Point–Counterpoint Review

Cancer Research

Counterpoint

The Need for Axillary Lymph Node Dissection in T1/T2 Breast Cancer Surgery

See Point and Reply by Morrow, p. 7151 and p. 7161

Michael S. Sabel

Abstract

For breast cancer patients, the role of the axillary lymph node dissection (ALND) in the management of clinically node negative breast cancer patient has shifted from routine, to selective, to increasingly rare. With the publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial results, some are ready to announce the time of death of this procedure. However, many questions remain regarding the design and statistical interpretation of the study, the treatments the patients actually received, and its applicability in clinical practice in light of other studies concerning regional management. Thus, the reports of the ALND's death may be greatly exaggerated. Careful acknowledgement of the study's strengths and shortcomings, and more recent trial data, suggest that although ALND may be safely avoided in a subset of sentinel lymph node positive, Z0011-eligible patients, others may require multidisciplinary review and consensus, and a careful conversation with the patient, before deciding it is not necessary. *Cancer Res; 73(24); 7156–60. ©2013 AACR.*

Introduction

The role of the axillary lymph node dissection (ALND) for breast cancer patients has long been debated. The morbidity of the procedure, specifically the risk of lymphedema, has long been troubling to both patients and physicians, particularly in the face of decreasing importance when making adjuvant systemic therapy decisions, and the absence of a demonstrable survival benefit. This is not a new controversy; one of the first prospective randomized trials in breast surgery was the National Surgical Adjuvant Breast and Bowel Project's (NSABP) B-04 protocol, which compared mastectomy with ALND to mastectomy alone to mastectomy with axillary radiation (1). First reported in 1977, this trial showed no benefit with respect to disease-free survival (DFS), relapse-free survival, or overall survival (OS). Despite this, ALND remained standard of care, primarily because the information was critical for adjuvant therapy decisions. With the introduction of sentinel lymph node (SLN) biopsy and the demonstration of its accuracy and safety in the ALMANAC and NSABP B-32 trials, it became evident that this prognostic information could be gained by less morbid means, and the ALND disappeared for SLN-negative patients (2, 3).

Although it remained standard of care for SLN-positive patients, the primary argument for ALND was for regional control, a concept buoyed by (i) the findings of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) on the importance of locoregional control on distant-disease free and OS (4) and (ii) the observation that 40% to 60% of patients with a positive SLN had additional positive nodes when they returned for a completion ALND (5). Alternatively, the increasing use and efficacy of adjuvant chemotherapy, hormonal therapy, and radiation called into question the importance of the completion ALND on providing regional control. This led to the American College of Surgeons Oncology Group Z0011 trial. Women undergoing lumpectomy and whole breast radiotherapy who had an H&E positive SLN were randomized to ALND versus no further axillary surgery. Only women with cT1-T2 tumors and no more than 2 positive SLN were included. At 6.3 years' follow-up, there was no significant difference in OS (91.9% vs. 92.5%) or locoregional recurrences (4.1% vs. 2.8%). Despite the fact that additional positive axillary nodes were identified in 27% of the patients undergoing ALND, the regional recurrence rates were quite low in both groups (0.5% vs. 0.9%).

Although these results seem somewhat definitive and provide strong support for the abandonment of the ALND for Z0011-eligible patients, there are several concerns regarding the design, accrual, and data collection (6). The trial was closed early with less than 50% of the targeted 1,900 patients, primarily because accrual was quite slow and there was a higher than expected survival in the pooled data from the 2 groups. Both of these suggest a selection bias that is discussed later. Also of concern is the missing or inaccurate data, a problem that is magnified in the context of the low accrual. There were 43 (5%) women who did not receive the assigned treatment. Several patients in the no ALND arm actually had negative SLN (7.0%). Many women in both groups were lost to follow-up (21% in the ALND arm and 17% in the no ALND arm), and 18%

Author's Affiliation: University of Michigan Comprehensive Cancer Center, Michigan

Corresponding Author: Michael S. Sabel, 3304 Cancer Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109. Phone: 734-936-4392; Fax: 734-647-9647; E-mail: msabel@umich.edu

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of the ALND arm are missing data on the number of positive nodes.

In their Canadian Association of General Surgeons and American College of Surgeons (CAGS and ACS) evidence-based review of the Z0011 trial (6), Latonsinsky and colleagues state that because of the methodologic limitations of Z0011, "the standard of care following a positive sentinel node 'may' still be an ALND." However, although the conversation tends to focus on the Z0011 trial, it is important to note that within the past 3 years there have actually been three other important studies examining the role of surgery and radiation on regional control in breast cancer. The first of these is the International Breast Cancer Study Group (IBCSG) 23-01 trial that was very similar to Z0011, however it was limited to patients with micrometastatic ($\leq$2 mm) disease within the sentinel node (7). Although breast-conserving surgery was not mandated, only 9% of patients underwent mastectomy. Regional recurrence was <1% for the ALND arm and 1% for the no ALND arm, with no differences in DFS, cumulative incidence, or OS.

At the 2013 ASCO meeting, the results of the European Organization for Research and Treatment of Cancer (EORTC) AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial were presented (8). Over 1,400 cT1-T2 patients with a positive SLN (micro- or macrometastasis) were randomized to ALND versus axillary radiation. There was no difference in 5-year OS or DFS. There was a significant decrease in lymphedema with radiation, but a nonsignificant trend toward decreased shoulder mobility.

These two studies focused on less aggressive axillary management for subsets of SLN positive patients. In contrast, the NCIC-CTG MA.20 trial, presented at the 2011 ASCO meeting, focused on more aggressive regional management, in the form of regional nodal irradiation (RNI; ref. 9). Similar to the Z0011 trial, this study was also limited to patients undergoing breast conserving surgery, but included high risk node-negative as well as node-positive patients. Over 1,800 women were randomized to either undergo whole breast irradiation, or whole breast irradiation plus RNI, which included radiation of the internal mammary, supraclavicular, and high axillary lymph nodes. With a mean follow-up of 62 months, the addition of RNI was associated with an improvement in isolated locoregional DFS (94.5% vs. 96.8%, HR = 0.59, $P = 0.02$), distant DFS (87.0% vs. 92.4%, HR = 0.64, $P = 0.002$), DFS (84.0% vs. 89.7%, HR = 0.68, $P = 0.003$), and a trend toward improvement in OS (90.7% vs. 92.3%, HR = 0.76, $P = 0.07$). This data supports prior prospective, randomized studies linking a reduction in regional recurrence with improved survival (10–12).

Obviously these studies all ask and answer different questions and included slightly different populations. However, there are three messages that we can take away and consider as we weigh the applicability of the Z0011 trial.

1. For patients with regional metastases, regional control, however this is accomplished, seems to decrease distant recurrence and improves OS.
2. For patients undergoing breast conservation surgery (BCS) with micrometastatic ($\leq$2 mm) disease in their SLN, completion axillary lymph node dissection does not seem to improve regional control and may be safely omitted.
3. For patients with micrometastatic or macrometastatic disease in their SLN, axillary radiotherapy is as effective as ALND in achieving regional control, with less toxicity.

Was the axilla truly untreated?

One of the most perplexing problems is whether or not the Z0011 trial was truly a study of axillary treatment versus no axillary treatment or in reality a study very similar to AMAROS, a trial comparing ALND to axillary radiotherapy. The Z0011 protocol expressly prohibited direct regional irradiation. In nearly half of cases, standard whole breast radiation encompasses axillary levels I and II (13). This in itself may explain the very low regional recurrence rate despite the presence of residual disease in the nonsentinel nodes and is why we must be very careful about applying the Z0011 results to patients not receiving standard whole-breast radiation. But beyond that, modifications of the field borders could allow for a more extensive coverage of levels I and II, without specifically using an additional axillary field (14, 15). More concerning is the possibility that several radiation oncologists, who were not co-investigators or in many cases not aware of the protocol specifics, went beyond adjustments in tangential field borders and directly treated the axilla in patients who had not had a complete ALND. A major concern is that Z0011 did not track that information and so there is no way to know to what degree the axilla was treated by radiation, which we now know from AMAROS is equivalent to surgery. A review of the radiation treatment plans is on-going, and those results are desperately needed to know how to best incorporate the Z0011 results into clinical practice.

What about the patients with micrometastatic disease in the SLN? Could radiation be responsible for the IBCSG results? It is possible, as the authors do not describe reviewing the radiation fields. However, in this study, 9% had mastectomy and of the BCS patients, 3% had no radiation and 22% had ELIOT partial breast irradiation, which would not sterilize the axilla. Thus, the evidence is slightly stronger that radiation oncologists do not need to adjust their tangents or specifically target the axilla when planning treatment for patients with micrometastatic disease in the SLN who did not undergo ALND.

One dilemma is that these studies are often interpreted through our own particular vantage point—very similar to the Indian parable of the blind men and the elephant, where 4 blind men touch a different part of the elephant to learn what it is like (trunk, side, tusk, tail), only to compare notes and realize they are in complete disagreement. As a surgeon, I can look at this data, see no clear benefit to the ALND, and conduct no further surgery in the face of a positive SLN. However, look at the same data from the point of view of the radiation oncologist, having data showing that (i) regional control with radiation improves survival (MA.20) and (ii) axillary radiotherapy is equal to surgery for macroscopic disease (AMAROS), and having no idea how radiation was delivered in Z0011. They would conclude that the patient I chose not to operate on should have axillary radiotherapy.

Is this a problem, or do we look at Z0011 and AMAROS together and change the standard of care from ALND for a positive SLN to axillary radiotherapy for a positive SLN? Axillary radiotherapy has less toxicity, so this could be considered a step forward. However, there is morbidity associated with axillary RT, either direct or via high tangents, and thus we may still be overtreating a subset of patients.

Should ALND be automatically avoided in Z0011-eligible patients?

Even if we accept that the methodological problems with Z0011 do not significantly impact the results, there still remains the question of whether any patient who would have been eligible for Z0011 can safely avoid a completion ALND. Eligibility and participation are two different things, and a selection bias could lead to the application of a treatment recommendation on a patient population not well represented in the study. It would be hard to believe that there was not some selection bias on the part of the participating surgeons, readily enrolling patients for whom they felt avoidance of ALND was safe while directing more worrisome patients toward surgery. The fact that patients on trial had a much better than anticipated outcome, and the skewing of the demographics toward more favorable characteristics (older, smaller tumors, a higher percentage of HR-positive patients, micrometastatic disease in only one positive SLN, etc.), argues that there was some selection bias at play. Patients with similarly favorable characteristics seem like ideal candidates to avoid ALND, but given the low accrual and small fractions of patients with worse characteristics (precluding meaningful subset analysis), there must be some concern about avoiding ALND in younger patients or patients with a more worrisome histology.

It is highly likely that the factor that biased selection more than any other might have been the tumor burden within the SLN. Several studies have shown that this is a powerful, if not the most significant, predictor of non-SLN involvement, and likely the burden of disease within the non-SLN (16, 17). The exact size of the SLN metastases for the Z0011 patients was not recorded, but 40% of the patients had either micrometastases or isolated tumor cells. The safety of avoiding ALND for this population is validated by NSABP-B32 and IBCSG 23-01 (7, 18). Thus, the gray zone, for example the safety of avoiding ALND for patients with more significant nodal tumor burden, is left to analysis of less than 500 patients, for whom metastases size is not known, and it would be reasonable to presume harbored smaller volumes of tumor.

This has to give one pause before stating that Z0011 gives definitive proof that any "eligible" patient can safely avoid ALND, and yet we have already expanded upon those findings. Many surgeons have advocated no longer obtaining axillary ultrasound and FNA biopsy of suspicious nodes (19), arguing that this labels women who would have been "SLN positive" as "clinically evident" and thus precludes them from avoidance of ALND. This seems to be a semantic argument rather than a biologic one, as the difference between an abnormal node on exam and one on ultrasound has as much to do with body habitus and physical exam skills as it does with tumor biology. However, this takes a population of patients who were never accrued to the Z0011 trial, and whom were clearly not represented, and now makes them "Z0011-eligible." It is not hard to imagine that if patients with this type of clinically evident disease had been included, the results might have been significantly different, as nodal disease identified by ultrasound is strongly correlated with nodal tumor burden and number of involved nodes (20). Thus we must be very careful about how radically we apply the Z0011 findings to clinical practice.

The need for multidisciplinary review

So can we simply say that ALND is no longer necessary in any patient with clinically node negative, T1/T2 invasive breast cancer with a positive SLN who was eligible for Z0011 or that ALND is mandatory in patients who were not eligible for Z0011? No, the trial data is too complex with too many unknowns and there are multiple variables to be considered. More importantly, one team member's decision could impact decisions downstream. Therefore, as is increasingly seen with many aspects of breast cancer treatment, these issues are best resolved in a multidisciplinary setting (Fig. 1). Several clinical and pathologic factors should be considered among patients with a positive SLN for whom we are considering avoiding ALND, including patient age, comorbidities, and life expectancy as one weighs the importance of locoregional control on long-term outcome, pathologic features including the primary tumor pathology (size, grade, angiolymphatic invasion, ER/PR, and Her-2/neu status) and the SLN pathology, specifically the number of involved nodes and the tumor burden with the SLN, and the planned adjuvant therapies.

As discussed, coordination with radiation oncology is imperative given the interplay between surgery and radiation on locoregional control. For Z0011-eligible patients, avoidance of ALND may still mean axillary radiotherapy, and given the different toxicity profiles, patients may prefer one method of regional control over another. Similarly, some patients may find themselves in a catch-22. SLN positive BCS patients who desire partial breast irradiation (PBI) would be Z0011 ineligible (thus requiring ALND) and therefore may have to decide between the conveniences of PBI versus the morbidity of ALND. However, multidisciplinary review may identify several Z0011-ineligible patients who may still safely avoid ALND, such as mastectomy patients for whom postmastectomy radiation is being considered (and an axillary field could be added).

Discussion with the medical oncologist regarding the adjuvant therapy decisions may also be important. On one hand, knowing whether finding additional positive non-SLN's would impact systemic therapy decisions could alter the decision to conduct a completion ALND. Today, most adjuvant therapy decisions are based on the primary tumor pathology and the SLN findings, so in many cases ALND would not provide additional information (21), but in some cases the non-SLN status might impact adjuvant therapy decisions (22). Conversely, the adjuvant therapy decisions might alter the surgical decision making. Many interpret the Z0011 and IBSCG results as saying that the ALND provides no added control because systemic therapy will eradicate residual disease in the non-SLN.

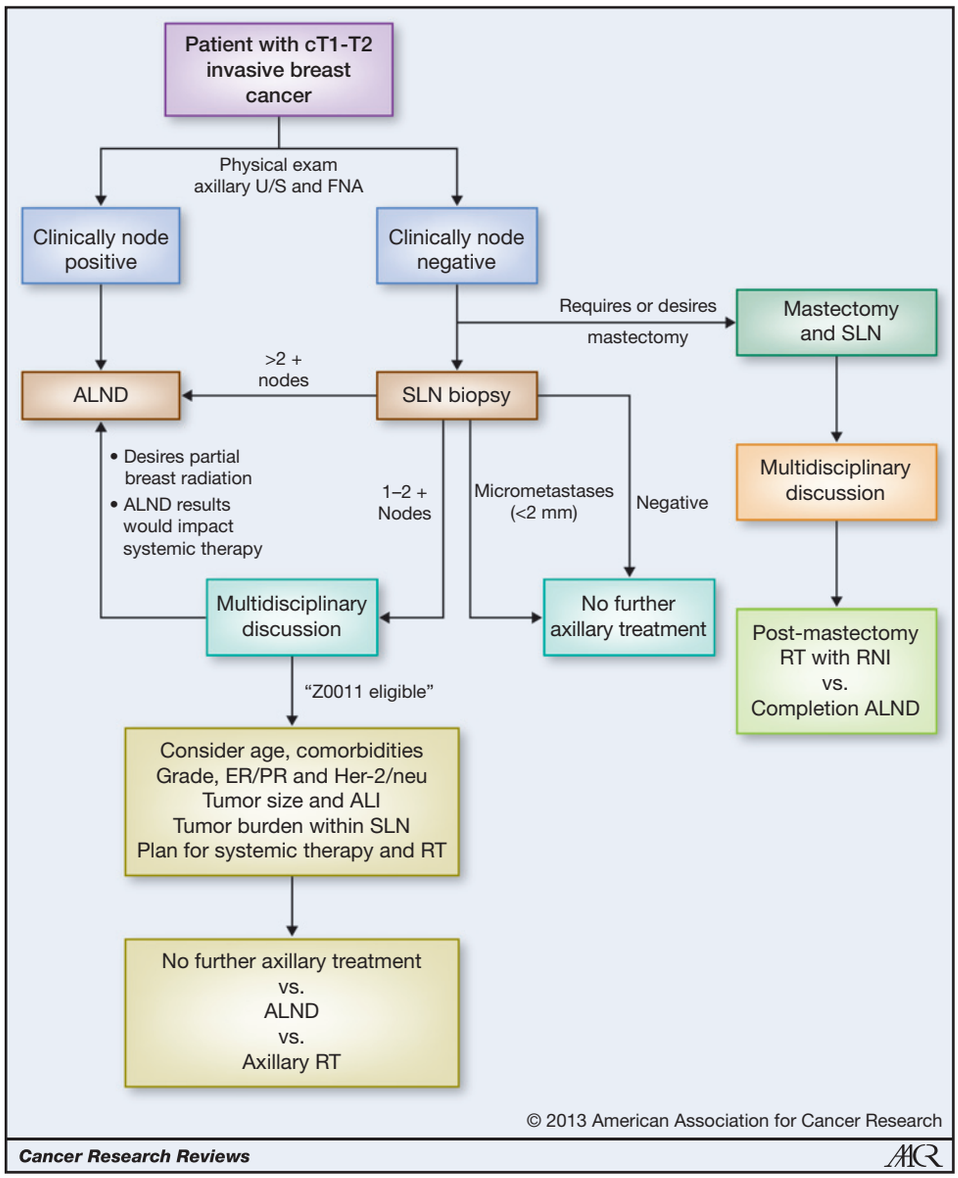

Figure 1. An algorithm for the management of the cT1-T2 node positive patient, incorporating multidisciplinary discussion. FNA, fine needle aspiration; ALI, angiolymphatic invasion; RT, radiotherapy; ER, estrogen receptor; PR, progesterone receptor.

Typically, we expect any node-positive patient to undergo chemotherapy, but some patients may not be receiving systemic therapy secondary to age or comorbidities, and others may not require it. Recent evidence suggests that some node-positive patients may not benefit from chemotherapy (23, 24), a notion presently being studied in a prospective randomized fashion. Patients at a higher risk of regional recurrence, but who may not be receiving systemic therapy, might be stronger candidates for ALND.

Conclusion

In a relatively short period of time, we have seen tremendous evolution within the field of breast cancer surgery. Today, women have several choices in treatment, and the morbidity of breast cancer surgery has, and continues to, decrease substantially without impacting outcome. The ACOSOG Z0011 trial is a major step forward but we must be careful not to overreach its applicability. These results, in combination with others, must be interpreted carefully and applied in a multidisciplinary manner, individualizing patient treatment. Further research into identifying which patients require axillary surgery, which require axillary RT and those who can safely avoid any form of axillary therapy, will help continue the trend of treating patients with better outcomes and significantly less morbidity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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