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CLINICAL TRIALS (JE LANG, SECTION EDITOR)

A Radiation Oncologist's Guide to Axillary Management in Breast Cancer: a Walk Through the Trials

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Abstract

Purpose of Review The axilla is the most common site for breast cancer nodal metastases. Aggressive management includes axillary lymph node dissection (ALND), radiotherapy, and systemic therapy, but carries the risks of lymphedema and "over-treatment". We review the clinical trials that led to de-escalation of axillary management and their nuances that are often overlooked.

Recent Findings With the rise of sentinel lymph node biopsy, several trials conclude that ALND can be omitted in specific populations. However, the subtleties in those trials, such as the role of chemotherapy and radiotherapy, have yet to be clarified. These discussions carry forward into the era of neoadjuvant chemotherapy, where ongoing trials investigate who needs ALND and/or radiation.

Summary This review examines the clinical trials that form the standard of care, and highlights why axillary management is individualized today.

Keywords Axilla · Radiotherapy · Breast cancer · Axillary lymph node dissection · Sentinel lymph node biopsy · Lymph node metastasis

Introduction

In the early 2000s, survival rates for breast cancer patients were excellent—approximately 95% 5-year disease-specific survival for those diagnosed at a localized stage and 80% for those with loco-regional spread [1]. At that time, decisions in breast cancer radiation oncology were relatively straightforward. Tangent fields covered the breast or chest wall. Patients with tumors greater than 5 cm and/or found to have four or more positive axillary lymph nodes on axillary lymph node dissection (ALND) received radiation to a "third field," the supraclavicular/axillary apex region (SCV). This SCV region was, and still is difficult to manage surgically, due to proximity of the axillary vessels and the brachial plexus. Internal mammary radiation was performed at the discretion of the radiation oncologist. This variation existed because coverage of the internal mammary region contributed significantly to cardiac morbidity, while failures in the internal mammary region were infrequent [2–7]. The concern for cardiac toxicity from the internal mammary field irradiation was compounded by the use of cardiotoxic doxorubicin and introduction of trastuzumab (approved for use in the USA in 1998).

Encouraged by excellent outcomes, clinicians drew their attention to reducing toxicity of multimodality treatment—starting with the axilla. Several prospective studies reported in the 1990s and early 2000s questioned the therapeutic advantage to ALND [8–13]. Axillary surgery increased the risk for lymphedema, with the highest risk (greater than 25% at 5 years) occurring in those receiving a combination of ALND with nodal radiation and/or chemotherapy [14•]. Efforts to de-escalate axillary surgery were well received. Physicians in Europe and the USA eagerly enrolled patients on the Z0011 and AMAROS trials which convincingly demonstrated that a full ALND was unnecessary in select patients with early-stage

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breast cancer and positive sentinel lymph nodes (SLN) [15–17]. When results from AMAROS and Z0011 were first reported in 2010–2011, medical oncologists still relied on the number of axillary lymph nodes involved on ALND to make decisions regarding systemic therapy [15, 16, 18]. By 2015, however, genomic profiling was in full bloom, and the number of positive axillary lymph nodes withered as a decision tool for systemic therapy [19–21, 22•, 23, 24••].

In contrast, radiation oncologists were, and are still, accustomed to using the number of pathologically involved axillary lymph nodes to decide on radiotherapy targets. This decision strategy strongly relies on an "adequate" ALND, traditionally held at greater than ten lymph nodes removed. To accommodate the surgeons' move towards sentinel lymph node evaluation alone (with fewer than 6 and typically only 1–3 lymph nodes removed), radiation oncologists turned to mathematical models to predict who would have "had" four or more positive nodes in the axilla, based on percentage of involved SLN and T stage [25–31].

Clinical trials evaluating regional nodal irradiation (MA.20, EORTC 22922-10925, and the EBCTG meta-analysis of postmastectomy radiation trials) seemingly eased the decision tree for radiation oncologists, demonstrating that even patients with 1–3 lymph nodes could be considered for regional nodal irradiation (RNI) [32–36]. Unfortunately, instead of de-escalating axillary management, conclusions drawn from these studies potentially increased the use of comprehensive RNI (to the ipsilateral axillary, SCV, and internal mammary regions). Escalation of RNI would increase risks of lymphedema and cardiopulmonary toxicity, and negatively impact reconstruction options for patients—especially patients with smaller tumors (cT1–2 tumors, less than 5 cm) and 1–3 lymph nodes positive, who previously would not have received SCV radiation and in the post-mastectomy setting would have avoided radiation altogether [37, 38, 39•]. Suspecting that not every patient with 1–3 lymph nodes positive needs SCV and internal mammary nodal irradiation, a tailored approach to radiation fields has been proposed using nomograms [29–31, 40]. In this approach, a SCV field would be strongly considered only if the risk of four or more positive nodes was high (that threshold to be determined), otherwise only low-mid axillary nodal coverage would be provided unintentionally by standard tangent fields or intentionally with high tangent fields [40].

Trials in neoadjuvant chemotherapy (NAC) further complicated management. Traditionally, with up-front surgery, radiation management decisions were based on initial tumor size, nodal status, and other clinicopathologic factors. When patients are treated with NAC followed by surgery, decisions regarding subsequent radiation management become more complex, with less robust data [41–43]. Fortunately, in patients with initial cN0 disease, SLN biopsy (SLNB) after chemotherapy is as accurate for axillary staging as SLNB prior to chemotherapy and reduces the number of positive SLN [44]. The rate of lower SLN positively results in lower ALND rates. Although NAC reduces mastectomy and ALND rates, there is still concern for increased local failure in patients with larger tumors downsized and treated with breast conservation [45]. Appropriate management of patients with initial node positive disease but complete pathological response after NAC have yet to be defined. At this time, standard of care is to provide axillary nodal radiation, although this is being evaluated in clinical trial NSABP B-51 (opened in 2013) [46].

The following summarizes the clinical trials of axillary radiation that affect our practice today and in the near future. An introduction to radiation fields is also provided for the non-radiation oncologists and radiation oncologists in-training. A basic understanding of radiation fields is critical to evaluation of the trials discussed and the conclusions drawn. These trials highlight the improvements made in breast cancer nodal management and expose the many questions yet to be answered.

Introduction to Radiation Fields for Breast Cancer

Modern three-dimensional computerized tomography-based treatment planning optimizes target coverage while minimizing dose to critical normal structures such as the lung and heart. With conventional fractionation schedules (50 Gy in 25 fractions), common restrictions limit the mean heart dose to 4 Gy and 20% of the ipsilateral lung to 20 Gy. In practice, the mean heart dose is typically less than 2.5 Gy for left-sided tumors, and less than 1 Gy for right-sided tumors. With hypofractionation schedules (e.g., 42.56 Gy in 16 fractions), the restriction on pulmonary dose (to 20% of the ipsilateral lung) is tightened to 16–18 Gy, and some studies (such as Alliance trial A221505) tighten the restriction on cardiac mean dose to 3 Gy [47]. While hypofractionated radiation is accepted as non-inferior to conventional fractionation after breast conserving surgery (BCS) with respect to recurrence, survival, and cosmesis [48–51], the question remains whether we can radiate the axillary apex and SCV region with the same compacted schedule without causing untoward side effects such as fibrosis, brachial plexopathy, and lymphedema. The Alliance A221505 trial (opened in 2018), which randomizes postmastectomy patients with planned reconstruction to a standard or hypofractionated regimen, will be important in answering this question [47].

The most common treatment position for external beam radiation therapy is supine. In the supine position, tangential beams are directed at the most likely site of recurrence, the chest wall after mastectomy or breast after BCS. The medial and lateral tangent beams are angled as a unit, to avoid entry and exit dose to the opposite breast and, if left-sided, to reduce dose to the heart. Another benefit of prioritizing the opposite

breast and heart, is that more of the low axilla is irradiated [52–54].

The superior border of the tangential beams is usually 1.5–2 cm above the breast or at the inferior aspect of the clavicular head. Standard tangents partially cover axillary level I and low level II (Fig. 1a, b). Depending on individual anatomy, more than 50% of level I and 20–30% of level II nodes usually receive 95% of the prescribed radiation dose with standard tangents [55–58]. A third field, anterior oblique field (or "SCV field"), is added to cover the axillary level II and III nodes, as well as medial SCV nodes (Fig. 1**c**). Current studies typically call for 45 Gy coverage to 95% of the axillary bed. Coverage of the deeper axillary bed may result in "hot spots" anteriorly, so some radiation oncologists will include a fourth field, a "posterior axillary boost" or PAB, to cover the posterior axilla and balance dose. The specific effect of low dose PAB on lymphedema risk and mobility with de-escalated surgery is unclear [59, 60]. As an alternative to using standard tangents, coverage can increase by using "high tangents", where the field is extended superiorly so that the superior border is below the humeral head (Fig. 1d). However, with high tangents alone, the coverage is inadequate for complete axillary coverage [55, 57].

The field descriptions above do not apply to patients treated in the prone position (in which significantly less of axillary level I nodes would be in the field compared with supine) and partial breast irradiation treated with either brachytherapy or external beam radiotherapy. Treating in the prone position or partial breast irradiation is more suitable for node-negative patients treated with BCS and with lower risk disease.

It remains a challenge for clinicians to separate the risks and benefits of axillary nodal irradiation from that of regional nodal irradiation. Studies supporting use of a SCV field also extended radiation coverage medially to include the internal mammary lymph node bed. When the radiation field is extended superiorly to include the undissected axilla, an additional 10% of the ipsilateral lung may be irradiated. When the target is extended medially to include the ipsilateral internal mammary region, another additional 5–10% of the ipsilateral lung may be irradiated (depending on length treated), and additional cardiac dose incurred, as well. When a treatment plan cannot meet acceptable standards based on dose constraints, clinicians must use their judgment to weigh the risks and benefits of a plan. For example, if the risks of pneumonitis and cardiac toxicity are significant for an individual and risk for internal mammary node recurrence is low, then a clinician may decide not to treat the internal mammary nodes. Higher cardiac and pulmonary doses may be acceptable in patients with higher risks of loco-regional failure. Within the recommended range, contours and fields are individualized to circumstance, balancing anatomical and technical constraints with urgency for coverage.

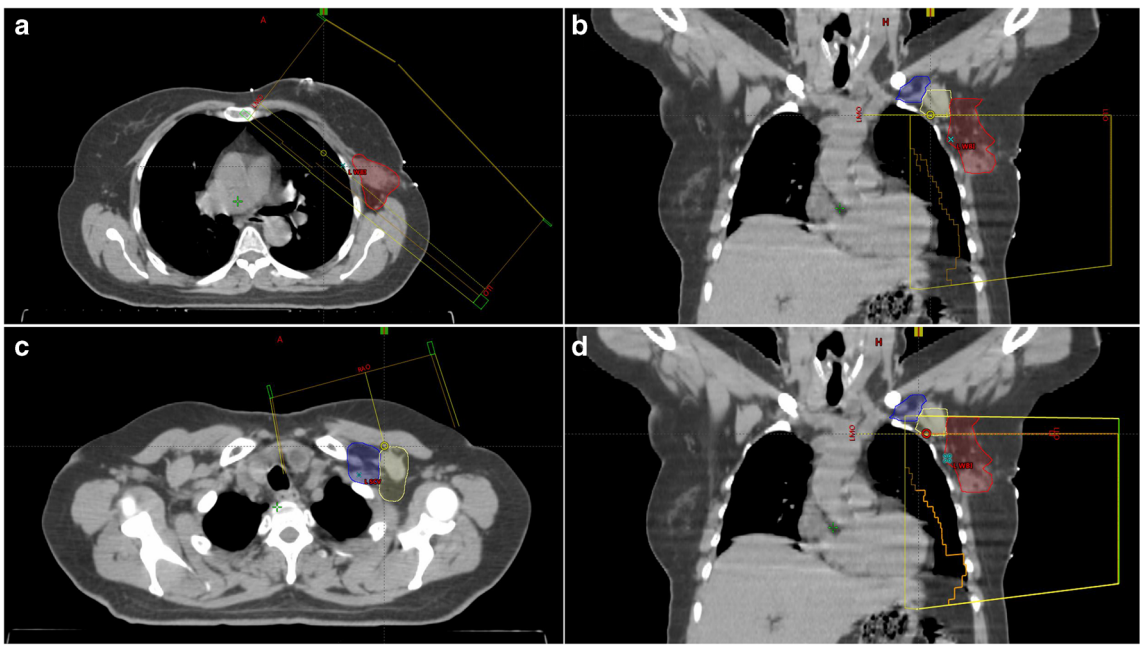

Fig. 1 Coverage of axillary lymph nodes with different breast radiation fields. Standard tangent fields coverage in axial (**a**) and coronal views (**b**). Standard anterior oblique or "supraclavicular/axillary apex field (SCV)" coverage (**c**). "High" tangent fields coverage (**d**). Axillary level I is shown in red, level II in yellow, and level III in blue. In this individual, standard tangent fields cover most of axillary level I and a small portion of level II. The SCV field is often added/matched to standard tangent fields in order to complete treatment of higher axillary level II and axillary level III lymph nodes. Alternatively, if no SCV field is used, the superior border of the tangent fields may be elevated to cover more of level II than would be covered with standard tangents alone.

Early-Stage Breast Cancer: in the Absence of Neoadjuvant Systemic Therapy, Who Can Avoid ALND?

The landmark NSABP B-04 trial (1971–1974) questioned the necessity of ALND by comparing radical mastectomy, which involves an ALND, to total mastectomy. Among patients with clinically node-negative (cN0) disease, there were no significant differences in survival between surgical modalities. Among patients with clinically node-positive (cN+) disease, patients receiving total mastectomy also received radiotherapy, and again, there were no significant differences in survival between total and radical mastectomies. The trial established that not all undissected nodal disease resulted in disease recurrence [10, 61, 62]. With that said, in patients with biopsy proven cN+ disease, ALND is still standard of care. SLNB can be considered in select cases where the nodal disease burden is small (image-detected but not apparent on exam) and radiotherapy is anticipated.

Historically, in the absence of an ALND, false negatives in cN0 disease were a concern. The false-negative rate of cN0 disease in the NSABP B-04 trial was 40% [61], although this rate is likely lower in the era of modern imaging. About three decades after the NSABP B-04 trial, SLNB offered a solution for nodal evaluation without compromising survival while causing less morbidity than ALND [63–65]. The NSABP B-04 trial and advent of SLNB paved way for the landmark Z0011 and AMAROS trials, re-evaluating the role of ALND in patients with cT1-2N0 (≤ 5 cm) breast cancer and positive SLN.

The ACOSOG trial Z0011 (1999–2004) was a phase III non-inferiority trial randomizing patients undergoing BCS and tangential whole breast radiation to completion of ALND or observation. Approximately 97% of patients received adjuvant chemotherapy and/or hormonal therapy at the discretion of the treating physicians. For the primary endpoint, the 5- and 10-year overall survival (OS) were non-inferior in the SLNB-alone group (92.5% and 86.3%, respectively) compared with the ALND group (91.8% and 83.6%, respectively) (non-inferiority p=0.008 and p=0.02, respectively) [15, 66, 67••]. Similarly, the SLNB-alone arm had non-inferior disease-free survival (DFS) and local recurrence at the 5- and 10-year time points [15, 16, 66, 67••, 68]. The cumulative incidence of nodal recurrence in the ipsilateral axilla were also similar between arms (0.5% versus 1.5%, $p = 0.28$) [68]. While the OS, DFS, and local and regional recurrences were similar between treatment groups, the rate of wound infections, axillary seromas, and paresthesia were higher for the ALND group than the SLNB-alone group (70% versus 25%, $p \leq 0.001$) [69].

The AMAROS trial (2001–2010) was a similar phase III non-inferiority trail randomizing patients to completion of ALND or axillary radiotherapy (50 Gy to axillary levels I, II, and III). Unlike the Z0011 trial, AMAROS included women undergoing BCS and breast radiation (82%) or mastectomy (18%). Most of the patients (90%) received some form of adjuvant systemic therapy. The 5- and 10-year axillary recurrence (primary endpoint) were similar between ALND (0.43% and 0.93%, respectively) and axillary radiotherapy (1.19% and 1.82%, respectively) (p=0.37) [17, 70••]. There were also no significant differences in survival between treatment groups at 5 and 10 years. The 5- and 10-year OS were 93.3% and 84.6% in the ALND, and 92.5% and 81.4% in the axillary radiotherapy group ($p = 0.34$ and 0.26, respectively) [17, 70••]. While survival and recurrences were similar between groups, lymphedema was more common in the ALND group compared with radiotherapy at 1, 3, and 5 years (5-year rate 23% versus 11%, $p < 0.0001$) [17].

Despite the low recurrences in both treatment arms, it should be noted that additional axillary radiation was allowed in the ALND arm if 4 or more nodes were involved. The trial cannot evaluate if combined ALND and radiation improved local control or survival over either modality alone in patients with high axillary disease burden. One could argue that ALND offers a diagnostic benefit that allows for multimodality treatment of the axilla. On the other hand, one might argue that the combination of both modalities in the axilla leads to greater side effects (e.g., lymphedema) that could have been avoided with radiotherapy alone.

The Z0011 and AMAROS trials demonstrated that the omission of ALND in patients with positive nodes on SLNB did not compromise survival or recurrence outcomes. We emphasize that the majority of patients received radiotherapy and systemic therapy. While axillary radiotherapy was not explicit in the Z0011 trial, tangents for whole breast irradiation would have likely included the low axilla. In addition, half of the patients received radiation with high tangent fields, which would have included level I and low level II, and 15% had an additional SCV field [71]. In other words, most of the observation group in Z0011 received some axillary radiation.

In both trials, about a third of the ALND group (27.3% in Z0011 and 33% in AMAROS) had additional lymph nodes involved after the SLNB [15, 17]. It is likely that a similar portion of patients receiving SLNB without ALND had residual undissected axillary metastases. Because most patients (> 90%) in both trials received systemic therapy (about 60% receiving chemotherapy), it is unclear if the adjuvant systemic therapy, axillary radiotherapy, or combination of both treated the residual nodal disease not removed during surgery.

In cN0 disease but with positive nodes on SLNB, ALND is not recommended if patients will receive axillary radiotherapy and systemic therapy based on Z0011 and AMAROS trials. In addition to providing no benefit in survival or recurrence rates, ALND resulted in worse lymphedema and paresthesia [17, 69, 72]. The conclusions from Z0011 and AMAROS should not be extrapolated to patients treated with partial breast irradiation or prone techniques, where less of the axilla would be treated.

Z0011 and AMAROS trials are supported by other prospective studies in which the recurrence in the undissected axilla was < 1% [72, 73]. The IBCSG 23-01 (2001–2010) was a similar phase III non-inferiority trial randomizing patients with only micrometastatic SLN disease to completion of ALND or observation. Most patients received BCS with some form of radiotherapy, while 9% received mastectomy. Like Z0011, at least 95% received some form of systemic therapy. The 5-year DFS were similar between the two treatment groups, but long-term lymphedema and neuropathy were more frequent and severe in the ALND group. Unlike Z0011 and AMAROS, 22% of patients in the no ALND arm received no radiation or only partial breast radiation (negligible radiation to the axilla) [72]. This raises the risky but interesting proposition that axillary radiotherapy may be unnecessary in low burden/micrometastatic axillary disease on SLNB in patients receiving systemic therapy, and warrants further investigation.

Several limitations to Z0011, AMAROS, and IBCSG 23-01 have been discussed and led to other clinical trials evaluating axillary management. The SERC trial (opened in 2012) is an ongoing phase III non-inferiority trial randomizing patients to ALND or SLNB and has greater inclusion criteria than the Z0011 trial. Thus far, SERC includes 289 patients non-eligible for Z0011, and also includes a greater percentage of post-mastectomy patients, who were underrepresented in AMAROS and IBCSG 23-01 and not at all represented in Z0011 [74]. The SERC trial will hopefully corroborate the preceding trials with greater external validity.

Other ongoing trials investigate de-escalation of axillary surgery. In patient with cN0 disease evaluated by ultrasound, the Italian SOUND study (opened in 2012) randomizes patients to SLNB versus no surgical axillary staging (i.e., no SLNB) [75]. Similarly, the German INSEMA trial (opened in 2015) evaluates (1) SLNB versus no surgical axillary staging for patients with a negative SLNB, and (2) ALND versus no further surgical intervention for patients with a positive SLNB [76]. In cN+ patients, the extent of axillary surgery is being investigated in the multicenter randomized trial TAXIS (opened in 2018). TAXIS randomizes cN+ patients to tailored axillary surgery (TAS, defined by SLNB in combination with selective removal of palpable disease and initially biopsy-proven and clipped lymph node metastases) and RNI of the full axilla versus ALND and RNI of the undissected axilla [77]. The investigators of TAXIS hypothesize that non-palpable residual disease in the axilla after TAS will not progress to recurrence, as suggested by Z0011, AMAROS, and IBCSG 23-01.

Further de-escalation of axillary management in patients receiving adjuvant systemic therapy are being evaluated in two trials in Europe, the Italian SINODAR ONE (opened in 2015) [78] and the English POSNOC (opened in 2015) [79]. The SINODAR ONE and POSNOC are exciting trials to follow Z0011 and AMAROS, as they set out to clarify whether adjuvant systemic therapy without axillary radiation is enough to treat residual undissected nodal disease.

Neoadjuvant Chemotherapy: Can We De-escalate Multimodality Therapy in the Axilla?

NAC offers the opportunity for downstaging disease without worsening survival [80–83]. With initial cN0 disease and no evidence of nodal disease after chemotherapy, SLNB of the axilla is sufficient [44]. In the setting of initial cN+, ALND is indicated, although SLNB can be considered following axillary restaging. Results from three prospective studies (ACOSOG Z1071 [84–86], SENTINA [87], and SN FAC [88]) support SLNB after NAC in patients with initial cN1 disease if (1) dual mapping with 99 m-technetium and a blue dye is used, (2) more than two SLN are removed, and (3) a clip is placed in the positive node with successful retrieval on SLNB. For further review of SLN evaluation following NAC, we direct readers to the review from Mamounas et al. [89]. Following surgery, current standard of care involves radiation based on the pre-chemotherapy disease. RNI, which includes the axilla, would be considered for cT3N0 disease and stage III (AJCC 8th edition) disease regardless of response to chemotherapy.

In the spirit of trying to de-escalate multi-modality treatment and reduce complications, several trials are open to clarify the role of radiation after NAC. NSABP B-51 (opened in 2013) evaluates radiation in the setting of pathologic complete response (ypN0) in the axilla after NAC [46]. The trial randomizes patients with cT1-3N1, ypN0 breast cancer to no RNI or RNI. If patients received BCS, they would receive adjuvant whole breast radiation with or without RNI. Patients receiving mastectomy would receive no further radiation or radiation to chest wall with RNI. This bold omission of radiation is based on analysis from NSABP B-18 and B-27 trials (NAC trials) which showed low nodal recurrence in patients with initial cN+ disease and ypN0 responses (range 0–2.4% in the post-BCS population and 0–8.1% in the post-mastectomy patients) [90]. While the number of patients with cN+ disease and ypN0 response in these trials is too low to change standard of care, it justifies prospective trials de-escalating adjuvant radiation in this setting.

In the setting of positive SLN after NAC, the ALLIANCE A11202 trial (opened in 2013) evaluates the omission of ALND [91]. The trial randomizes cT1-2N1 patients with ypN+ on SLNB to complete ALND with radiation to the undissected regional nodes or RNI without ALND. As previously discussed, axillary surgery is the greatest risk factor for lymphedema, and that risk increases with the addition of radiation [14•]. The risk further increases with additional chemotherapy. By omitting ALND following chemotherapy and

preceding radiotherapy, this trial may have a big impact on reducing the co-morbidities associated with axillary treatment.

Outcomes from ACOSOG Z1071 (2009–2011), which enrolled women with cT0-4N1-2 breast cancer treated with NAC, support the underlying principles behind NSABP B-51 and A011202. In this single-arm trial evaluating SLNB, radiation was given at the discretion of the treating physicians. Although data is subject to selection bias, the omission of post-mastectomy radiation or RNI was associated with higher risk of locoregional relapse in patients with residual ypN+ disease but not in patients with ypN0 [42]. In patients with triple negative disease, there was a trend towards higher locoregional relapse rates in patients who did not receive regional nodal or post-mastectomy radiation, but it was not statistically significant [42]. Until results of NSABP B-51 and Alliance A011202 are available, node-positive triple negative disease should be treated aggressively despite response to NAC.

Conclusion

While the trials discussed above will elucidate which clinical scenarios may benefit from axillary management, they have yet to incorporate tumor biology into their main focus. Subsequent analysis from the chemotherapy trial NSABP B-28, which prohibited postmastectomy radiation and RNI in post-BCS patients, demonstrated that 10-year locoregional recurrence only exceeded 10% for patients with 4 or more positive lymph nodes and intermediate or high Oncotype DX scores [92••]. The study suggests that genomic profiling could potentially identify a favorable subset of patients for whom the role of radiotherapy could be revisited. This concept is being evaluated in the recently initiated TAILOR RT (CCTG MA.39) (opened in 2018), which compares RNI with no RNI in patients with ER+ breast cancer, 1–3 positive axillary lymph nodes, and Oncotype DX scores less than 18 [93]. The trial is a major milestone for radiation oncology in using personalized breast cancer biology in decision-making.

Clinicians are always looking for portions of the population that may not need further axillary management, such as patients with minimal axillary disease or favorable tumor biology, and to reserve aggressive nodal management for those who need it the most. The upcoming trials discussed will hopefully streamline treatment decisions regarding axillary management.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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