

Peer Review File

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Reviewer A

“Omission of axillary surgery in cN0, postmenopausal ER-positive/HER2-negative breast cancer patients undergoing breast-conserving treatment” is a study that evaluates the factors associated with high nodal burden among postmenopausal women with early stage breast cancer to establish criteria for patient in whom axillary sampling can be omitted. Amidst calls to omit the surgical nodal assessment in these low-risk cases this paper is timely. Specifically, the purpose of our study was to determine whether axillary surgery including SLNB can be replaced with preoperative imaging modalities (ultrasound and MRI). The data show low event rates with median follow-up of 71 months and 5-yr recurrence free survival of 97%, despite 24.3% of patients having nodal metastasis. The authors conclude that their data supports the possibility of carefully omitting axillary surgery including SLNB in cN0, postmenopausal ER-positive/HER2-negative patients undergoing BCT with cT1 stage.

Overall, the manuscript is well written and address a controversial topic. Data from Korea also adds an element of novelty.

I have the following comments:

Please edit for minor grammatical errors example: abstract page 2 line 2, “had” should be before lower

R: Thank you for your detailed review. It has been modified.

Introduction: line 6, please clarify “since the start of breast cancer surgery”. The next sentence talks about sentinel lymph node biopsy which was describe in the 1990s. Previous axillary surgery was in the form of complete lymph node dissection.

R: Thank you for your accurate comment. This part has been clearly modified.

Pg 6, line 17: neoadjuvant chemotherapy is not included in studies on which we established indications for nodal omission (that was reviewed in the paragraph prior). Your explanation for why that group is excluded because of inability to determine the pathologic nodal status is a secondary reason.

R: Thank you for your accurate comment. The content has been corrected.

In methods:

What was the technique for identifying the nodes (dual tracer)? Page 10 states average number of nodes is 4.8 which is higher than other studies (e.g. Z11) where the average was 2.

R: Thank you for your precise comment. Our institutions routinely utilize dual tracers (radioactive tracer and isosulfan blue dye) when performing SLNB. This is done to secure as many sentinel lymph nodes as possible, aiming for a more accurate assessment of axillary nodal status. In addition, in our study, we considered all LNs identified through SLNB including LNs that were non-SLN, strictly speaking, as SLNs. This information has been added to the “Method” section.

Were there other indications for the MRI beyond the axillary evaluation? It is an expensive test to utilize for this purpose unless the pt is recommended to have one for another purpose (density)

R: Thank you for your comment. Breast MRI is performed not only to assess clinically nodal status but also to evaluate breast density and determine the extent of the tumor such as non-mass enhancement. Furthermore, breast MRI can also detect additional hidden malignancy in contralateral breast or a different quadrant of the same breast. Most importantly, in South Korea, the cost of breast MRI is very affordable due to the national health insurance system. As a results, all patients diagnosed with breast cancer in our country routinely undergo MRI before starting treatment.

In discussion:

Please be careful of abbreviations such as SOUND trial (initial mention should have full name of study)

R: Thank you for your comment. It has been modified (TAILORx, RxPONDER and SOUND).

A mention of the Choosing Wisely initiative which is recommended in the US would be appropriate. Is a similar national push going on in Korea?

R: Thank you for your comment. Korean has also recognized the importance of addressing unnecessary medical practices and improving healthcare quality. However, there isn't a direct equivalent to the Choosing Wisely initiative under the same name. While it is not a single initiative like Choosing Wisely, various organizations and institutions in Korea are also working to improve healthcare quality and efficiency by reducing unnecessary medical interventions.

Pg 15, line 11- remove “a” before many.

R: Thank you for your detailed review. It has been modified.

Reviewer B

The study shows the necessity of axillary surgery, including SLNB, in post-menopausal ER-positive/HER2-negative breast cancer patients with cN0 status undergoing BCT. The study found that 24.3% had LN metastasis despite negative preoperative imaging, with only 4.5% having a HNB of ≥ 3 LN metastases.

Clinical tumor size cT1 had significantly lower rates of LN metastasis and HNB compared to those with cT2 tumors.

I have some comments:

- Page 6, line 14, it belongs to results;

R: Thank you for your precise comment. The sentence has been moved to the “Results” section.

- "Definition of menopausal status" paragraph can be removed;

R: Thank you for your detailed review. The paragraph has been deleted

- Please cite radiotherapy guidelines used for adjuvant radiotherapy to the breast/axilla;

R: Thank you for your detailed review. We have added the guidelines for radiotherapy as a citation.

- Main limitation: why did the authors chose ≥ 3 LN metastases and not ≥ 4 LN metastases (pN2). Please perform a sub-analysis of your breast cancer population;

R: Thank you for your comment. When we first designed our study, our question was whether we could safely omit axillary surgery without deviating from the current guidelines for surgical treatment and adjuvant therapy. Therefore, we determined the cut-off for high nodal burden (HNB) by focusing on clinical practice rather than anatomic stage. Specifically, the ACSOG Z0011 trial allows omission of ALND for patients with up to 2 positive LN, and the RxPONDER trial uses a multi-gene assay to determine chemotherapy eligibility for patients with up to 3 positive LN. Hence, we decided on a cut-off of 3 positive LN to satisfy both criteria.

However, we agree with your opinion that N2 (≥ 4 LN metastases) status is also an important criterion in the anatomic stage. Therefore, we conducted additional analysis on patients with ≥ 4 LN metastases and included the results in the supplementary materials.

- Additional factors other than cT are predictors of LN involvement including lobular

histology, G, and 2 SLNB metastasis. Please cite this study DOI: 10.1097/AS9.0000000000000405 to improve the quality of your manuscript;

R: Thank you for your detailed review. I have additionally mentioned the study you recommended in the “Discussion” section.

- Figures 2 and 3 are redundant, please remove and summarize in Tables;

R: Thank you for your comments. Following your suggestion, we have removed Figure 2 and incorporated its contents into Table 1. However, we concluded that Figure 3, being essential to illustrating the main results of our study, should remain as a figure rather than be converted to a table for easier comprehension of the results. Nevertheless, if you still believe Figure 3 should be deleted, we will consider revising it accordingly.

- Add a limitations paragraph.

Reviewer C

Congratulations for this manuscript, interesting and on a current issue.

This manuscript is easy to read.

The low number of patients is underlined in chapter study limitations.

In chapter methods, "HER2-positive breast cancer, triple-negative breast cancer (TNBC) were excluded". I agree that the most interesting population is postmenopausal, ER-positive/HER2-negative breast cancer. In SOUND trial all age groups of patients and all tumor subtypes were included. I think that it is very important, to discuss these exclusions in chapter Discussion.

R: Thank you for your precise comment. We have added the points you mentioned to the “Discussion” section as follows.

“Furthermore, the latest results from the Sentinel Node vs Observation After Axillary Ultra-Sound (SOUND) trial, announced since the initiation of our research, indicate that SLNB can be cautiously omitted in cT1N0 patients (22,23). Although this study was conducted on patients of all ages and subtypes, the authors, considering clinical practice, mentioned that omission of axillary surgery is feasible only in postmenopausal ER-positive/HER2-negative patient group. Our study also, in accordance with current guidelines, excluded HER2-positive and TNBC patients.”

Chapter Results: the average number of sentinel lymph nodes was 4.8. It is very high. Why? Identification procedure(s) for sentinel lymph node biopsy and surgical

procedure should be report in chapter Methods.

R: Thank you for your comment. In our institutions, we typically used dual tracer for SLN detection. Additionally, in our study, we considered all LNs identified through SLNB procedure as SLNs. Therefore, we anticipated a potentially higher average number of SLNs compared to previous studies. This information has been added to the “Method” section.

A significant criterion for LN metastasis is lack: lympho vascular invasion: to discuss.

R: Thank you for your comment. We completely agree with your opinion that lympho-vascular invasion (LVI) is a risk factor for LN metastasis. However, the purpose of our study is to omit axillary surgery. Clinically, axillary surgery and breast surgery are usually performed simultaneously, so as mentioned in the “Method” section, the pathologic features of the patients in our study were reflected by the information from the core biopsy samples, not the surgical specimen. In our institution, as well as in most others, we do not report on LVI in core biopsy sample. Furthermore, pathologically, identifying LVI in core biopsy samples is of little significance.

For reference, we conducted a multivariate analysis on risk factor for LN metastasis, including LVI in surgical specimen, which is attached below. As you mentioned, LVI was a significant risk factor for LN metastasis.

Uni- and multivariate analysis of risk factors for axillary LN metastasis including lympho-vascular invasion

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
<70	Ref.*		Ref.	
≥70	0.33 (0.11-0.97)	0.044	0.38 (0.13-1.12)	0.079
Result of cN0 modality				
AUS and MRI or nor performed MRI	Ref.			
AUS cN0 and MRI cN+	0.38 (0.10-1.45)	0.155		
MRI cN0 and AUS cN+	0.69 (0.13-3.84)	0.676		
Number of SLN	1.09 (0.96-1.24)	0.195		
cT stage				
I	Ref.		Ref.	
II	2.92 (1.70-5.03)	<0.001	2.34 (1.32-4.15)	0.004
PR				
Negative	Ref.			

Positive	0.98 (0.54-1.76)	0.935		
Histologic grade				
I/II	Ref.			
III	0.97 (0.45-2.09)	0.943		
Nuclear grade				
I/II	Ref.			
III	0.99 (0.46-2.12)	0.971		
LVI (surgical specimen)				
Negative	Ref.		Ref.	
Positive	3.42 (1.88-6.23)	<0.001	2.68 (1.43-5.02)	0.002

*Reference value

LN, lymph node; OR, odds ratio; CI, confidence intervals; AUS, axillary ultrasound; MRI, magnetic resonance imaging; SLN, sentinel lymph node; PR, progesterone receptor; LVI, lympho-vascular invasion

LN metastases: definition should be report: macrometastases only or also micrometastases and isolated tumor cells? How were LN analyzed: serial sections and immuno-histo chemistry?

R: Thank you for your comment. We evaluated LN metastasis by serially cross-sectioning and microscopically examining them. We did not performed immunohistochemistry. Metastasis was defined as the presence of LN metastasis > 0.2mm, according to the American Joint Committee on Cancer 8th edition anatomical stage classification (1). We included micrometastasis in the LN metastasis group. Malignant cell clusters classified as isolated tumor cells that are ≤0.2mm were considered as not having LN metastasis.

(1) Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol 2018;25(7):1783-5.

"Eighty-one patients (24.3%) were pathologically diagnosed with LN metastasis after axillary surgery among patients with cN0": please report rates with CI 95% for all patients and cT1 - cT2, respectively. Also, CI 95% for HNB.

R: Thank you for your comment. We have added the 95% CI information to each of the rates.

There was no significant difference of RFS between HNB patient's and others, but with only 15 patients with HNB. Results of RFS could or should be removed with a negative value for the study and without interest with this very low number of patients.

R: We absolutely agree with our advice. We have completely removed the content regarding RFS analysis from our manuscript.

No contribution of MRI should be report, more clearly in chapter Results and Discussion.

R: Thank you for your comment. We have added the contents you point out in the “Result” section. In addition, we have already mentioned in the “Discussion” section that MRI contributes little to the differentiation of cN0, as follows.

“Although one study reported that the detection of axillary LN metastasis improved when breast MRI was performed together with AUS alone, our study did not clearly demonstrate the benefit of MRI.”

In chapter conclusion: "Therefore, in patients with cT1, omission of axillary surgery such as SLNB could be carefully considered". Yes, but very important, with more criteria analyzed, as lympho vascular invasion and small tumors cT1a, cT1b, cT1c <15mm.

R: Thank you for your comment. We have added the points you mentioned to the “Conclusion” section.