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EDITORIAL

Does the Rapid Acceptance of ACOSOG Z0011 Compromise Selection of Systemic Therapy?

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The acceptance of sentinel lymph node (SLN) biopsy as standard care in cN0 breast cancer is one of the great success stories in contemporary surgical oncology and is supported by the results of at least 69 observational studies, 7 randomized trials, and extensive literature covering all aspects of the procedure.[1,2] The logical next question in the evolution of axillary staging is to ask whether all SLN-positive patients require axillary lymph node dissection (ALND), and it is clear that for many American surgeons they do not. In a retrospective study from the National Cancer Data Base, Bilimoria et al. report on 97,314 SLN-positive patients treated nationwide between 1998 and 2006.[3] They show 23 % of patients with SLN macrometastases (>2 mm, pN1) and 55 % with SLN micrometastases (0.2–2 mm, pN1mi) did not have ALND, yet for both pN1 and pN1mi SLN disease, axillary local recurrence and 5-year relative survival were the same with or without ALND.

These suggestive results are of course subject to selection bias, but are confirmed by ACOSOG Z0011, a unique and visionary prospective trial that randomized 813 SLN-positive patients with clinical stage T1-2N0 breast cancer to ALND vs no further surgery.[4,5] All patients were SLN-positive by routine H&E (not immunohistochemical) staining, and all had breast conservation including whole-breast RT. Patients with 3 or more positive SLN (or with matted nodes) were excluded, and formal axillary RT was not allowed. Additional positive nodes were found in 27 % of the patients who had ALND, but at 6 years' follow-up there were no differences between the ALND and no-ALND arms in local (3.6 % vs 1.9 %), regional (0.5 % vs 0.9 %), or overall locoregional recurrence (4.1 % vs 2.8 %), nor were there any differences in disease-free or overall survival.[4,5] Over the last 2 years many institutions and surgeons in the United States (and to a lesser extent in Europe and worldwide) have found the results of Z0011 to be persuasive and practice-changing, incorporating into their treatment guidelines a policy of "no-ALND" for SLN-positive patients who meet the Z0011 selection criteria.

In this issue of the *Annals,* Montemurro and colleagues[6] ask whether the growing acceptance of Z0011 may have been premature. Among 321 of their own SLN-positive breast cancer patients who matched the Z0011 selection criteria, all of whom had ALND, they ask how often the results of ALND were sufficient to change the systemic therapy. In their study design, 2 medical oncologists retrospectively reviewed each patient's chart twice, first making a recommendation for systemic therapy based on SLN status alone, and then incorporating the results of the ALND. They found that the information gained from the ALND changed the recommended treatment in 16 % of patients, most of them ER-positive/her2-negative (luminal A and B) and most in the direction of "ACT" (doxorubicin, cyclophosphamide, and paclitaxel) chemotherapy. They conclude by suggesting that to avoid undertreatment ALND may be appropriate for some, if not all, SLN-positive patients meeting the Z0011 criteria. Their argument deserves serious consideration, but I do not share their concerns, for the following reasons.

First, the subtext of their study is the hypothesis that there are node-positive patients who do not require chemotherapy. This is expressed obliquely in the 2011 St. Gallen Consensus document: "the Panel did not believe that node positivity per se was an indication for use of chemotherapy, though a strong majority would use it if more than 3 lymph nodes were involved."[7] This fits with the authors' observation that ALND changed therapy primarily by finding additional positive nodes in those SLN-

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positive patients with histologically favorable luminal A (ER positive, her2 negative, Ki67 $\leq$ 13) and luminal B tumors (ER positive, her2 negative, Ki67 >13) who might not otherwise receive ACT (from at least some of the St. Gallen panelists). In distinction to St. Gallen, the current NCCN Guidelines (version 1.2012) make a Category 1 recommendation (based on high-level evidence and uniform consensus) that patients with pN1 and those with tumors >1 cm and pN1mi should receive adjuvant chemotherapy.[8] This recommendation is consistent with the observations in 2 most recent Early Breast Cancer Trialists' Collaborative Group Overviews that the proportional mortality reduction from chemotherapy was similar regardless of patient age, nodal status, extent of node involvement, tumor size, tumor grade, hormone receptor status, or tamoxifen use.[9,10] Of note, both St Gallen and NCCN strongly support chemotherapy for all node-positive patients with her2 positive or triple negative cancers. To the extent that standard US practice is to recommend chemotherapy for virtually all node-positive patients, the importance of finding additional positive nodes is moot.

Second, they categorize their recommendations as (1) "recommend chemo" (i.e., ACT is mandatory), (2) "discuss chemo" (i.e., ACT is reasonable but not essential), and (3) "no chemo" (i.e., ACT is not recommended). The "discuss" category is somewhat vague, and 83 % of those for whom treatment changed (43 of 52) moved between "discuss" and the other categories; only 15 patients (4.6 %) moved from "no chemo" to "discuss" or "recommend." If "recommend" and "discuss" are combined, then 75 % of patients would receive/discuss chemotherapy based on the SLN status alone, and only 3 % more, 78 %, based on the results of ALND. Interestingly, 77 % of their patients actually received ACT, suggesting that most "discuss" patients were treated. Since the addition of ACT for 3 % of patients would yield a survival benefit for only 1 %, one must question the value of ALND in this setting.

Third, their analysis is retrospective and applies current treatment guidelines to patients treated over an 11-year period (2000–2011) during which treatment guidelines were changing. Also, 2 more recent prospective randomized trials clearly show that the performance of ALND in SLN-positive patients did not change systemic therapy. In ACOSOG Z0011, an identical proportion of patients in the ALND and no-ALND arms received chemotherapy (58 % vs 58 %), hormonal therapy (46 % vs 47 %), and systemic therapy overall (96 % vs 97 %, respectively).[11] EORTC AMAROS (a randomization of SLN-positive patients between ALND and axillary RT) has made a similar observation, finding no significant difference between the ALND and axillary RT arms in the usage of hormonal, chemo, or chemo-hormonal therapy, or in the pattern of breast/chest wall RT.[12]

These considerations aside, the authors ask an important question: Are there subsets of SLN-positive (pN1 and pN1mi) breast cancer patients who do not benefit from the addition of chemotherapy? The answer is almost certainly yes. Will the answer come from ALND? The answer is almost certainly no. The 21-gene recurrence score, already in widespread use, allows the identification of those node-negative/ER positive patients who will benefit from chemotherapy, and more importantly those who will not.[13,14] Albain et al. suggest a similar role for node-positive disease, and prospective randomized trials (TailoRx and RxPonder (www.swog.org)) are under way to confirm and refine these early results.[15,16] Going forward, one answer is clear: what our breast cancer patients most need is better science, not more surgery.

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