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EDITORIAL – BREAST ONCOLOGY

Local Regional Recurrence Rates Are Low Following Neoadjuvant Endocrine Therapy: What Are the Remaining Barriers to its Widespread Adoption?

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The ability of neoadjuvant endocrine therapy (NET) to downsize breast tumors in postmenopausal patients with hormone receptor (HR)-positive breast cancer is well-established,[1] yet several unanswered questions have limited widespread adoption of this approach. These questions include, but are not limited to, the optimal length of treatment, the best way to assess response, how to manage the axilla, the long-term oncologic outcomes, and whether or not adjuvant therapy recommendations should be based on response to NET. In this current issue of *Annals of Surgical Oncology*, Hunt et al.[2] report local regional recurrence (LRR) rates among 509 women treated with NET on the landmark American College of Surgeons Oncology Group (ACOSOG) Z1031 trial, providing much needed reassurance that LRR rates after NET are low, even among patients who required downstaging to achieve breast-conserving surgery (BCS).

ACOSOG Z1031 was conducted in two parts. Cohort A randomized postmenopausal women with stage II–III estrogen receptor (ER)-enriched (Allred 6–8) breast cancer to 16–18 weeks of letrozole, anastrozole, or exemestane to determine the optimal aromatase inhibitor(s) (AIs)[3] for use in future trials comparing NET with neoadjuvant chemotherapy (NAC). Patients treated with letrozole or anastrozole exhibited higher clinical response rates compared with exemestane, and subsequently these agents were utilized in Cohort B of the trial, which included similar postmenopausal patients treated with 2 weeks of an AI followed by an on-treatment biopsy to determine endocrine resistance, as defined by a Ki67 staining level >10%. Per protocol, patients with Ki67 >10% were triaged to NAC or surgery,[4] with a primary endpoint of pathologic complete response (pCR) among patients with AI-resistant disease treated with NAC. Among 236 patients in Cohort B, 49 had Ki67 levels that exceeded 10%, and 35 of these were treated with NAC before surgery, with only 5.7% experiencing a pCR, leading many to question the utility of NAC in this ER-enriched population.

In this surgical substudy of ACOSOG Z1031, 342 (67.2%) women underwent BCS. Among the 221 patients who, according to pretreatment surgical evaluation, were not felt to be BCS candidates, 114 (50.4%) underwent BCS after NET. The reported 5-year cumulative LRR incidence rate was low at 1.53% (95% confidence interval 0.7–3.0%).[2] Examining the data more closely, there were 12 total LRR events versus 57 distant recurrences and 40 second primaries (one with a concurrent regional recurrence) as first events. These data highlight that distant recurrence events surpass LRR events among postmenopausal patients with stage II–III breast cancer treated with NET. Furthermore, there were only two LRR events among the 114 patients who achieved BCS after downstaging, reinforcing that BCS after NET is safe and appropriate in properly selected patients, including those who were initially felt to require mastectomy. As with any decision to pursue BCS, patient selection remains important and it should be noted that 72.7% of the patients in this

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study were cN0, 77.4% had cT2 tumors, and all were strongly ER-positive (Allred 6–8), providing some guidance for the use of NET in clinical practice.

Although the ability of NET to downsize breast tumors has been studied for years, axillary surgical management following NET is largely a data-free zone, and the ACOSOG Z1031 trial did not prescribe axillary surgery, which allows a unique glimpse into axillary surgery decision making of the treating surgeons. In the current report, there was an increased use of sentinel lymph node biopsy (SLNB) in Cohort B only (enrolled 2009–2011) compared with Cohort A (enrolled 2006–2009), i.e. 63.3 and 45.6%, respectively,[2] suggesting that surgeons became more comfortable with SLNB after NET over time. The fact that 46.7% of patients in Cohort B had at least one positive lymph node, yet only 35.5% underwent axillary lymph node dissection, also suggests that surgeons may have been extrapolating axillary management strategies from trials of upfront surgery to NET patients.

Hypothesis-generating data from the National Cancer Database (NCDB) suggest that the prognostic significance of lymph node metastases following NET is similar to that of lymph node metastases in the upfront surgery setting,[5] a finding that may be explained by minimal nodal response to NET.[6] The overall pCR rate in the current combined cohort was only 5/509 (1.0%) following NET,[4] thus it is reasonable to deduce that lymph node metastases are likely to be unchanged after NET and therefore the significance of response is negligible. Furthermore, patients treated with NET have only received a small portion of their overall endocrine therapy regimen, which supports the hypothesis that the prognostic significance of nodal disease after NET likely mirrors that of an upfront surgery population and has led some to advocate that upfront surgery axillary algorithms should be applied to patients treated with NET,[7] although long-term outcomes data supporting this approach are needed.

Another data-free zone is selection of the appropriate adjuvant systemic therapy regimen following NET and surgery. The authors note that a weakness of the current study is the heterogeneity of adjuvant treatments; however, this is a 'real world' scenario. There are no current data to guide adjuvant treatment selection after NET. Should patients with poor clinical response receive a different endocrine therapy agent postoperatively? Should they receive chemotherapy based on their response to NET, regardless of pretreatment genomic assay results (if available)? The finding that one-third of the postmenopausal patients selected for NET in ACOSOG Z0131 received adjuvant chemotherapy is notable. In another NCDB study, Sella et al.[8] found that 740/3624 (20.4%) pre- and postmenopausal patients who were selected for NET and completed surgical therapy went on to receive adjuvant chemotherapy. In this 'real world' analysis, the decision to administer adjuvant chemotherapy seemed to be driven by younger patient age (i.e., $\leq$50 years), node positivity, tumor size, and higher Oncotype DX recurrence scores.[8] Unfortunately, it is difficult to reliably assess if clinical response to NET did or should impact adjuvant therapy recommendations in the NCDB, yet as noted by Hunt et al., the results of the ALTERNATE trial (NCT01953588) are expected to shed light on this question.

The ALTERNATE trial randomized 1299 postmenopausal patients with stage II–III ER+ breast cancer to 24 weeks of anastrozole and/or fulvestrant. Patients underwent on-treatment biopsy at 4 weeks, and those with a Ki67 staining level >10% were switched to NAC. For patients with Ki67 levels <10% who continued on NET and then underwent surgery, the protocol recommended adjuvant systemic therapy based on their response to NET, as assessed by the modified-Preoperative Endocrine Prognostic Index (m-PEPI) score.[9] Patients who did not respond to NET (m-PEPI $\geq$1) were recommended to receive adjuvant chemotherapy. The lack of randomization of an adjuvant therapy regimen for those with mPEPI $\geq$1 (chemotherapy versus endocrine therapy) is a weakness of the ALTERNATE study and the long-term outcomes may or may not validate this approach; however, extensive molecular profiling efforts led by the ALTERNATE investigators should provide additional insight into a biomarker-driven approach.

In summary, although there remain many unanswered questions regarding optimal use of NET, this report by Hunt et al. is impactful, showing that LRR rates are low following NET and BCS, even among those who required downstaging to achieve BCS. As genomic assay results from core biopsy specimens gain increased acceptance in patient selection for neoadjuvant therapy,[10] and adjuvant chemotherapy administration continues to decrease among postmenopausal patients with ER+/HER2− breast cancer based on Oncotype DX recurrence scores,[11] it is anticipated that NAC administration will also decline. NET can and should be considered for postmenopausal patients with stage II–III strongly ER+ breast cancer who require tumor downsizing to achieve BCS.

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REFERENCES

1. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2(11):1477–86. https://doi.org/10.1001/jamaoncol.2016.1897.
2. Hunt KK, Suman VJ, Wingate HF, et al. Local-regional recurrence after neoadjuvant endocrine therapy: Data from ACOSOG Z1031 (Alliance), a randomized phase 2 neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor–positive clinical stage 2 or 3 breast cancer. *Ann Surg Oncol*. 2022. https://doi.org/10.1245/s10434-022-12972-5.
3. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype–ACOSOG Z1031. *J Clin Oncol*. 2011;29(17):2342–9. https://doi.org/10.1200/jco.2010.31.6950.
4. Ellis MJ, Suman VJ, Hoog J, et al. Ki67 proliferation index as a tool for chemotherapy decisions during and after neoadjuvant aromatase inhibitor treatment of breast cancer: results from the American college of surgeons oncology group Z1031 Trial (Alliance). *J Clin Oncol*. 2017;35(10):1061–9. https://doi.org/10.1200/JCO.2016.69.4406.
5. Kantor O, Wong S, Weiss A, Metzger O, Mittendorf EA, King TA. Prognostic significance of residual nodal disease after neoadjuvant endocrine therapy for hormone receptor-positive breast cancer. *NPJ Breast Cancer*. 2020;6:35. https://doi.org/10.1038/s41523-020-00177-6.
6. Weiss A, Wong S, Golshan M, et al. Patterns of axillary management in stages 2 and 3 hormone receptor-positive breast cancer by initial treatment approach. *Ann Surg Oncol*. 2019;26(13):4326–36. https://doi.org/10.1245/s10434-019-07785-y.
7. Weiss A, Mittendorf EA, King TA. Strategies to optimize axillary surgery in patients with breast cancer receiving neoadjuvant endocrine therapy. *Oncology (Williston Park)*. 2020;34(10):397–404. https://doi.org/10.46883/ONC.2020.3410.0397.
8. Sella T, Kantor O, Weiss A, Partridge AH, Metzger O, King TA. The prevalence and predictors of adjuvant chemotherapy use among patients treated with neoadjuvant endocrine therapy. *Breast Cancer Res Treat*. 2022;194(3):663–72. https://doi.org/10.1007/s10549-022-06647-8.
9. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst*. 2008;100(19):1380–8. https://doi.org/10.1093/jnci/djn309.
10. Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. *Breast Cancer Res Treat*. 2019;173(1):123–33. https://doi.org/10.1007/s10549-018-4964-y.
11. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336–47. https://doi.org/10.1056/NEJMoa2108873.