The use of ultrasound in the clinical re-staging of the axilla after neoadjuvant chemotherapy (NACT).

Anastasia Peppe, Robin Wilson, Romney Pope, Kate Downey, Jennifer Rusby

Abstract

Introduction: Ultrasound (US) is the imaging modality of choice for staging the axilla prior to surgery in patients with breast cancer (BC). High pathological complete response rates in the axilla after NACT mean a more conservative approach to surgery can be considered. Radiological re-staging is important in this decision making. After the presentation of results from ACOSOG Z1071 in December 2012, formal ultrasound re-assessment of the axilla after primary therapy was specifically requested in our institution. We report on the accuracy of axillary US (aUS) for identifying residual axillary disease post-NACT.

Methods: Data were collected on patients who had proven axillary disease prior to NACT and underwent axillary lymph node dissection after NACT between January 2013 and December 2015. Post-chemotherapy aUS reports and axillary pathology reports were classified as positive or negative for abnormal lymph nodes and for residual disease (cCR and pCR respectively).

Results: The sensitivity and specificity of aUS was 71% and 88% respectively. The negative predictive value (NPV) was 83%. The false negative rate was 29%.

Conclusions: Axillary ultrasound provides clinically useful information post-NACT, which will guide surgical decision-making. Patients with aUS-negative axillae are likely to have a lower false negative rate of SLNB after NACT (Boughey et al). However, aUS does not replace the need to identify and biopsy the nodes which were proven to be positive prior to NACT.

Introduction

The advent of Sentinel Lymph Node Biopsy (SLNB) represented a radical change in the surgical management of early breast cancer. In that setting it provides adequate staging while allowing node negative patients to avoid the short and long term consequences of an unnecessary Axillary Lymph Node Dissection (ALND), such as shoulder stiffness and lymphoedema, introducing the notion of axillary conservation for patients who have no disease in their axilla (1-3).

Concurrently, neoadjuvant chemotherapy (NACT) has a continuously increasing role in a) converting inoperable to operable and b) downsizing the primary cancer to enable breast conserving surgery (BCS) in patients who would otherwise require a mastectomy. An area of current interest, however, is the management of the axilla in conjunction with NACT. SLNB can safely be offered after NACT to patients who were node negative at the outset (4-6). In women who have ultrasound guided biopsy-proven involved nodes at diagnosis, NACT results in a pathological complete response in the axilla more frequently than in the breast (7-9). Clinicians have been quick to recognise the benefit of downsizing the primary to permit breast conservation, but the possibility of downstaging the axilla to allow axillary conservation is not yet widely practised.

There are already two prospective observational studies, the Alliance Z1071 and SENTINA trials (10, 11), reporting the False Negative Rate (FNR) of SLNB post NACT in initially node positive patients. The FNRs were 12.6 and 14.2% respectively, both above the current accepted cut off of 10% (1). Reasons for the higher FNR include residual disease in the nodes, or fibrosis in response to treatment resulting in errant mapping to a normal but non-sentinel node. Both of these studies suggest that the dual localisation technique (with radioisotope and blue dye) and the number of harvested nodes increase the accuracy of SLNB in this particular group of patients but concerns persist about the safety of this approach.

Axillary ultrasound (aUS) is widely used in the initial loco-regional staging of breast cancer and is accurate in this setting. The reported sensitivity (27%-94%) and specificity (53%-100%) vary widely (12, 13). Although the performance of aUS is operator-dependent, historically it has outperformed other imaging modalities in the axilla. The accuracy and FNR of aUS are improved by the additional testing of the lymph nodes identified on aUS by FNA cytology or core biopsy (10, 14-20). It has the added advantages of not involving ionising radiation, and is cost-effective (13).

In an attempt to lower the FNR of SLNB after NACT, Boughey et al (14) reported the use of aUS after neoadjuvant chemotherapy and before surgery. However, the diagnostic accuracy of their aUS was low. Nonetheless, the selection of patients for SLNB by aUS resulted in a FNR for

combined aUS and SLNB staging of 9.8%. They therefore propose the combined technique as a safe option for patients post NACT who were biopsy proven node positive at outset. Acceptable accuracy is difficult to define and was arbitrarily set at the same threshold of 10% in Z1071 as in NSABP-B32 (2, 3), though this may not be adequate in women such as those with triple negative cancers who have already received all of their systemic treatment, hence some of the concern about adopting this approach.

The presentation of Z1071 and SENTINA at the San Antonio Breast Cancer Symposium in December 2012 (10, 11) led to a change of practice in our unit from an ad hoc comment at the time of re-evaluation of the breast lesion, to a formal radiological restaging of the axilla by aUS thereafter. This now includes a description of size and morphology and a comment on the number of residual abnormal lymph nodes. The aim of this study was to evaluate the diagnostic accuracy of aUS post NACT in women who were proven node positive at diagnosis since this change in practice.

Patients & Methods

Consecutive patients with proven axillary disease at diagnosis who received NACT and went on to ALND (our routine practice until December 2015) were identified from prospective Electronic Patient Records (EPR). These were also used for retrospective collection of data. Patients were managed at one of three sites of the same Trust connected on the same database with uniform guidelines and overlapping multidisciplinary teams. All patients had US for evaluation of response during NACT.

There are no universally-agreed guidelines on imaging criteria for the abnormal lymph node. The widely accepted criteria, however, are a) eccentric or concentric cortical thickness >2.5mm, b) absent fatty hilum, c) rounded morphology and d) increased blood flow in the thickened cortex on Doppler (12, 21). Ultrasound is not accurate in the evaluation of fibrosis (21). All US studies were performed on one of four GE machines (LOGIQ^{TM}) with a 15MHz ultrasound probe at two sites by either a consultant breast radiologist (n=6) or specialist breast sonographer/radiographer (n = 6).

Post-NACT aUS reports were compared to the gold standard, which was the post NACT pathology report, classified as positive or negative for abnormal lymph nodes and residual disease respectively. Diagnostic characteristics of aUS were calculated. These results were used in conjunction with Boughey's algorithm (14) (fig 2) to calculate the combined accuracy of aUS with SLNB as this is the clinically relevant result. Data were also collected on age, tumour phenotype, grade, stage, chemotherapy regime, and use of trastuzumab.

Results

Three hundred and eight patients were identified as fulfilling the eligibility criteria and had their preoperative aUS between January 2013 and December 2015. All of them were female with a mean age of 50 years (SD 10.2).

The patient demographic data and clinico-pathological features shown in **table 1**, reflect the patient group in which NACT is used in our institution: the low grade, ER positive, Her2 negative cases make up a decreasing proportion, being replaced by a greater proportion of the other subtypes, particularly grade 3, triple negative or Her2 positive cases. All Her2 positive patients received trastuzumab and most received a taxane.

	Jan 2013-Dec 2015
No of patients	308
Age	50 years (SD 10.1)
ER+Her2-	100 (32.4%)
ER+Her2+	68 (22%)
ER-Her2+	48 (15.6%)
ER-Her2-	92 (30%)
Grade I	1 (0.35)
Grade II	80 (26%)
Grade III	227 (73.7%)
IDC	296 (96%)
ILC	6 (2%)
Mixed	6 (2%)
Inflammatory	29 (9.4%)
EC-T	231 (75%)
Taxanes	292 (94.8%)
Herceptin	116 (37.7%)

**Table 1. Patient demographics and clinico-pathological features**

Most women underwent axillary ultrasound just after the second cycle of chemotherapy (mean 12.2 weeks prior to surgery, range 7-17, 95% CI 8.1-16.2). A small number of patients (~10%) had a repeat ultrasound 1-2 weeks before surgery. The sensitivity and specificity of aUS were 71% and 88% respectively. The FNR was 29%. The Negative and Positive Predictive Values (NPV and PPV) were 83% and 79% respectively. The accuracy of the technique was 82% (**Table 2**).

Jan 13-Dec 15 n=308	Axillary USS - residual disease	Axillary USS - no residual disease	
No pCR	True positive TP = 85	False negative FN = 35	Sensitivity = 71%
pCR	False positive FP = 22	True negative TN = 166	Specificity = 88%
Accuracy = 82%	Positive predictive value = 79% (precision)	Negative predictive value = 83%	FNR = 29%

Table 2: Diagnostic characteristics of aUS.

pCR = pathological complete response

The diagnostic accuracy of the aUS is also illustrated by the receiver-operator characteristic (ROC) curve(22) (Figure 1). The area under the curve (AUC) was 0.80.
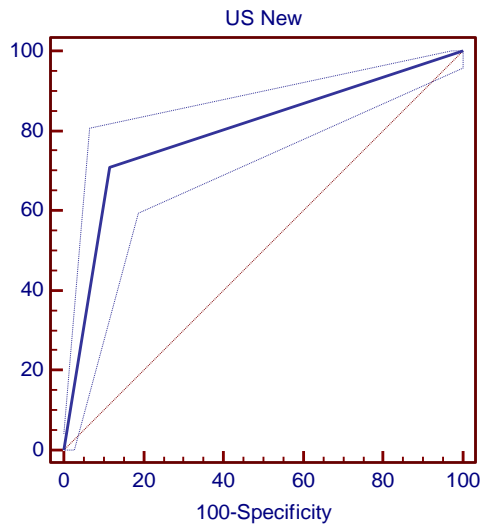
AUC = 0.8

Fig. 1: ROC curve to illustrate sensitivity and specificity.

Tumour biology plays a key role in response to treatment so diagnostic characteristics were also calculated for the various phenotypes of tumours. Negative and Positive Predictive Values are the characteristics most easily understood as they indicate the chance of a correctly positive or negative answer, hence guiding axillary management. These are shown in Table 3. There was a notable variation in NPV and PPV according to phenotype, with Her2 positive cases having a higher NPV and more modest PPV, while Her2 negative cases had a higher PPV and more modest NPV.

ER+Her2-	90%	69%
ER+Her2+	67%	87%
ER-Her2+	50%	90%
ER-Her2-	81%	80%

Table 3: Diagnostic PPV and NPV according to phenotype.

Discussion

Surgical management of the breast post-NACT is tailored according to response. However, surgical management of the axilla in current standard practice is still determined by the nodal status at presentation (23).

Axillary US has been used extensively and is now an established imaging tool to assess the axilla as part of the diagnostic evaluation of a suspicious breast mass and in patients with newly diagnosed breast cancer. In the post-neoadjuvant chemotherapy setting, it has already been shown that when combined with SLNB, the FNR falls below the arbitrary acceptable cut off of 10% (1, 2, 14), but the diagnostic accuracy of aUS in Boughey's study was only 52% If our data on the accuracy of aUS replace the results in the flowchart in figure 2 of Boughey's paper on the subject (14), assuming the same SLNB FNR, the FNR of the combined procedure falls to 4% (**Figure 2**), indicating that aUS can help to identify patients who may benefit from SLNB in this setting.
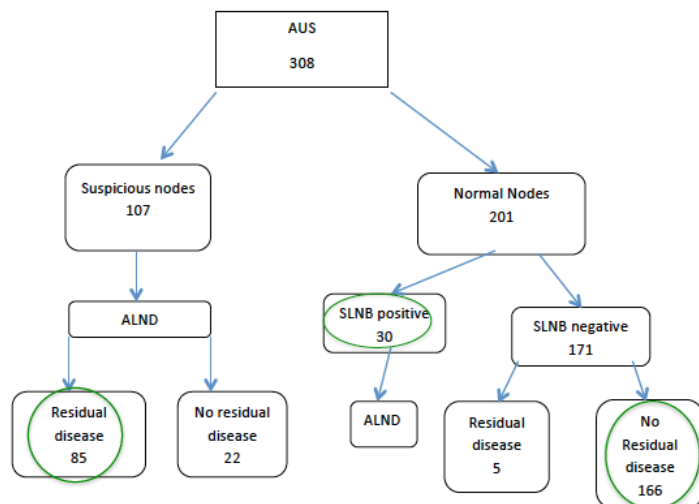
FNR with SLNB FNR 12.6% and our improved US characteristics

FNR = FN/ (TP+FN) = 5/ (85+30+5) = 4%

Fig. 2: FNR estimated with the improved aUS characteristics on SLNB-FNR of 12.6%.

Implications of and strategies to avoid a false positive aUS result

When evaluating a diagnostic test, it is important to consider the implications of a false-positive or false negative result. In this scenario, the 21% of patients whose positive test result is false will be advised to have an ALND, which would then be negative. Thus they would be treated as is currently standard, with oncological safety, but adverse consequences in terms of lymphoedema

and shoulder dysfunction. Conversely, the 79% majority with residual disease have moved directly to their definitive axillary treatment.

In the early breast cancer setting, fine needle aspiration cytology, or core biopsy of the abnormal looking nodes is performed before committing a patient to ALND (2, 24-28). This could be considered here, in order to minimise the possibility of a second operation, though the volume of residual disease may lead to sampling errors and cytology may be hard to interpret post chemotherapy. Nonetheless, a false negative axillary cytology would be followed by surgical axillary staging in the form of SLNB, which provides a safety net.

One limitation of our study was that the ultrasound was performed at the time of breast ultrasound, often after only the second cycle of chemotherapy. Some patients, particularly the Her2 positive cases who had a PPV of only 50-67% must have achieved their pCR in the subsequent weeks of treatment. The false positive rate of aUS is therefore likely to be reduced if a final aUS is performed after completion of NACT, and this is now our practice. The optimal timing has yet to be determined in order to achieve maximum accuracy of axillary re-staging through US imaging.

Implications of and strategies to avoid a false negative aUS and SLNB post-NACT

A false negative aUS result would lead clinicians to offer a patient SLNB. An estimated 86% of women with residual axillary disease would be identified by SLNB and managed accordingly. A false negative SLNB has greater potential implications for patients. It means that residual disease is present in a patient thought to have a pCR in the axilla while also implying understaging of the axilla, potentially affecting adjuvant treatment decisions. When patients are selected for SLNB using aUS of the diagnostic accuracy that we report, the combined FNR is estimated at 4%. In the post-NACT scenario, most patients with a false negative result will have ongoing systemic therapy in the form of trastuzumab and / or endocrine therapy. The timing of surgery after chemotherapy is historical, but it is possible that, after a further 14 doses of trastuzumab, any residual disease in the axilla would have been eradicated. Eradication may be less likely in women undergoing treatment for **ER positive Her2 negative** disease, but loco-regional control is likely with long-term endocrine therapy. Lack of clinically meaningful response in the breast means they are making up a decreasing proportion of our neoadjuvant chemotherapy population. Furthermore, based on our results according to phenotype, these patients will be largely protected by a high PPV such that only a small proportion will be offered SLNB. For patients with **triple negative breast cancer** and residual disease in the axilla no further adjuvant systemic treatment will be planned (though the lower axilla may be within the radiotherapy fields in those receiving

whole breast or post-mastectomy radiotherapy). This subgroup of patients exhibits a high PPV and NPV. Risk of axillary recurrence should be taken in context of risk of distant disease. Since pCR is associated with better prognosis, those with a false negative SLNB have, by definition, not had a pCR and distant disease may manifest prior to any axillary recurrence. Nonetheless, the level of concern about false negative results should be higher for these women and the thresholds for treatment, perhaps, lower.

Options to reduce the false negative rate include use of dual localisation (radioisotope and blue dye) and removal of at least 3 lymph nodes, but the logical step would be to ensure removal of the node, which was originally proven to be abnormal. One technique which is being used to ensure identification of the initial positive (index) node is targeted axillary dissection (TAD). This involves the pre-NACT marking of the positive node with subsequent post NACT retrieval of that specific "index" node along with the lymph nodes obtained with the standard SLNB localisation (15) (29). Placing radioactive iodine seeds or metal markers in the nodes have been suggested but are not yet widely accepted, because of the learning curve associated with these techniques (15, 29).

The ACOSOG Z0011 study (30-33) led clinicians treating breast cancer to question the role of axillary treatment as residual disease does not, even at 10 years follow up (34), appear to result in a considerable risk of loco-regional or distant relapse. In an editorial (35) commenting on Z1071, it is also suggested that "in patients already committed to NACT, axillary recurrence is probably the most meaningful outcome measure and not the FNR". A recent publication by Galimberti et al (17) provides reassuring oncological outcome data on 147 women who had SLNB post NACT without specific marking or retrieval of the index node. Seventy had a negative SLNB and did not receive any further axillary treatment. After a median of 61 months follow up none of these women had presented with an axillary recurrence while one of the 77 women with a positive SLNB and ALND did recur in the axilla. Further work is required in this area to quantify the risk of axillary recurrence in the different phenotypes.

Conclusion

Axillary US is a widely available, reliable test to guide the surgical management of the axilla post-NACT in women who were node positive at diagnosis. While not adequate to re-stage the axilla in its own right, it has negative and positive predictive values which are clinically meaningful in assisting surgical decision-making and, when combined with SLNB, has an acceptable FNR. An attempt at axillary conservation should be offered to women, identified by aUS, who are likely to be among the 61% of patients who have achieved an axillary pCR, allowing them to potentially avoid the morbidity of ALND.

Acknowledgements

Ethical approval

Full ethical approval was not required as the work presented in this paper was based on retrospective data collection and analysis of aggregated data. There was no study intervention. It has institutional approval as a service evaluation.

Conflict of Interests

None of the authors has any conflict of interests to declare.

References

1.   Krag D, Harlow S, Julian T. Breast cancer and the NSABP-B32 sentinel node trial. Breast Cancer. 2004;11(3):221-4; discussion 64-6.
2.   Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 2007;8(10):881-8.
3.   Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927-33.
4.   Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer. 2002;95(4):681-95.
5.   Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2005;23(12):2694-702.

6.   Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg. 2006;93(5):539-46.

7.   Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72.

8.   Zhang GC, Zhang YF, Xu FP, Qian XK, Guo ZB, Ren CY, et al. Axillary lymph node status, adjusted for pathologic complete response in breast and axilla after neoadjuvant chemotherapy, predicts differential disease-free survival in breast cancer. Curr Oncol. 2013;20(3):e180-92.

9.   Pennisi A, Kieber-Emmons T, Makhoul I, Hutchins L. Relevance of Pathological Complete Response after Neoadjuvant Therapy for Breast Cancer. Breast Cancer (Auckl). 2016;10:103-6.

10.   Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, 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(14):1455-61.

11.   Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, 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.

12.   You S, Kang DK, Jung YS, An YS, Jeon GS, Kim TH. Evaluation of lymph node status after neoadjuvant chemotherapy in breast cancer patients: comparison of diagnostic performance of ultrasound, MRI and ^{18}F-FDG PET/CT. Br J Radiol. 2015;88(1052):20150143.

13.   Atkins JJ, Appleton CM, Fisher CS, Gao F, Margenthaler JA. Which imaging modality is superior for prediction of response to neoadjuvant chemotherapy in patients with triple negative breast cancer? J Oncol. 2013;2013:964863.

14.   Boughey JC, Ballman KV, Hunt KK, McCall LM, Mittendorf EA, Ahrendt GM, et al. Axillary Ultrasound After Neoadjuvant Chemotherapy and Its Impact on Sentinel Lymph Node Surgery: Results From the American College of Surgeons Oncology Group Z1071 Trial (Alliance). J Clin Oncol. 2015;33(30):3386-93.

15.   Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.

16.   Erdahl LM, Boughey JC. Use of sentinel lymph node biopsy to select patients for local-regional therapy after neoadjuvant chemotherapy. Curr Breast Cancer Rep. 2014;6(1):10-6.

17.   Galimberti V, Ribeiro Fontana SK, Maisonneuve P, Steccanella F, Vento AR, Intra M, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol. 2016;42(3):361-8.

18.   Hieken TJ, Boughey JC, Jones KN, Shah SS, Glazebrook KN. Imaging response and residual metastatic axillary lymph node disease after neoadjuvant chemotherapy for primary breast cancer. Ann Surg Oncol. 2013;20(10):3199-204.

19.   Harvey SC, Wolff AC. Does a Picture Make a Difference? Ultrasound Guidance in the Management of the Axilla After Neoadjuvant Chemotherapy. J Clin Oncol. 2015;33(30):3367-9.

20.   Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). Ann Surg. 2015;261(3):547-52.

21.   Ecanow JS, Abe H, Newstead GM, Ecanow DB, Jeske JM. Axillary staging of breast cancer: what the radiologist should know. Radiographics. 2013;33(6):1589-612.

22.   Park SH, Goo JM, Jo CH. Receiver operating characteristic (ROC) curve: practical review for radiologists. Korean J Radiol. 2004;5(1):11-8.

23.   Schwartz TL, Margenthaler JA. Axillary Ultrasound Before Neoadjuvant Chemotherapy for Breast Cancer: Don't Discount the Benefits Yet! Ann Surg Oncol. 2017.

24. Hunt KK, Ballman KV, McCall LM, Boughey JC, Mittendorf EA, Cox CE, et al. Factors associated with local-regional recurrence after a negative sentinel node dissection: results of the ACOSOG Z0010 trial. Ann Surg. 2012;256(3):428-36.

25. Dihge L, Grabau DA, Rasmussen RW, Bendahl PO, Rydén L. The accuracy of preoperative axillary nodal staging in primary breast cancer by ultrasound is modified by nodal metastatic load and tumor biology. Acta Oncol. 2016;55(8):976-82.

26. Houssami N, Ciatto S, Turner RM, Cody HS, Macaskill P. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. Ann Surg. 2011;254(2):243-51.

27. Houssami N, Diepstraten SC, Cody HS, Turner RM, Sever AR. Clinical utility of ultrasound-needle biopsy for preoperative staging of the axilla in invasive breast cancer. Anticancer Res. 2014;34(3):1087-97.

28. Houssami N, Turner RM. Staging the axilla in women with breast cancer: the utility of preoperative ultrasound-guided needle biopsy. Cancer Biol Med. 2014;11(2):69-77.

29. Rubio IT. Sentinel lymph node biopsy after neoadjuvant treatment in breast cancer: Work in progress. Eur J Surg Oncol. 2016;42(3):326-32.

30. Caudle AS, Hunt KK, Tucker SL, Hoffman K, Gainer SM, Lucci A, et al. American College of Surgeons Oncology Group (ACOSOG) Z0011: impact on surgeon practice patterns. Ann Surg Oncol. 2012;19(10):3144-51.

31. Gainer SM, Hunt KK, Beitsch P, Caudle AS, Mittendorf EA, Lucci A. Changing behavior in clinical practice in response to the ACOSOG Z0011 trial: a survey of the American Society of Breast Surgeons. Ann Surg Oncol. 2012;19(10):3152-8.

32. Galimberti V, Chifu C, Rodriguez Perez S, Veronesi P, Intra M, Botteri E, et al. Positive axillary sentinel lymph node: is axillary dissection always necessary? Breast. 2011;20 Suppl 3:S96-8.

33. Yi M, Kuerer HM, Mittendorf EA, Hwang RF, Caudle AS, Bedrosian I, et al. Impact of the american college of surgeons oncology group Z0011 criteria applied to a contemporary patient population. J Am Coll Surg. 2013;216(1):105-13.

34. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg. 2016;264(3):413-20.

35. Boughey JC, Dietz JR. Editorial: Management Based on Risk: Individualizing the Care of the Breast Cancer Patient. Ann Surg Oncol. 2016;23(10):3083-7.