Should Sentinel Lymph Node Biopsy for Patients with Early Breast Cancer Be Abandoned? Not So Fast

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ABSTRACT: As major advances are made in the management of early breast cancer, the role of sentinel lymph node biopsy (SLNBx) has been called into question. However, before abandoning SLNBx, a critical appraisal of its role should be done because we believe that it remains a critical component of care, especially when tailoring patient's adjuvant therapy. This commentary provides cogent arguments in favor of SLNBx in the management of patients with early breast cancer.

KEYWORDS: sentinel node early breast cancer, sentinel node relevance, sentinel node importance

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Given the recent advances in the management of early breast cancer (EBC), a number of investigators have called into question the current and future role of sentinel lymph node biopsy (SLNBx) since it is thought that the information it offers is of little use.[1] After all, patients with HER-2 overexpression are treated with chemotherapy and trastuzumab, those with luminal A receive endocrine therapy alone, and those with triple-negative breast cancers are offered cytotoxic drugs. In addition, the risks associated with SLNBx, albeit small, include bleeding, pain, seroma, infection, and allergic reaction to the dye used. At first view, avoiding SLNBx makes a whole lot of sense since we know that nodal sampling only helps stage the patient, not improve survival.

Knowing the status of the node(s), however, does help determine whether additional chemotherapeutic regimen is necessary. We do know that node-positive patients are a high-risk group and that they do benefit from having taxanes added to their standard chemotherapeutic regimen. Multiple clinical trials as well as several meta-analyses have substantiated this.[2–5] A meta-analysis of 14 randomized phase III trials of over 25,000 patients confirmed that patients receiving docetaxel-containing regimen had improved disease-free survival and overall survival over non-docetaxel-containing regimen in node-positive patients.[2,5] The 2012 Early Breast Cancer Trialists' Collaborative Group meta-analysis of 100,000 women in 123 randomized trials of adjuvant chemotherapy also reported that compared to non-taxane anthracycline regimen, the taxane plus anthracycline regimen resulted in a significant eight-year relative risk reduction of recurrence and breast cancer mortality by 16% and 14%, respectively, which translates to an absolute benefit of 4.6% and 2.8% for reduction of breast cancer recurrence and breast cancer mortality, respectively.[3,5] In another recent trial by Tolaney et al.[6], excellent outcomes are reported by de-escalating therapy (with weekly paclitaxel and herceptin for 12 weeks followed by 3-weekly Herceptin for total 1 year) in patients with tumor size ≤3 cm and negative nodes. Up to 30% of patients with T1 lesions have nodal involvement.[7] Without SLNBx information, these patients would have been understaged and possibly undertreated and sometimes could be overtreated. To our knowledge, we are not aware of any compelling trial that demonstrate that taxanes can be omitted from a subset of patients with node-positive disease.

One might argue that the above trials were old and failed to take into account current knowledge of molecular basis of breast cancer. After all, breast cancer is a molecularly heterogeneous disease that can be grouped into distinct subtypes and that classifying these subtypes can help tailor treatment.[8] Studies have found that hormone receptor (HR)-enriched tumors such as the luminal A and luminal B are not likely to respond to chemotherapy[9,10] and that the excellent prognosis of luminal A has led many to question the role of chemotherapy. Therefore, what useful information can be gained from sentinel lymph nodes (SLNs)?

However, a closer appraisal of the literature reveals that the picture is not as clear-cut. Two published randomized trials, the Breast Cancer International Research Group 001 and the PACS 01,[11,12] and the pooled analysis of these trials[13] have found that there is not only a subset of estrogen receptor (ER)-positive cancers that are highly sensitive to chemotherapy but there is also no interaction between ER status and docetaxel efficacy. In other words, one cannot discount the role of chemotherapy for a subset of patients with HR-positive tumors since they do benefit equally with chemotherapy as those with HR-negative tumors. The subset that will derive most benefit by chemotherapy will be clarified from results of ongoing prospective trial - TAILORx.[14]

The exciting results of the recently reported TAILORx found that patients belonging to the specified low-risk cohort (low recurrence score of 0–10 based on the Oncotype DX® platform) can safely forgo chemotherapy, this applies mainly to those with HR-positive, node-negative tumors.[14] Of course, how else would one begin to select such a patient without performing an SLNBx?

What if the same platform is applied to identify a subset of low-risk node-positive patients? The ongoing RxPONDER trial[15] (utilizes the Oncotype DX® platform) and MINDACT[16] (utilizes MammaPrint 70-Gene Breast Cancer Recurrence Assay) are doing exactly the same. Women with not only HR-positive tumors but also node-positive tumors are enrolled, and if the results of the RxPONDER mirror those of the TAILORx trial, then, indeed the days of SLNBx are numbered. But even so, one must be cognizant that these trials are restricted only to those with HR-positive tumors, a group that makes up roughly 60% of women below the age of 50 years and 80% of those above the age of 50 years.[17] What approach should one employ for the other 20%–40% of patients with HR-negative tumors?

The American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) trial[18] demonstrated that in patients with clinically node-negative axilla with T1–T2 tumors, 1–2 positive SLNs, whole breast radiation and systemic therapy can replace axillary lymph node dissection (ALND) in preventing axillary recurrence in patients with macrometastatic and micrometastatic SLNs. These results only tell us whether ALND is needed following a positive SLNBx, and not whether SLNBx is necessary. To answer such a question, we would need to know the specific systemic therapy regimen. In other words, we would need to know who received taxanes and who did not and whether the receipt of taxanes really made a whole lot of difference. If we were to discover that there was no significant difference in survival between the two groups, then we could make a compelling argument against SLNBx. Unfortunately, information on specific chemotherapeutic regimen was not specified in the protocol. Perhaps, it might be a worthwhile endeavor to retrospectively analyze such a data from ACOSOG Z0011.

Although axillary ultrasound is widely used in Europe as a standard modality in the preoperative staging of EBC, there is a concern in terms of its reliability when US-guided biopsy results are negative. A 2014 meta-analysis found that one in four women with a US-guided biopsy-proven negative axilla has a positive SLNBx.[19] Currently, there is an ongoing prospective multicenter international randomized trial comparing SLNBx with no surgery in the axilla for those with negative ultrasonographic findings (Sentinel node vs. Observation after axillary UltrasouND trial [SOUND trial]).[20] Hopefully, the results from this trial will reconcile some of the concerns raised.

Finally, EBC encompasses a heterogeneous spectrum of diseases, spanning from a tumor measuring less than 2 cm to the one that measures up to 5 cm. In addition, a subset of N1 disease (ie, T0–T2N1) can also be considered as EBC. Neoadjuvant chemotherapy plays an important role for those with large tumor since it increases the rate of breast conserving therapy as demonstrated by NSABP B–27.[21] For those with clinically negative nodes, SLNBx after neoadjuvant chemotherapy is an acceptable procedure. However, SLNBx following neoadjuvant chemotherapy for those with clinically positive axillary lymph nodes is not reliable. ACOSOG Z1071[22] (Alliance trial) and SENTinel NeoAdjuvant[23] (SENTINA) found that the procedure had resulted in a high false-negative rate; in ACOSOG Z1071, the false-negative rate was 12.6%, while it was 18.5% in the SENTINA trial. Most of the EBC studies, challenging old paradigms (including SOUND trial), are conducted in a highly select group of patients, mainly those with T1 tumors. In fact, 67%–71% of patients in the ACOSOG Z0011 trial had T1 disease and 80% of those in the AMAROS[24] trial had T1 disease. Will results from these studies also be applicable to those with stage II diseases?

We have come a long way since the days of performing a Halstedian radical mastectomy. The medical and surgical community has made major strides in improving the lives of thousands of patients as we learn more about the biology of breast cancer. Perhaps the day will come when SLNBx will be of historic interest. However, given the clinically important information that can be gained from SLNBx and the low risk associated with the procedure, we remain reluctant to abandoning it at this point of time.

Author Contributions

Conceived and designed the experiments: QC, PP. Analyzed the data: QC, PP. Wrote the first draft: QC. Contributed to the writing of the manuscript: QC, PP. Agree with manuscript results and conclusions: QC, PP. Jointly developed the structure and arguments for the paper: QC, PP. Made critical revisions and approved final revision: QC, PP. Both authors reviewed and approved of the final manuscript.

REFERENCES

1. Gentilini O, Veronesi U. Staging the axilla in early breast cancer will imaging replace surgery? *JAMA Oncol*. 2015;1(8):1031–2.
2. Jacquin JP, Jones S, Magné N, et al. Docetaxel-containing adjuvant chemotherapy in patients with early stage breast cancer. Consistency of effect independent of

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nodal and biomarker status: a meta-analysis of 14 randomized clinical trials. *Breast Cancer Res Treat*. 2012;134(3):903–13.
3. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432–44.
4. Chu QD, McDonald JC, Li BD. Adjuvant therapy for patients who have node-positive breast cancer. *Adv Surg*. 2006;40:77–98.
5. Chu Q, Kim R. Early breast cancer. In: Chu Q, Gibbs J, Zibari G, eds. *Surgical Oncology: A Practical and Comprehensive Approach*. New York: Springer; 2014: 61–112.
6. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med*. 2015; 372(2):134–41.
7. Sparano JA, Zhao F, Martino S, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. *J Clin Oncol*. 2015;33(21):2353–60.
8. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747–52.
9. Conforti R, Boulet T, Tomasic G, et al. Breast cancer molecular subclassification and estrogen receptor expression to predict efficacy of adjuvant anthracyclines-based chemotherapy: a biomarker study from two randomized trials. *Ann Oncol*. 2007;18(9):1477–83.
10. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA*. 2006;295(14):1658–67.
11. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med*. 2005;352(22):2302–13.
12. Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol*. 2006;24(36):5664–71.
13. Andre F, Broglio K, Roche H, et al. Estrogen receptor expression and efficacy of docetaxel-containing adjuvant chemotherapy in patients with node-positive breast cancer: results from a pooled analysis. *J Clin Oncol*. 2008;26(16):2636–43.
14. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373(21):2005–14.
15. National Cancer Institute (NCI). Tamoxifen Citrate, Letrozole, Anastrozole, or Exemestane with or without Chemotherapy in Treating Patients with Invasive RxPONDER Breast Cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT01272037. Accessed May 28, 2016.
16. European Organization for Research and Treatment of Cancer-EORTC. Genetic Testing or Clinical Assessment in Determining the Need for Chemotherapy in Women with Breast Cancer That Involves No More Than 3 Lymph Nodes (MINDACT). Available at: https://clinicaltrials.gov/ct2/show/NCT00433589. Accessed May 28, 2016.
17. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. *Breast Cancer Res Treat*. 2002;76(1):27–36.
18. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg*. 2010;252(3):426–33.
19. Diepstraten SC, Sever AR, Buckens CF, et al. Value of preoperative ultrasound-guided axillary lymph node biopsy for preventing completion axillary lymph node dissection in breast cancer: a systematic review and meta-analysis. *Ann Surg Oncol*. 2014;21(1):51–9.
20. European Institute of Oncology. Sentinel Node vs Observation after Axillary Ultra-Sound (SOUND). Available at: https://clinicaltrials.gov/ct2/show/NCT02167490. Accessed March 20, 2016.
21. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2003;21:4165–74.
22. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(4):1455–61.
23. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609–18.
24. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303–10.

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