has also been a major consideration in decisions regarding NST. This consideration has been prompted by data demonstrating superior rates of pCR in women with triple-negative or HER2-positive breast cancer.[24,25] In particular, the findings of the current generation of clinical trials, previously mentioned, testing the addition of postoperative therapy for women with significant residual disease render the use of NST more attractive. One example is an Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) trial randomly assigning women with triple-negative breast cancer who have residual disease of at least 1 cm following a non–platinum-containing regimen to carboplatin or capecitabine (Platinum-Based Chemotherapy or Capecitabine in Treating Patients With Residual Triple-Negative Basal-Like Breast Cancer Following Neoadjuvant Chemotherapy; NCT02445391). Another is NSABP B-55 (OlympiA), in which women with high-risk HER2-negative breast cancer or a *BRCA1*/*BRCA2* mutation and residual disease following chemotherapy can be randomly assigned to olaparib (Lynparza, AstraZeneca) or placebo (Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer; NCT02032823).

Surprisingly, the occurrence of a significant clinical and radiologic response that allows the possibility of BCS does not necessarily translate into breast conservation in many patients.[26,27] Two large analyses of pooled clinical trial results have shown that despite the occurrence of a clinical response rendering breast conservation feasible, only 30% to 40% of women in this category pursue breast conservation, with the main drivers of mastectomy being preoperative tumor size and multicentricity.[27] These findings also apply to subgroups with high rates of response to NST, such as women who have HER2-positive disease treated with HER2-directed therapy.[28]

Another emerging indication for the consideration

of NST, particularly in women with HER2-positive or triple-negative disease, is the presence of clinically positive axillary nodes that are then proved to be pathologically positive with ultrasound-guided core or fine-needle biopsy. In this setting, the conversion of clinically abnormal nodes to cN0 status allows the use of sentinel node biopsy[29] with appropriate precautions (use of dual tracers, identification of 3 sentinel nodes, and localization of the originally biopsied and clipped node[30]). For women with a conversion from node-positive status at pre-chemotherapy ultrasound-guided core needle biopsy to node-negative status at post-chemotherapy sentinel node biopsy, the accuracy of sentinel node biopsy is in the range of 90%, and the omission of axillary dissection seems reasonable in this situation.

Finally, the next phase of change in local therapy approaches in the neoadjuvant setting is represented by a series of trials in Europe and the United States, exemplified by the phase 2 NRG-BR005 trial (Assessing the Accuracy of Tumor Biopsies After Chemotherapy to Determine if Patients Can Avoid Breast Surgery; NCT03188393). Here, women whose tumors display a complete clinical response on physical examination and imaging can undergo core needle biopsy sampling of the tumor bed followed by usual surgical resection of the tumor site. This study will recruit 175 patients and will provide an estimate of the accuracy of image-guided core needle biopsy of the tumor bed in establishing pCR, aiming for a false-negative rate of 10%. If successful, these trials will lead to an era of nonsurgical therapy for primary breast cancer.

Surgical Procedure

Breast-Conserving Surgery: Need for Re-excision of the Margins?

The vexing issue of re-excision of the margins has been clarified to some degree over the past few years, although a need for clinical judgment remains. Free margins of BCS specimens were originally defined in NSABP B-06 as "no ink on tumor,"[22] and subsequent NSABP protocols have adhered to the same standard. However, a series of single-institution retrospective studies subsequently evaluated the value of wider margins (>1, >2, and >5 mm) and reported a decrease in the rates of in-breast recurrence with the use of wider margins. These data led to varying institutional standards for the definition of free margins and consequently a wide variation in re-excision rates.[31] A consensus panel was therefore convened in 2013 that included representatives of the major oncologic societies (Society of Surgical Oncology, American Society for Radiation Oncology [ASTRO], American Society of Clinical Oncology [ASCO], and United States and Canadian Academy of Pathology [USCAP]), which commissioned a meta-analysis of the existing data with the support of Susan J. Komen.[32,33] This meta-analysis, in combination with the perspectives of experts from the various oncologic disciplines, was used to formulate consensus recommendations regarding required margin width for women with stage I or II breast cancer receiving BCS, radiotherapy, and optimal postoperative systemic therapy. The process was performed separately for stages I and II invasive cancer and ductal carcinoma in situ (DCIS) management (use of radiotherapy assumed) and led to the publication of consensus guidelines[34,35] that have resulted in a reduction in re-excision rates following BCS.[36]

The panel's major recommendation for invasive cancer stated that a margin without ink on tumor is sufficient to minimize in-breast recurrence, and that wider margins do not provide additional advantage. As a result, routine re-excision to achieve margins wider than those with no ink on tumor is not indicated. This statement applies regardless of the patient's age, histologic or biological subtype of tumor, and other features. However, clinical judgment is needed for women not receiving radiotherapy or optimal systemic therapy and those who have undergone NST because these categories were not included in the foundational meta-analysis. In addition, subsequent commentary on these guidelines has pointed out that the effect of young age and an extensive intraductal component on risk for in-breast recurrence should be recognized, as should the effect of multiple close margins or a large tumor volume close to the margin. Thus, although routine re-excision is not justified if tumor cells do not reach ink, re-excision is appropriate in selected circumstances.[37]

For DCIS, following a similar process of literature evaluation and expert consensus, the optimal margin appears to be 2 mm between tumor and ink[35]; again, however, in special circumstances (older age, small DCIS size, low grade) narrower margins may be acceptable. Among women who do not receive radiation therapy, wider margin standards may be justifiable, but evidence is limited.

Mastectomy

Alterations in the traditional approaches to mastectomy include nipple preservation, in which the breast tissue resection is similar to that in skin-sparing mastectomy but the nipple-areolar complex is preserved. The main advantage of this is greater patient satisfaction and improved cosmetic outcomes, with greater psychosocial and sexual well-being.[38,39] Concerns about compromised cancer outcomes are being addressed as longer-term data accumulate. Local recurrences in the nipple itself are infrequent (in the range of 2%), and flap recurrence rates do not differ from those following skin-sparing mastectomy.[40,41] This may change, however, as selection criteria are relaxed and as longer-term follow-up of large series becomes available; most series report on highly selected patients. Complication rates are acceptable,[42] and nipple necrosis

occurs in fewer than 5% of patients in experienced hands. Contraindications to nipple-sparing mastectomy include tumors within 2 cm of the nipple, microcalcifications in the subareolar region, tumors larger than 4 cm, and a nipple base biopsy that shows tumor. In addition, women with ptotic or large breasts may have suboptimal results.[42] Thus, for many patients, nipple preservation is a viable and safe option that is changing the acceptability of mastectomy as an option for breast cancer therapy. Nevertheless, these women should be cautioned about the loss of sensation and possibility of nipple necrosis.

Another decision point for patients considering mastectomy is the optimal timing and type of breast reconstruction, particularly when post-mastectomy radiation therapy (PMRT) may be indicated. Preoperatively, there is usually some uncertainty as to whether PMRT will be required. Immediate reconstruction most frequently involves the use of tissue expanders that are later exchanged for permanent implants. The cosmetic outcomes of implant reconstruction in the PMRT setting are often unsatisfactory, however. A meta-analysis of 7 studies that included 2921 patients examined the effects of PMRT on implant reconstruction. The analysis showed that radiation use is associated with a 10-fold increase in rates of capsular contracture, roughly 2-fold increases in implant failure and revisional surgery, and decreased patient satisfaction and cosmetic outcomes.[43] Similar findings were reported from a second meta-analysis of the effects of PMRT on reconstruction: failure rates in the range of 17% to 20% with grade III/IV capsular contractures in about one-quarter of patients, leading to inferior cosmetic results.[44] In a prospective, multicenter evaluation of the effects of radiation on reconstruction following mastectomy, Jagsi and colleagues found that autologous reconstruction yielded better patient-reported satisfaction and lower complication rates than implant reconstruction.[45] However, there is some concern regarding the effect of radiotherapy on the long-term quality of results when an autologous flap is radiated, and autologous reconstruction is therefore frequently delayed if PMRT is a possibility. At the moment, therefore, when preoperative evaluation suggests a possible need for PMRT, a discussion of the optimal timing of reconstruction with the patient is necessary. If the main determinant of the need for PMRT is the pathologic nodal status, one option is to perform the sentinel node biopsy as a separate procedure before mastectomy. This approach establishes the pathologic nodal status preoperatively and allows optimal reconstruction planning.

Sentinel Node Biopsy

Axillary lymph node involvement is one of the most important prognostic indicators in the diagnosis and treatment of breast cancer. Over the past decade, sentinel lymph node biopsy has emerged as a feasible and reliable method to assess the axilla at the time of surgery. When introduced, the concept was for clinically node-negative patients; if pathologic positivity was demonstrated in a sentinel node, axillary dissection was routinely performed.[46,47] Subsequently, the ACOSOG Z0011 trial demonstrated that among women with 1 to 2 involved sentinel nodes and no gross extracapsular extension, 10-year local and distant cancer outcomes were not improved by routine axillary dissection.[11] It is now widely accepted, therefore, that axillary dissection may be reserved for women with 3 or more positive sentinel nodes. However, the evidence for this is in the setting of primary breast conservation (without NST). For women undergoing mastectomy, the standard of care remains axillary dissection for any positive sentinel nodes, although this too is beginning to shift in view of recent data regarding the substitution of nodal radiotherapy for axillary dissection.[48]

In patients undergoing NST, the use of sentinel node biopsy is now firmly established if the axilla is clinically negative at the outset.[49,50] Initial controversy regarding the timing of sentinel node evaluation (ie, before or following NST) is now largely resolved in favor of post-neoadjuvant timing. This allows the patient to benefit from the approximately 40% chance of pathologic downstaging of the axilla, particularly if the tumor is triple-negative or HER2-positive.[51] Among women with pathologically involved nodes at the start of therapy, the accuracy of sentinel node biopsy following NST was initially questioned, but results from the ACOSOG Z1071 trial have demonstrated that with appropriate attention to technical details, the accuracy is in an acceptable range.[29] These technical issues include the use of 2 tracers for mapping and the retrieval of at least 2 sentinel nodes (preferably 3). A further gain in accuracy has been reported with the localization and retrieval of the lymph node that was biopsied and marked with a clip before systemic therapy,[52] but the magnitude of the improvement appears variable, and technical issues regarding the most reliable approach to node clipping and retrieval remain open.

Radiotherapy

Nodal Radiation

The indications for irradiation of the regional lymph nodes (axillary, internal mammary, or supraclavicular) are expanding. Formerly recommended only in patients with a significant nodal burden (ie, 4 or more involved nodes), nodal irradiation is now considered in patients with a range of high-risk features. The NCIC (National Cancer Institute of Canada) Clinical Trials Group MA.20 trial (Radiation Therapy in Treating Women Who Have Undergone Surgery for Early-Stage Invasive Breast

Cancer; NCT00005957) investigated the addition of regional nodal irradiation to whole-breast irradiation in women who had early breast cancers with node-positive or high-risk, node-negative disease. It revealed that OS was not significantly different between the 2 groups, but the DFS was improved in the arm that underwent nodal irradiation (82% vs 77% at 10 years).[53] Lower rates of locoregional recurrence and distant metastases were observed with the addition of nodal irradiation, but at the cost of more frequent pneumonitis (1.2% vs 0.2%) and lymphedema (8.4% vs 4.5%).

A similar trial has assessed the value of extending radiation to the internal mammary and supraclavicular chains. The European Organization for Research and Treatment of Cancer (EORTC) initiated a phase 3 trial (Lymph Node Radiation Therapy in Patients With Stage I, Stage II, or Stage III Breast Cancer That Has Been Surgically Removed; EORTC 22922-10925; NCT00002851) that tested the addition of internal mammary and medial supraclavicular lymph node irradiation to whole-breast irradiation or chest wall irradiation in patients who had node-positive or node-negative breast cancer with medial or centrally located tumors. The study demonstrated that the addition of regional irradiation showed modest benefits in 10-year OS (82.3% vs 80.7%), DFS (72.1% vs 69.1%), and distant disease–free survival (78% vs 75%).[54]

The decision to radiate the undissected axillary lymph nodes, internal mammary lymph nodes, and supraclavicular lymph nodes depends on clinical risk factors (number of involved nodes, extracapsular extension) and the extent of surgical dissection. National Comprehensive Cancer Network (NCCN) guidelines recommend irradiation to the supraclavicular and infraclavicular lymph nodes and part of the undissected axillary lymph nodes in women with 4 or more positive nodes (category 1).[1] On the other hand, for patients with involvement of 1 to 3 lymph nodes, the NCCN strongly recommends consideration of regional nodal irradiation (category 2a). Lymphedema is common in patients who undergo combined axillary lymph node dissection and irradiation, affecting 20% of them. It is now less frequently encountered owing to the increased use of sentinel lymph node biopsy alone.

Another twist to decision making in axillary management relates to the substitution of axillary radiation therapy for axillary dissection, as tested in the AMAROS trial (Comparison of Complete Axillary Lymph Node Dissection With Axillary Radiation Therapy in Treating Women With Invasive Breast Cancer). Here, 1425 women with a clinically negative axilla and a positive sentinel lymph node were randomly assigned in a 1:1 ratio to axillary dissection or axillary radiation therapy. At a median follow-up of 6.1 years, the recurrence rate in the axillary dissection group was 4 of 744 patients (0.54%) compared with 7 of 681 patients (1.02%) in the axillary radiation therapy arm.[48] In this trial, recurrence rates were similar for axillary dissection and nodal radiation therapy; however, the rate of lymphedema was significantly higher in the axillary dissection group (23% vs 11% at 5 years). Caveats include the fact that about 17% of the population in each arm underwent mastectomy, and only 5% in each arm had 3 or more involved sentinel nodes. Therefore, these results are most valid for women undergoing breast conservation and those with a small nodal burden.

Breast Radiotherapy

The gold standard radiation method following breast surgery is shifting from standard whole-breast irradiation (WBI), which is delivered over 4 to 6 weeks in 25 fractions of 50 Gy, to hypofractionated WBI, which uses 16 fractions of 42.5 Gy.[55] This change is supported by long-term outcome data from randomized trials that have demonstrated the efficacy and safety of these techniques. The advantages relate to a shorter length of treatment, improved quality of life, lower cost, and convenience. Whelan and colleagues compared 50 Gy in 25 fractions vs 42.5 Gy in 16 fractions in patients who had T1-2N0 tumors with tumor-free surgical margins.[56] At 10-year follow-up, no difference was found in the rates of local control or survival, with similar cosmetic results. Similarly, the UK START (Standardisation of Breast Radiotherapy) A and B trials reported similar local recurrence rates and superior cosmetic outcomes when hypofractionated radiation was compared with standard radiation.[57] These, among other trials, did not demonstrate a significant difference between local control rates with standard WBI and control rates with hypofractionated WBI. The results of these trials have led ASTRO to update guidelines in 2018 for the use of hypofractionated WBI[58] as follows:

- The preferred dose is 4000 cGy in 15 fractions or 4250 Gy in 16 fractions.
- Patients can be of any age.
- The tumor can be at any stage, provided the intent is to treat the whole breast.
- Any use of chemotherapy does not affect the decision to use hypofractionated WBI.
- The decision to offer hypofractionated WBI should be independent of tumor grade, hormone receptor status, HER2 receptor status, and margin status.

Beyond the use of WBI, local recurrence can be further reduced by the addition of tumor bed radiation boost. The rationale behind this approach is that most potential residual tumor cells, which may lead to recurrence within 10 years of therapy, are within the tumor bed.[59] Thus, providing additional radiation boost to the tumor bed was theorized to reduce recurrence risk further and was shown to be useful in a randomized phase 3

trial.[60] On the basis of this and subsequent experience, the consensus now is that radiation boost to the tumor bed in indicated in women younger than 40 years, who derive the greatest benefit from it. Radiation boost to the tumor bed is also recommended for women aged 40 to 49 years. Those 50 years or older are likely to benefit if the tumor is high-grade or large with lymphovascular invasion, positive or close margins, and a high mitotic rate.[61] Radiation boost to the tumor bed has therefore become part of the standard plan for the treatment of breast cancer in young patients and for patients with high-risk features (as previously outlined).

Partial breast radiotherapy. Given that a significant percentage of cases of breast cancer recurrence occur in proximity to the primary tumor site, interest has been shown in the use of localized radiation to the primary site, sparing the surrounding tissue. This approach, called accelerated partial breast irradiation (APBI), allows a higher dose of radiation to be delivered over a shorter time (average of 10 days) to a targeted tumor area, which can limit adverse effects and improve treatment adherence.

Several techniques to deliver APBI to breast cancer patients have emerged. These include 3-dimensional conformal external beam radiotherapy, intracavitary brachytherapy, and intraoperative radiation. The short- and long-term results of APBI vs those of WBI have been reported in several randomized trials, and the results are mixed. In a meta-analysis of 8 studies with 8653 randomized patients (which was largely influenced by intraoperative radiotherapy trials), APBI was associated with a higher local recurrence rate than WBI. No statistically significant differences in the rates of nodal or distant metastasis, OS, or mortality were observed.[62] Although ASTRO articulated guidelines for the use of APBI in 2009 (updated in 2016) that identified patients for whom APBI was suitable, cautionary, or unsuitable,[63] the persistent risk for ipsilateral breast tumor recurrence over time was recognized. The use of APBI across the United States has plateaued since 2009.[64] Ongoing large randomized trials, such as NSABP B-39/RTOG 0413 (Radiation Therapy in Treating Women Who Have Undergone Surgery For Ductal Carcinoma In Situ or Stage I or Stage II Breast Cancer; NCT00103181), are expected to resolve issues related to the long-term efficacy, safety, and cosmesis of WBI compared with APBI in the treatment of unicentric, node-negative, stages 0, I, and II breast cancers. Currently, APBI should be considered only for patients who seek it and who meet ASTRO guidelines.

Postmastectomy radiation. The evidence for PMRT in selected subsets of patients continues to accumulate, and the subsets continue to expand with the recent generation of nodal irradiation trials. Mature outcome data from older studies that tested the value of PMRT in combination with systemic therapy[65] show, at 20-year follow-up, substantially higher OS, DFS, and event-free survival rates with the addition of PMRT (47% vs 37%, 48% vs 31%, and 38% vs 25%, respectively). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 22 randomized control trials of PMRT in 8135 women reported on the efficacy and complication rates associated with radiation.[66] It revealed that when women with node-positive breast cancer (pN1-3) received axillary lymph node dissection with systemic therapy, the risk for locoregional recurrence decreased in patients treated with radiation from 21% to 4.3% at 10 years. Similarly, the 20-year breast cancer mortality rate was reduced from 49.4% to 41.5%. In women with 4 or more positive nodes, the locoregional recurrence rates at 10 years were 13% vs 32.1% and the 20-year breast cancer mortality rates were 70.7% vs 80% in the radiated vs the nonradiated arms. Nonetheless, with improved systemic therapies, the absolute risk in reduction for local recurrence and mortality rates can be expected to be smaller with the use of PMRT. However, ASTRO, ASCO, and other organizations recommend the use of PMRT in women with 4 or more involved nodes, patients with 1 to 3 positive nodes and large tumors (>5 cm), and those at high risk for locoregional recurrence (>20%) without radiation therapy. Additional studies are investigating the role of PMRT in patients with node-negative disease and biologically aggressive tumors.

Despite the observed benefits of radiation in patients with T1-2 tumors and 1 to 3 positive nodes, there may be a subset of patients who are at sufficiently low risk for locoregional recurrence that the absolute benefit of PMRT is outweighed by the potential toxicities. The guidelines therefore recommend that the use of PMRT be considered in a multidisciplinary fashion and that patient risk factors for recurrence, such as young age, larger tumor size, the presence of lymphovascular invasion, and the effectiveness of systemic therapy, should be considered along with patient preferences in making recommendations. The new MA39 trial (Trial of Regional Rtx in Biomarker Low Risk Node Positive Breast Cancer) from the Canadian Cancer Trials Group will evaluate the omission of PMRT and/or regional nodal irradiation in patients who have 1 to 3 positive nodes, estrogen receptor–positive tumors, and an Oncotype DX recurrence score of less than 18.

Omission of breast radiotherapy. Among older women with favorable tumors, variously defined (older than 70 years with tumors ≤2 cm[67] or older than 65 years with tumors <3 cm[68] and pathologically node-negative), breast radiation therapy following BCS offers a reduction in

risk for local recurrence but no demonstrable improvement in survival, at least in the Cancer and Leukemia Group B (CALGB 9343) trial with 10 years of follow-up. In both the CALGB 9343 trial and the PRIME II trial (Breast-Conserving Surgery With or Without Irradiation in Women Aged 65 Years or Older With Early Breast Cancer), estrogen receptor positivity of the tumor was required, and endocrine therapy was widely used or mandated. The omission of radiotherapy in this setting increased the risk for local recurrence (from 2% to 10% at 10 years in CALGB 9343 and from 1.3% to 4.1% at 5 years in PRIME II), but other outcomes were not affected. Considering the competing causes of mortality in this age group, it appears reasonable to offer omission of radiotherapy to women who meet the criteria for entry into the CALGB 9343 trial, given the long follow-up of this population, but uptake by physicians of this consensus recommendation[6] has been slow.[69]

Conclusion

The past 2 to 3 decades have seen enormous scientific and technologic advances in the local therapy of breast cancer. Radical mastectomy was abandoned as the standard local treatment more than 4 decades ago, breast conservation became established more than 20 years ago, and axillary management has changed dramatically in the past decades. The increasing use of neoadjuvant therapy allows more women to be eligible for limited breast and axillary surgery, and shorter-course WBI is now widely accepted as efficacious. Similarly, new targeted endocrine therapies and chemotherapies have improved patients' OS and reduced local recurrence. As we continue to improve our understanding of tumor biology, the treatment of breast cancers will become increasingly patient-specific and less toxic.

Disclosures

The authors have no conflicts of interest to disclose.

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