Locoregional Management of Early-Stage Breast Cancer

Presented by Benjamin O. Anderson, MD, and Janice A. Lyons, MD

ABSTRACT

Locoregional management of early-stage breast cancer has been trending toward less-extensive axillary resections, based on increasing evidence showing that patients with 1 or 2 positive sentinel nodes and/or micrometastases can safely be managed with sentinel node biopsy alone, thereby avoiding complete axillary lymph node dissection (cALND) in the significant majority of patients. Because of the 15% to 20% lymphedema risk associated with cALND, increasing efforts are being made to avoid the procedure when evidence suggests that more limited procedures are safe, as reflected by acceptable locoregional recurrence rates. Axillary radiotherapy (RT) has been shown to be an effective alternative to ALND for patients fitting criteria from the pivotal AMAROS trial: patients with T1/T2 disease and are clinically node-negative, who undergo either breast-conserving therapy or mastectomy. Considerations for RT begin with the question of nodal involvement, with treatment planned accordingly. With more neoadjuvant therapy being used, there are nuances in locoregional management that clinicians must now appreciate, both in terms of ALND and axillary RT.

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Introduction

In the locoregional management of early-stage breast cancer, surgically aggressive procedures are being questioned as more conservative approaches are being shown to provide comparable outcomes with decreased toxicity in selected subsets of patients. The appropriate uses of complete axillary lymph node dissection (cALND) and sentinel lymph node biopsy (SLNB) were discussed at the NCCN 2020 Virtual Annual Conference by Benjamin O. Anderson, MD, Professor of Surgery and Global Health at the University of Washington and Seattle Cancer Care Alliance, and a joint member of Fred Hutchinson Cancer Research Center. Related radiotherapy (RT) strategies were presented by Janice A. Lyons, MD, Associate Professor of Radiation Oncology, and Director, Breast Cancer Services, Department of Radiation Oncology, Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center.

cALND Is Being Used Less

cALND is performed to accurately stage tumors for adjuvant treatment planning while avoiding axillary recurrences in patients who have developed nodal metastases. Its use can limit the extent of nodal irradiation and therefore the risk of radiation-associated toxicity. “Early on, we thought of cALND as a tool for regional disease control, but this comes at a significant cost—primarily, the potential for lymphedema, which is a lifelong problem

that requires daily management.” Dr. Anderson said. “It is for this reason that SLNB evolved in the 1990s. Now the question is: How far can we go with this? We have been actively addressing this at NCCN.”

Dr. Anderson outlined how NCCN stratifies patients on diagnosis:

- Clinically node-negative at diagnosis, with at most 1 or 2 suspicious nodes on imaging, and no preoperative systemic therapy planned.
- Clinically node-positive (≥ 3 positive nodes on imaging or palpable nodes on physical examination at diagnosis), or $\geq T2$ or $\geq N1$ disease and preoperative systemic therapy planned; or T2–4, N1–3, M0 disease.

For patients with clinically node-negative disease, high level evidence supports the use of SLNB as the standard of care based on outcomes observed in NSAPB B-32.¹ This study showed SLNB alone to be acceptable in patients with clinically node-negative disease based on low axillary recurrence rates for both approaches: 0.4% with SLNB and 0.2% with SLNB + cALND. The 10-year update found no differences in disease-free survival (DFS) or overall survival (OS), with a false-negative rate for SLNB of 9.8%, which is under the desired threshold of 10%.^{2,3} This study provided the first pivotal evidence that cALND is not always required.

Other studies have shown SLNB to be associated with fewer complications and excellent outcomes, thus leading to its widespread adoption. The questions have

thus become: Where does cALND fit in the management strategy, and are there situations when cALND can be avoided if the sentinel nodes are positive? Dr. Anderson asked.

Avoiding Axillary Surgery in Node-Positive Disease

In appropriately selected patients who are clinically node-negative but found to have 1 to 2 positive lymph nodes on SLNB, cALND can be avoided with low rates of locoregional recurrence. The ACOSOG Z0011 trial evaluated patients with T1/T2 clinically node-negative disease and 1 or 2 positive sentinel nodes.⁴ This landmark study showed that SLNB alone or SLNB + cALND resulted in “acceptable” nodal recurrence rates (1.5% and 0.5%, respectively) and no difference in DFS or OS between the approaches. “That is why the Z0011 criteria are listed explicitly in the NCCN Guidelines,” Dr. Anderson said.

The IBCSG 23-01 trial evaluated 934 patients with T1–T2, clinically node-negative disease and at least one micrometastasis in the sentinel nodes.⁵ Again, no differences in DFS or OS were found between cALND versus SLNB alone. Disease recurrences in the undissected axilla remained low at <1%. “We now have excellent evidence that when we only see micrometastases in the sentinel node, we have adequate justification for no further axillary surgery,” he commented.

cALND Versus Axillary RT

Axillary RT is also a standard of care based on the results from the AMAROS trial, which evaluated 1,425 patients with T1/T2, clinically node-negative disease and positive sentinel nodes treated primarily with breast-conserving surgery (some had undergone mastectomy).⁶ In the 10-year update, axillary recurrence was rare, with rates of 0.93% for ALND and 1.82% for axillary RT, which were not significantly different.⁷ A highly significant difference was seen, however, in the occurrence of lymphedema, which at 5 years occurred in 29.4% of those in the cALND arm and 14.6% of those the RT arm ($P<.0001$). The authors’ conclusion was that axillary RT can be substituted for cALND in patients fitting the AMAROS criteria: those with T1/T2, clinically node-negative disease who underwent either breast-conserving surgery or mastectomy.

The NCCN Guidelines Panel members added an extra note to address the mastectomy subset: For patients with clinically negative axilla who are undergoing mastectomy and for whom RT is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.⁸ In the mastectomy setting, for patients who were initially clinically node-negative with positive nodes on SLNB and have no prior axillary dissection, RT should

include the chest wall and supraclavicular nodes with or without internal mammary nodes.

Radiation Recommendations for Node-Positive Disease

Dr. Lyons said that considerations for RT begin with the question of nodal involvement. “Thinking through the way we treat patients with node-positive disease, we must first ask how much we think the lymph node regions are at risk, and whether systemic therapy may be sufficient so that we are not required to treat extensive fields,” she said.

For patients with 1 to 3 positive nodes, whole-breast RT with or without a boost to the tumor bed is a category 1 recommendation. Historically, radiation was indicated for patients with ≥ 4 positive nodes; however, recent studies show a benefit for postmastectomy radiation in those with 1 to 3 positive nodes as well.⁹ Based on these findings, radiation to the infraclavicular region, supraclavicular area, and internal mammary nodes (and any other part of the axillary bed at risk) should be “strongly considered.” This is based on data showing that local recurrences are reduced from 30% to 10% with the addition of comprehensive nodal irradiation of these areas, she explained.

In the NCIC MA-20 trial of patients with node-positive disease who were treated with whole-breast RT alone or with comprehensive nodal irradiation (most of whom had breast-conserving surgery, cALND, and systemic therapy), locoregional recurrence risk was small (<7%), although nodal irradiation conveyed an absolute 2.5% improvement in recurrence.¹⁰ This improvement in outcome came with an increased risk for lymphedema, pneumonitis, and dermatitis; however, there was no increase in cardiac toxicity.

In the similar phase III EORTC trial of >4,000 patients (24% had undergone mastectomy), a 2% improvement in locoregional recurrence was observed with the addition of comprehensive nodal irradiation. There was also an improvement in 10-year DFS, distant DFS, and OS, with some small increased risk of lymphedema.¹¹

In the AMAROS trial, researchers evaluated comprehensive nodal irradiation versus axillary cALND in patients with positive sentinel nodes.⁶ DFS was similar, but risk of lymphedema was markedly higher in the ALND arm (28% vs 14%; $P<.0001$). “With these studies, we feel like we should comprehensively treat the nodes, but the question is whether it’s worth the toxicity of doing so for an increase in local control of only a few percentages,” Dr. Lyons offered. “For patients who we know will undergo comprehensive nodal irradiation and who

are clinically node-negative, you should make every effort *not* to do a cALND because their risk for lymphedema goes way up.”

Does Neoadjuvant Therapy Change the Picture?

Dr. Anderson then addressed the nuances involved when using locoregional therapy in the setting of neoadjuvant treatment. For patients with large tumors or more extensive nodal involvement who have not undergone preoperative chemotherapy, the options are axillary dissection level I/II or SLNB if the patient meets all of the Z0011 trial criteria. For the same patients who have received preoperative chemotherapy, treatment options are axillary dissection level I/II if there is residual disease (standard of care) or SLNB if nodes are clinically negative after preoperative therapy. “The latter is a category 2B recommendation. There was disagreement among the panelists as to limiting treatment to SLNB when you know the nodes were positive before starting neoadjuvant treatment,” he said.

The 4-arm SENTINA trial concluded that SLNB is reliable before neoadjuvant chemotherapy is given.¹² But after neoadjuvant chemotherapy and with conversion from clinically positive to clinically negative, SLNB has a high false-negative rate (24%) when 1 node is removed. This rate does drop, however, to <10% when ≥ 3 sentinel nodes are removed, and to 8.6% if SLNB uses dual tracers (radiocolloid and blue dye).

The subsequent Z1071¹³ and SN FNAC¹⁴ trials provided similar supportive data for these findings, assuring clinicians that false-negatives can be kept below the 10% safety threshold. “Putting these together—the removal of ≥ 3 sentinel nodes and the use of dual technology—argues for doing SLNB *after* the neoadjuvant chemotherapy when there seems to be clinical resolution of disease,” Dr. Anderson said.

Axillary Staging of More Extensive Disease

Patients with clinical stage N3 disease with extensive nodal disease are excluded from randomized trials evaluating cALND in the neoadjuvant setting. The question is whether N3 disease before neoadjuvant chemotherapy demands cALND after chemotherapy, even after complete resolution seems likely by clinical examination and imaging.

The argument in favor of cALND for these patients is that the false-negative rate and axillary recurrence rates for SLNB in the setting of N3 disease are unknown. On the other hand, cALND does not involve the removal of supraclavicular, level III, or internal

mammary nodes, all of which are managed with RT and do not require surgery. Prior studies of radical nodal extirpation (ie, extended radical mastectomy) have never shown superior regional disease control, he said.

Many NCCN Member Institutions report that they are continuing to use cALND in this population, but some are transitioning away from this practice. “We don’t have uniformity and we need more data,” Dr. Anderson commented.

RT After Neoadjuvant Therapy

There is strong retrospective data suggesting that patients with stage III disease who achieve a pathologic complete response after neoadjuvant therapy still warrant RT, with a significant reduction in the risk of locoregional recurrence, distant metastasis-free recurrence, and death.¹⁵ For patients with clinical stage I or II disease, however, there does not appear to be a benefit, Dr. Lyons noted. With the emergence of better systemic therapies, it is possible there are subsets of patients with clinical stage III disease who have achieved excellent response to neoadjuvant chemotherapy, and whose RT can be limited to the breast and not include the nodes, Dr. Lyons added. She emphasized that shared decision-making is critical in situations such as this. “The patient may want to accept a higher risk of locoregional recurrence versus higher risk of toxicity, such as lymphedema,” she said. “But outside of a clinical trial, we would not recommend withholding RT for patients with clinical stage III disease achieving a pathologic complete response in the nodes.”

She also touched on the possibility of omitting RT after breast-conserving therapy in low-risk, hormone receptor-positive patients aged ≥ 65 years with tumors ≤ 3 cm. In the PRIME II trial of such patients, radiation provided a local advantage that did not translate into an OS benefit.¹⁶ Reassuringly, she added, local recurrence rates were quite low (3.2%) for patients whose estrogen receptor expression was high ($>20\%$).

For patients who undergo a second lumpectomy (for local recurrence or new primaries), a reasonable option is partial breast reirradiation, based on the recent RTOG 1014 that found DFS and OS to be 95% at 5 years.¹⁷ “For patients who are very motivated to keep their breasts, this can be an effective alternative to mastectomy,” she commented.

Disclosures: Dr. Anderson has disclosed that he received a consulting fee from Allergan and was a scientific advisor for UE LifeSciences. Dr. Lyons has disclosed that she has no relevant financial relationships.

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