ABSTRACT

The latest version of NCCN Guidelines for Breast Cancer on locoregional management of early-stage breast cancer contains numerous updated recommendations, particularly focusing on management of the axilla, locoregional management after neoadjuvant therapy, and radiation delivery. Recommendations for axillary staging have been separated for patients who have undergone breast-conserving surgery and those who have had a mastectomy, creating 2 individual pathways. The section on locoregional treatment after neoadjuvant therapy has been reformatted; optimal management of this patient group continues to evolve. Lastly, specifics regarding the delivery and sequencing of radiotherapy have been updated.

There have been numerous important changes to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer on locoregional management of early-stage breast cancer. For radiation therapy (RT), the criteria for axillary radiation instead of axillary node dissection have been modified. In addition, the recommendations for regional nodal irradiation (RNI) have been further refined. The management of patients with node-positive disease after sentinel lymph node biopsy (SLNB) remains a challenge. For surgery, an important goal is de-escalation of axillary surgery without adversely affecting survival and locoregional control. These and other issues related to locoregional management were discussed at the NCCN 2022 Annual Conference by Meena S. Moran, MD, Professor of Therapeutic Radiology, Yale School of Medicine, and Chief, Breast Radiation, Yale New Haven Hospital Health system. Dr. Moran is also Vice Chair of the NCCN Breast Cancer Panel. Also contributing to the discussion was A. Marilyn Leitch, MD, Professor of Surgery, Surgical Oncology, and the S.T. Harris Family Distinguished Chair in Breast Surgery, The University of Texas Southwestern Simmons Comprehensive Cancer Center, Dallas.

Regional Nodal Radiation for Node-Negative Disease

For patients with early-stage breast cancer and no positive lymph nodes, the NCCN Guidelines panel has further refined the recommendations for RNI. The general recommendations for delivering RNI come from pivotal trials that have shown that in selected high-risk patients, the addition of RNI has the potential to affect long-term distant outcomes, Dr. Moran said. Two pivotal trials were MA-20 and EORTC 22922, which randomly assigned patients with high-risk node-negative (N0) disease to RNI or standard RT without RNI, which in these trials included the internal mammary nodes, supraclavicular fossa, and any undissected axilla. The 2 trials demonstrated modest but statistically significant benefits, not only in reducing locoregional events at 10 years but also in improving distant outcomes and breast cancer mortality beyond 10 years. The EORTC trial involved a broader population of patients, allowing all patients with pathologically N0 disease if they had centrally or medially located tumors.

"In the most recent update, we refined the NCCN Guidelines to state that RNI should be considered for patients with N0 disease if they have centrally or medially located tumors [based on EORTC 22922], as well as for patients with T3N0 or T2N0 tumors with <10 nodes and an adverse prognostic feature—such as grade 3 disease, extensive lymphovascular invasion, or estrogen receptor-negative status" [based on MA-20] (Figure 1).3

Positive Nodes After Breast-Conserving Surgery

The panel continues to support the avoidance of axillary lymph node dissection (ALND) in many patients. This recommendation is largely based on findings from ACOSOG Z0011 and SINODAR-ONE, in which patients with clinical T1/T2N0 disease with up to 2 positive sentinel nodes fared equally well with SLNB alone or ALND, with low rates of both locoregional recurrence (~6%; P=.36) and nodal recurrence (<2%; P=.28) irrespective of treatment.4,5 Compared with ACOSOG Z0011, the SINODAR-ONE population almost
exclusively had macrometastatic rather than micrometastatic disease, with approximately 20% of patients enrolled having had mastectomy, whereas ACOSOG Z0011 included patients only undergoing breast-conserving surgery. SINODAR-ONE, therefore, may allow for future broadening of the criteria to include patients who have undergone a mastectomy, and may provide more information to guide radiation decisions in future recommendations, Dr. Moran said.

For patients with positive sentinel nodes not fitting the ACOSOG Z0011 criteria, the AMAROS trial aimed to determine whether axillary RT can replace ALND for patients with positive nodes on SLNB. The study found low axillary recurrence rates in both arms (≤2%); however, the risk of lymphedema with ALND was nearly double that of axillary radiation (23% vs 11%; \( P = .0001 \)). These findings were confirmed by the OTOASAR trial. Together, the AMAROS and OTOASAR studies suggest that axillary RT should be considered a comparable therapeutic approach to dissection in patients with up to 2 positive sentinel nodes.

Together, the ACOSOG Z0011, SINODAR-ONE, AMAROS, and OTOASAR studies provide strong evidence to suggest that in clinically node-negative T1/T2 disease with up to 2 positive nodes (macrometastatic or micrometastatic disease), ALND is not required. After breast-conserving surgery, regardless of whether the axilla is intentionally targeted with RT, it appears that axillary events are rare. In contrast, if a patient with clinically node-negative T1/T2 tumors undergoes mastectomy, then the RT recommendations were modified in this year’s NCCN Guidelines to reflect that ALND may be similarly omitted; however, the undissected axilla at risk should be treated (based on AMAROS and OTOASAR) with RNI.

**Modifications to Axillary Management**

Another major modification in the guidelines separates breast-conserving therapy and mastectomy in the axillary staging section, creating 2 individual pathways (Figure 2). Dr. Leitch noted that the surgical management of early-stage breast cancer continues to foster de-escalation approaches, which began decades ago. Although the avoidance of ALND in favor of SLNB for patients with clinical node-negative disease undergoing breast-conserving surgery is well accepted even when 1 or 2 sentinel nodes are positive, management of positive sentinel nodes in patients undergoing mastectomy has been considered controversial to date.

For patients undergoing a mastectomy in the non-neoadjuvant setting, a major modification discussed by both Dr. Moran and Dr. Leitch was that ALND may be omitted for those with clinically node-negative T1/T2 tumors and up to 2 positive nodes by SLNB, for whom postmastectomy RT is intended. This is a change from the previous version of the guidelines, which stated that if a patient with sentinel node–positive disease did not meet ACOSOG Z0011 criteria, ALND was required. This revised recommendation is based on the AMAROS and OTOASAR trials, which have confirmed no differences in long-term outcomes between ALND and RT to the axilla after either breast-conserving surgery or mastectomy, with RT associated with less morbidity, according to...
Dr. Moran and Dr. Leitch. Approximately 20% of enrolled patients on both studies were postmastectomy, had clinical N0 disease, and were found to have pathological node-positive disease on SLNB. Based on these results, the panel now recommends that if a mastectomy patient meets the above criteria and has not undergone ALND, then RT should be delivered to include the undissected axilla at risk, with or without treatment of the other nodal basins (RNI).

“As radiation oncologists, we should be moving away from nomogram estimations of additional nodal involvement after SLNB and our requests for surgeons to take patients back to the operating room for completion dissection,” Dr. Moran said. “Instead, we should be shifting our thought process to careful patient selection for replacing ALND with axillary RT, to provide similar therapeutic outcomes while diminishing lymphedema morbidity.”

Dr. Leitch, a surgical oncologist, elaborated on the discussion of this patient subset: “Patients with micrometastases alone in the sentinel node can reasonably forgo further axillary surgery. Those with macrometastases, where adjuvant RT is planned and there is intentional inclusion of the undissected axilla, ALND can be avoided. However, there remains a lot of angst about whether RT should be applied in all these circumstances in patients with positive sentinel nodes.”

Answers may come from the TAILOR RT trial (CCTG MA.39), a randomized, noninferiority phase III trial comparing no regional RT to regional radiotherapy in patients with estrogen receptor-positive, biomarker-low-risk breast cancer (Oncotype Dx Recurrence Score ≤25) (Clinical-Trials.gov identifier: NCT03488693). This study will include patients with breast-conserving surgery or mastectomy. Eligible patients who have undergone ALND may have 1 to 3 positive nodes (macrometastases >2 mm), and those who have undergone only SLNB can have 1 to 2 positive nodes (macrometastases >2 mm). Patients with disease limited to nodal micrometastases are also eligible. “This study will help us decide if we really need to apply radiation to the nodal basins of all patients with positive sentinel nodes,” Dr. Leitch said.

Debates Over RNI

Although RNI clearly decreases the risk of locoregional relapse and distant events in higher-risk patients, the independent contribution of radiation to the internal mammary nodes carries the highest risk for long-term cardiac and lung toxicity, thus its routine inclusion as a component of RNI is debated. Previously, the NCCN Guidelines recommendation was to “strongly consider radiation to the supraclavicular fossa, the undissected axilla at risk, and the internal mammary chain when recommending comprehensive RNI,” according to Dr. Moran.

It has been difficult to demonstrate the independent contribution of individual nodal basins when delivering RNI. Recently, the phase III KROG 08-06 trial sought to determine the independent effect of RT to the internal mammary nodes. Study participants were stratified by N stage and surgery type. Although the study found no significant effect on outcomes, regardless of whether the internal mammary nodes were radiated, an unplanned subset analysis showed inclusion of the internal mammary nodal chain resulted in a 10% improvement in disease-free survival in patients with centrally or medially located tumors (hazard ratio, 0.42; P = 0.03).
Dr. Moran suggested weighing the potential long-term benefits of inclusion of the internal mammary nodes against the potential toxicity to the heart and lungs. However, she added the following comment: “Certainly, in centrally or medially located tumors, where the risk of internal mammary involvement is higher, radiation to the internal mammary should be strongly considered.”

**Locoregional Management After Neoadjuvant Therapy**

The section of the NCCN Guidelines on neoadjuvant therapy has undergone major reformatting. Assessment of complete versus partial response has been replaced with assessment of the ability to undergo breast-conserving surgery. The wording has also been made consistent with previous sections, such as recommending comprehensive RNI in many cases and targeting the undissected axilla for clinical or pathological node-positive disease. The same principles apply to patients undergoing mastectomy, with the updated guidelines specifically stating that for patients with positive nodes after neoadjuvant therapy, the radiation field should include the undissected axilla; for those who have clinical or pathological node-negative disease following SLNB, no postmastectomy RT is needed.

Dr. Leitch described the ACOSOG Z1071 (Alliance) study, which aimed to identify patients who may safely avoid ALND after achieving a pathologic complete response to neoadjuvant chemotherapy. The goal of this study was to determine whether the sentinel node procedure could be safely applied post neoadjuvant chemotherapy in patients with needle biopsy–proven positive nodes pretreatment who had evidence of resolution of nodal metastases by clinical examination.

It was proposed that an acceptable false-negative rate of SLNB after neoadjuvant chemotherapy in this circumstance would be \( \leq 10\% \).

This study included 663 patients with T0–4N1–2M0 disease who underwent SLNB followed by ALND after neoadjuvant treatment. Although the goal of a false-negative rate of sentinel node surgery after chemotherapy of up to 10% was not met (12.6%), further analysis found false-negative results were less frequent in the setting of dual mapping agents (10.8%), examination of \( \geq 3 \) sentinel nodes (9%), and retrieval of the clipped node (6.8%).

Locoregional management standards after neoadjuvant therapy will continue to further evolve, with data expected from Alliance A11202 and NRG NSABP B-51/RTOG 1304 (NCT01872975). “Although the results from these important preoperative therapy trials may change our current treatment paradigms, until then, the existing data suggest that clinical stage at presentation and pathologic node plus disease after NAT appear to be clinically relevant for LRR, and so, if ALND has not been performed, RNI should be strongly considered to cover the undissected axilla,” said Dr. Moran. “The decisions for radiation should not be solely based on pathologic response in the axilla.”

“The NCCN Guidelines update reflects concerns that were raised in the ACOSOG Z1071 trial about the accuracy of SLNB after neoadjuvant chemotherapy,” Dr. Leitch added. For needle biopsy of lymph nodes prior to surgery, clip placement is recommended rather than being listed as “optional.”

**Axillary Staging After Neoadjuvant Endocrine Therapy**

Patients with hormone receptor–positive breast cancer are increasingly receiving neoadjuvant endocrine therapy. There are opportunities in this setting for de-escalated treatment of the axilla, according to Dr. Leitch.

A study of >4,000 patients from Dana-Farber Cancer Institute and the National Cancer Database examined residual tumor burden after neoadjuvant endocrine therapy in patients who underwent SLNB or ALND. In both clinically node-negative and node-positive subsets, survival rates were similar, regardless of axillary staging procedure, with a 5-year overall survival rate exceeding 90% in all categories.

“Although this was a retrospective study, it led the authors to conclude that for patients with clinical node-negative disease who have undergone neoadjuvant endocrine therapy, their axillary management can be similar to up-front surgery. In other words, it’s reasonable to do a sentinel node procedure and manage the findings similarly as in up-front surgery.”

**Expanding Sentinel Node Evaluation in Local Recurrence**

The NCCN Guidelines note that patients with a local breast recurrence after breast-conserving surgery and who had a prior SLNB can consider a repeat SLNB, although its accuracy is unproven. The guidelines also state that the data for attempting SLNB after mastectomy are limited; although it may be considered, there are no data on identification rates or false-negative rates in this setting. Previously, its use was discouraged.

**Principles of RT**

Based on 2 pivotal trials, FAST and FAST-Forward, the panel continues to endorse the FAST regimen of hypofractionated radiation (28.5 Gy delivered as 5 once-weekly fractions) for patients aged \( \geq 50 \) years with tumors \( \leq 5 \) cm and pathological node-negative disease after breast-conserving surgery. Clinicians can also consider ultra-hypofractionated radiation (26 Gy in 5 daily fractions over 1 week), although data beyond 5 years are not available.
Sequencing RT With Systemic Agents

The NCCN Guidelines panel has added a section to address the sequencing of RT with systemic therapy. Although RT is generally delivered after chemotherapy, the only chemotherapy regimen that can be given concurrently with RT is cyclophosphamide/methotrexate/fluorouracil. Capecitabine (a radiosensitizer) and olaparib should be given after RT is completed. Endocrine therapy may be given sequentially or concurrently with RT, although concurrent delivery may compound the acute adverse effects of treatment. Adjuvant HER2-targeted therapy is typically delivered concurrently with RT (with and without endocrine therapy).

Ultrasonography of Lymph Nodes

Dr. Leitch also touched upon this emerging question: How can ultrasonography of the nodes impact clinical decisions about SLNB up-front? “We are now seeing patients who have already had axillary ultrasound and perhaps even a needle biopsy before they see a surgeon,” she said. Furthermore, she noted that with effective neoadjuvant therapies, the rate of positive nodes has declined to approximately 50%. “We need to begin to alter our surgical approaches to respond to this,” she said.

Yong-Hing et al recently proposed an algorithm for managing suspicious nodes on initial ultrasound evaluation. They suggested that any suspicious nodes be biopsied and clipped; for up to 2 suspicious nodes, SLNB may be performed and the clipped node removed. Patients with 1 or 2 pathologically positive nodes should undergo observation or RT, whereas patients with ≥3 positive nodes should undergo ALND. For 3 suspicious nodes on ultrasound and a positive needle biopsy, ALND is recommended, but neoadjuvant systemic therapy can be considered and SLNB performed thereafter.

Not All Patients Want De-escalation

“We have to remember that de-escalation is not always what patients want. Even with an excellent response to chemotherapy, many patients will elect aggressive surgery,” Dr. Leitch noted. A patient may opt for mastectomy to avoid radiation or for peace of mind. The improvements in autologous reconstruction and nipple-sparing techniques have increased the appeal of mastectomy. There are also an increasing number of patients choosing to “go flat” after mastectomy. Surgeons should adapt their techniques accordingly, she said.

This trend has been recognized in the NCCN Guidelines: “The option to undergo mastectomy alone with a surgically optimized closure should be offered to all patients as part of a comprehensive discussion of reconstructive options. Achieving the optimal result in this scenario may require additional procedures beyond the initial mastectomy,” Dr. Leitch advised.

Disclosures: Dr. Moran has disclosed having no relevant financial relationships. Dr. Leitch has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP and Puma Biotechnology.

Correspondence: Meena S. Moran, MD, Yale University School of Medicine, Therapeutic Radiology, 15 York Street, Smilow YNHH, New Haven, CT 06510. Email: meena.moran@yale.edu; and A. Marilyn Leitch, MD, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. Email: marilyn.leitch@utsouthwestern.edu

References

3. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guide-