

Extending ACOSOG Z0011 to Encompass Mastectomy: What Happens Without RT?

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The initial premise of sentinel lymph node (SLN) biopsy for breast cancer, that patients with negative SLN could safely avoid axillary lymph node dissection (ALND), is well established. A substantial worldwide literature documents low rates of axillary node recurrence (0.3 %), and five randomized trials show no difference between ALND and SLN biopsy in local, regional, or distant control of node-negative disease.^{1–4}

Could subsets of SLN-positive patients also avoid ALND? In fact, a policy of selective non-ALND dates back almost to the advent of SLN biopsy. Bilimoria et al. retrospectively analyzed 403,167 stage I to III breast cancer patients in the National Cancer Data Base (1998–2005) and found that 23 % of those with SLN macrometastases (pN1) and 36 % of those with SLN micrometastases (pN1mi) did not have ALND; uncorrected for selection bias, there was no adverse effect on axillary local recurrence or 5-year relative survival.⁵

Two randomized trials are more definitive, ACOSOG Z0011 was performed for hematoxylin and eosin–detected SLN metastases (cT1–2N0 patients with 1 to 2 positive SLN treated by breast conservation with whole-breast radiotherapy [WBRT]).^{6,7} International Breast Cancer Study Group (IBCSG) 23-01 was performed for SLN micrometastases (cT1–2N0 patients with SLN micrometastases <2 mm).⁸ Each study randomized SLN biopsy alone versus SLN biopsy plus ALND and found no differences in 5-year local, regional, or distant disease-free survival. These results were particularly striking in that

ALND identified residual axillary disease in 27 % of the Z0011 and in 13 % of the IBCSG 23-01 patients, yet axillary recurrence at 5 years developed in only 0.9 and 1 %, respectively, of the SLN-only arms. Both trials have been practice changing; at our own institution, 84 % of patients who met the Z0011 selection criteria were able to avoid ALND, and in Europe, ALND is no longer routine for patients with SLN micrometastases.⁹

Although Z0011 required WBRT without nodal radiotherapy (RT), a lingering concern is that the excellent results may reflect the use of “high tangents” to extend the breast RT field into the axilla. Indeed, an audit of the RT fields in a subset of the Z0011 patients confirmed that about half received high tangents, 17–21 % had supraclavicular RT, and 6–10 % had a posterior axillary boost. (These protocol violations were equally distributed between the study arms).¹⁰

Can ALND be avoided for SLN-positive patients outside the Z0011 selection criteria, specifically those who are treated by mastectomy without RT? My colleagues and I first addressed this question in 2012, comparing outcomes in SLN-positive breast cancer patients treated by mastectomy ($n = 210$) or breast conservation ($n = 325$) without any axillary-specific treatment.¹¹ At a median follow-up of 5 years, there were no significant differences in the rates of local (1.7 vs. 1.4 %) or regional node recurrence (1.2 vs. 1.0 %) even though 94 % of the breast conservation patients had received WBRT. These patients were a highly selected population with relatively small tumors, a median of 1 positive node (range 1–3 nodes), low-volume nodal disease (54–58 % pN0i+, 35–37 % pN1mi, 7–9 % pN1), and low predicted rates of residual axillary disease by the Memorial Sloan Kettering Cancer Center nomogram (8–9 %), but even after excluding patients with pN0i+ disease (where prognosis approaches that of pN0), the 5-year rates of local (1.2 vs. 1.8 %) and regional node recurrence (2.5 vs. 1.5 %) remained very low.

In this issue of *Annals of Surgical Oncology*, we have a report from the MD Anderson Cancer Center of 58 SLN-positive patients treated by mastectomy without ALND or nodal RT.¹² These patients were also highly selected: compared to those who had mastectomy with ALND, they had smaller tumors, less lymphovascular invasion, smaller size of nodal metastasis, less extranodal extension, lower N stage (72 % pN1mi, 28 % pN1), and a lower predicted rate of non-SLN metastasis by nomogram (10 %). Compared to those who had mastectomy with axillary RT, they were also more favorable. At a median follow-up of 5.5 years, 2 of the 58 developed regional node recurrence, 1 axilla only and 1 supraclavicular coincident with distant metastases. Both had low predicted rates of non-SLN disease (4 and 7 %).

Our data and that of the MD Anderson Cancer Center suggest that non-ALND is reasonable for a low-risk subset of SLN-positive mastectomy patients who will not be receiving postmastectomy RT (PMRT), but what else do we need to know?

- (1) *Axillary RT and ALND are equally effective* The AMAROS (after mapping of the axilla: radiotherapy or surgery) trial randomized 1425 cT1–2N0 SLN-positive breast cancer patients to axillary RT versus ALND.¹³ Although 33 % of the ALND arm had additional positive nodes, at 5 years, axillary local recurrence was rare (ALND 0.4 %, RT 1.2 %), disease-free and overall survival were comparable, and the morbidity of axillary RT was significantly less.
- (2) *PMRT improved survival for patients (1964–1986) with 1 to 3 positive nodes* The Early Breast Cancer Trialists' Overview found that PMRT increased 20-year survival by 8 % for patients with 1 to 3 positive and by 9 % for >3 positive nodes, but this is not representative of present-day practice.¹⁴ Two trials more reflective of the modern era found a much smaller benefit from regional node RT, with a 2 % reduction in nodal recurrence and 1 % gain in overall survival at 10 years.^{15,16} These results are much debated but suggest that PMRT could be expanded to include some (if not all) patients with 1 to 3 positive nodes.
- (3) *New randomized trials will address the SLN-positive mastectomy patient* The U.K. POSNOC (Positive Sentinel Node: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy) trial is a "Z0011 including mastectomy" design for patients with 1 to 2 positive SLN.¹⁷ A new trial from Holland (BOOG 2013-07) is a "Z0011 for mastectomy" design for patients with 1 to 3 positive SLN; both trials will randomize to axillary treatment

(ALND or axillary RT) versus none.¹⁸ Interestingly, Yao et al. reported from the National Cancer Data Base that even in the pre-Z0011 era (1998–2011) 22 % of mastectomy patients who were otherwise Z0011 eligible did not undergo ALND.¹⁹

- (4) *Systemic therapy reduces locoregional recurrence* Hormone therapy in estrogen receptor (ER)-positive disease, chemotherapy in ER-negative disease, and trastuzumab in HER-2-positive disease all significantly reduce locoregional relapse.^{20–22} With advances in systemic adjuvant therapy, locoregional events represent a declining proportion of all breast cancer events.²³
- (5) *Local control is related to biologic subtype and gene expression profile* Locoregional recurrence is more common among HER-2 or basal subtype cancers and is more frequent for those cancers with high-risk gene expression profiles.^{24,25}
- (6) *The Z0011 model does not yet apply to neoadjuvant chemotherapy* Patients who remain node positive after neoadjuvant chemotherapy are a group with resistant disease at high risk for future events and for whom ALND remains standard care.²⁶ A new trial, Alliance 11202 (<http://www.allianceforclinicaltrialsincancer.org/>), randomizes node-positive patients who remain SLN positive after neoadjuvant therapy to ALND versus no further surgery, with nodal RT for both arms.

What can we conclude for now? The decision for no axillary treatment in SLN-positive mastectomy patients is clearly multivariate. The ideal candidate would be one who does not already meet criteria for PMRT; who is low risk by demographics, histopathology, nomogram, biologic subtype, and gene profile; and who will be receiving appropriate systemic therapy. It remains unclear which of these variables (or which combination of variables) we could use to generate a surgical guideline, but it is very clear indeed that the role of ALND will continue to decline.

DISCLOSURE The author declares no conflict of interest

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