Original Article

Diagnostic Accuracy of Ultrasonography in Axillary Staging in Breast Cancer Patients

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Abstract

Background: Breast cancer is the most common malignancy affecting women all over the world and represents 7% of all cancer-related deaths in the UK. One of the most crucial elements in assessing a patient's prognosis and chance of survival with breast cancer is the condition of their axillary lymph nodes. Ultrasonography (US) is now used as a routine preoperative diagnostic tool for pretherapeutic axillary evaluation. The aim of the current study is to investigate the diagnostic accuracy of US in axillary staging in breast cancer patients. **Methods:** We carried out this retrospective study for all invasive breast cancer patients who had surgery in addition to preoperative axillary staging using US during the period from January 2020 to February 2021. The final histology results were compared with the preoperative US findings to ascertain the sensitivity, specificity, positive predictive value, and negative predictive value of AUS in axillary staging. **Results:** One hundred and twenty-eight patients were included in our study. The average age of diagnosis was 63.9 ± 12.3 years of age. We calculated sensitivity rate of 59.6%, specificity rate of 95.1%, positive predictive value of 87.5%, and negative predictive value of 80.2% with overall diagnostic accuracy of 82.2%. **Conclusion:** Despite the important role of preoperative US in axillary staging in breast cancer patients; it failed to detect metastatic diseases in 14.8% of our patients. These findings necessitate the routine histological evaluation of the axilla for more accurate staging of the disease.

Keywords: Axilla, breast cancer, diagnostic accuracy, histology, ultrasonography

Introduction

Breast cancer is the most frequent cancer among women worldwide.[1] Breast cancer is responsible for 15% of all new cases of cancer in the United Kingdom (UK) (2016–2018).[2] In addition, breast cancer is the second most common cause of death among females and the fourth most common cause of cancer death in the United Kingdom (2018) accounting for about seven percent of all cancer deaths. In England, about 98% of people with breast cancer who are diagnosed at its earliest stage will live for at least 5 years, compared to about one in four (26%) who are diagnosed at its later stage.[2] The prognosis and overall survival of breast cancer patients are heavily influenced by the presence of axillary lymph node (LN) metastases.[3]

Axillary lymph node dissection (ALND) was the standard procedure for axillary staging for many years, but it has a higher risk of complications.[4] In early stage breast cancer, sentinel lymph node biopsy (SLNB) is currently the gold standard for axillary staging.[5] When compared to complete ALND, the SLNB is associated with significantly fewer complications.[6,7] In addition to avoiding unnecessary ALND, SLNB aids in determining the number of involved nodes, which is crucial in determining the appropriate postoperative adjuvant treatment. However, it was discovered that other affected LNs in the same region was found in 1 − 15 percent of patients who had a negative sentinel node biopsy for metastases.[8] Large LN metastases in the first drainage node account for the majority of these false negative results.[9]

Axillary ultrasonography represents a cost-effective and noninvasive important technique for the preoperative

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assessment of axillary node status.[10,11] Currently, Axillary ultrasonography (AUS) is routinely used for axillary assessment in most European breast cancer units (BCUs).[12] Preoperative axillary staging by ultrasonography (US) may change the management in several ways such as the choice of the operation, the neoadjuvant chemotherapy, etc., However, studies have reported different sensitivity (26%–94%) and specificity (53%–98%) rates for axillary ultrasound.

In the current study, we assessed the diagnostic accuracy of preoperative axillary ultrasonography in breast cancer cases in our clinical setting by comparing the findings with the final histological results obtained during surgery.

Patients and Methods

We carried out this retrospective study in our breast unit for all patients who had breast cancer and axillary surgery, during the period from January 2020 to February 2021. Data were retrospectively collected from the hospital recording system. Inclusion criteria included (1) patients who had breast cancer and axillary staging by preoperative US scan, (2) patients who had either mastectomy or breast conservative surgery, and (3) of any age group. Exclusion criteria included (1) patients with *in situ* tumor, (2) patients who had neoadjuvant chemotherapy, and (3) patients who did not have any axillary surgery.

All the patients had triple breast assessment in our breast unit. All patients had preoperative axillary assessment by a senior radiologist. General ultrasound machine with breast package was used (Phillip brand) with standard transducer frequency of 18.5 MHz and 12.5 MHz for dense breast tissues. Patients with suspicious LNs during the initial breast assessment, had ultrasound guided tru-cut biopsy. Criteria of suspicious LNs on US included loss of the fatty hilum, irregular appearance of the LN, cortical thickening >3 mm, markedly hypoechoic cortex, and round shape. 14-gauge core-needle were usually used. Biopsy results again were reviewed by a senior pathologist. Results were discussed in our breast multidisciplinary team (MDT) prior to surgery. An informed consent was obtained from every patient before any surgical intervention.

All patient with negative axillary US had SLNB. On the other hand, patients with positive axillary LN as confirmed by US-guided core biopsy had axillary management according to the breast MDT decision. Specimens obtained by either SLNB or axillary dissection were fixed in formalin and sent to the lab for assessment of the number of involved nodes and the degree of involvement (micro or macro-metastasis). Patients with positive axillary LNs again were discussed in our post-operative breast oncology MDT for the assessment of any further axillary management.

The findings from the preoperative axillary US were compared with the results of either SLNB or ALN dissection to assess the diagnostic accuracy of axillary US. Indeterminate LNs on US were included in the same group with the suspicious nodes. We calculated the sensitivity, specificity, positive predictive value, and negative predictive value of AUS based on the final pathology reports.

IRB approval was exempted by our local IRB as all the data was collected retrospectively, fully anonymized, and all images were de-identified.

Results

During the period from January 2020 to February 2021, more than 200 breast operations were performed in our breast surgery department. Our study included 128 patients who met the inclusion and exclusion criteria. Average age of diagnosis was 63.9 ± 12.3 years of age. 63 patients had right-sided breast cancer and 65 had left-sided cancer. Ninety-four patients (73.4%) were diagnosed with invasive ductal carcinoma, 20 patients (15.6%) had invasive lobular carcinoma, while 14 patients (10.9%) had other malignancies including metaplastic carcinoma, tubulolobular carcinoma, mucinous carcinoma, and others. In terms of tumor grading, 16 patients (12.5%) had tumor grade 1, 57 patients (44.5%) had tumor grade 2, and 55 patients (43%) had tumor grade 3. Regarding the tumor size, 46 patients (35.9%) were diagnosed with T1 tumor, 67 (52.3%) with T2, 13 (10.2%) with T3 and 2 (1.6%) with T4 tumor. Receptors status was identified in all our patients and we found that estrogen receptors were positive in 96 patients and negative in 32 patients, while HER2 receptors were positive in 19 patients and negative in 109 patients [Table 1].

Table 1: Patients' demographics

Variable	*n* (%)
Age	63.9±12.3
Laterality	
Right	63 (49.2)
Left	65 (50.8)
Tumor type	
IDC	94 (73.4)
ILC	20 (15.6)
Others	14 (10.9)
Tumor grade	
G1	16 (12.5)
G2	57 (44.5)
G3	55 (43)
Tumor size	
pT1	46 (35.9)
pT2	67 (52.3)
pT3	13 (10.2)
pT4	2 (1.6)
Estrogen receptor status	
ER positive	96 (75)
ER negative	32 (25)
HER2 receptor status	
HER2 positive	19 (14.8)
HER2 negative	109 (85.2)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, ER: Estrogen receptors, HER2: human epidermal growth factor receptor 2

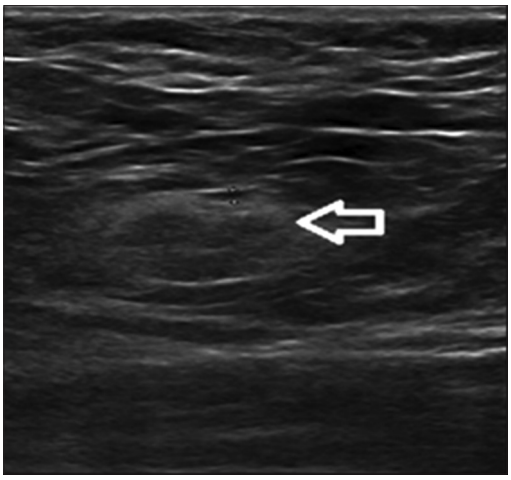

Figure 1: US of the left axilla showing normal LN. US: Ultrasonography, LN: Lymph node

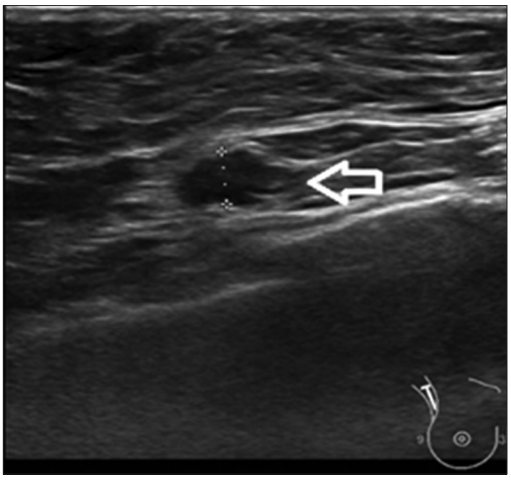

Figure 2: US of the right axilla showing abnormal LNs with cortical thickness of 4.6 mm. US: Ultrasonography, LNs: Lymph nodes

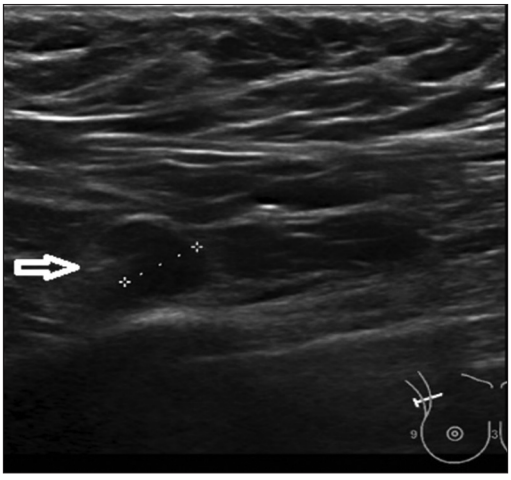

Figure 3: US of the right axilla showing abnormal LN with cortical thickness of 6.3 mm. US: Ultrasonography, LN: Lymph node

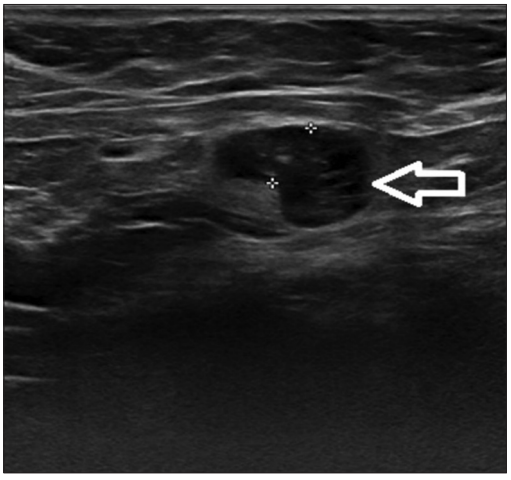

Figure 4: US of the left axilla showing abnormal LN with cortical thickness of 5.5 mm. US: Ultrasonography, LN: Lymph node

US was utilized for axillary assessment in all our patients [Figures 1-4]. We compared the US findings with the final pathology results. US revealed unremarkable findings in 96 patients. The number of true negative patients was 77 (60.2%), while 19 patients (14.8%) were false negative. Of the 19 patients, 15 had macro-metastatic disease and four had micro-metastasis as confirmed with SLNB. The average number of the involved LNs after axillary surgery was two LNs. Of 32 patients who had abnormal LNs on US, true positive patients were 28 (21.9%) and false positive were four patients (3.1%). We calculated sensitivity rate of 59.6%, specificity rate of 95.1%, positive predictive value of 87.5%, and negative predictive value of 80.2% [Tables 2 and 3].

Discussion

In the United Kingdom, breast cancer is the most common type of malignancy, causing 15% of all new cases between 2016 and 2018. Breast cancer is the most common cancer among females in the UK, accounting for approximately 55,500 new cases annually. According to the reports, breast cancer is the fourth most common cause of cancer-related death in the United Kingdom, causing seven percent of all cancer-related deaths.[2] Early diagnosis is associated with excellent prognosis as compared with late diagnosis. A significant prognostic factor in patients with invasive breast cancer is the status of their axillary LNs.[3] Preoperative axillary staging was solely based on the physical examination for many years; the sensitivity of physical examination is low (34%–76%).[13] Moreover, physical examination is unable to differentiate between reactive and metastatic LNs.[7]

Currently, patients with breast cancer are routinely evaluated prior to surgery with axillary ultrasound (AUS) in the majority of the BCU.[14] Bruneton *et al*. compared the diagnostic accuracy of preoperative axillary ultrasound with palpation in the detection of nodal metastasis in breast cancer and reported that US had sensitivity and specificity rates of 72.7% and 97.3%, respectively, whereas palpation had sensitivity and specificity rates of only 45.4% and 97.3%, respectively.[15] US

Table 2: Pathology results compared with ultrasonography results

AUS results	Pathology results	
	Positive nodes	Negative nodes
Positive	28 (TP)	4 (FP)
Negative	19 (FN)	77 (TN)

AUS: Axillary ultrasound, TP: True positive, FN: False negative, FP: False positive, TN: True negative

Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography in axillary assessment in breast cancer patients

Variable	Results
Sensitivity	59.6
Specificity	95.1
PPV	87.5
NPV	80.2

PPV: Positive predictive value, NPV: Negative predictive value

is noninvasive, widely available and inexpensive diagnostic technique. It can also evaluate the morphological characteristics of LNs that are palpable and those that aren't. Loss of the fatty hilum, cortical thickening >3 mm, irregular shape, markedly hypoechoic cortex, round shape, and increased peripheral blood flow were ultrasound findings that raised the possibility of axillary metastasis.[16-18] The morphology and cortical thickness, according to many authors, are the most crucial parameters for determining metastatic LNs[17,19,28] [Figures 1-4].

Different studies reported variable sensitivity and specificity rates for AUS; Bonnema *et al*., reported sensitivity rate of 87% and specificity rate of 56%,[21] Podkrajsek *et al*., in a study including 165 patients published a sensitivity and specificity rates for AUS of 58% and 89%, respectively.[22] Moreover, Nori *et al*. concluded a sensitivity rate of 45.2%, a specificity rate of 86.8%, with a positive predictive value of 61.3% and negative predictive value of 77.2%.[23] The variability in the sensitivity and specificity rates may be attributed to many factors. The use of different sonographic criteria for evaluating axillary LNs and the radiographer's experience levels may contribute to this wide variation.[19,24] Furthermore, Dihge *et al*. determined an association between the accuracy of AUS with the metastatic size (odds ratio [OR] = 1.11), obesity (OR = 2.46), and histological grade (OR = 4.43),[25] and concluded that the variable sensitivity and specificity rates may also be influenced by the tumor type and LN size,[26] as well as patients' characteristics like obesity, which may limit the detection of axillary LN involvement due to the fat mass.[27] Other factors that may contribute to the variable rates in sensitivity and specificity include the difference in the equipment and transducer frequencies used. In addition, sentinel node biopsy may result in verification bias due to false-negative results.[19]

In our study, AUS was performed by at least a senior radiologist. All patients with breast cancer had US assessment of the axilla regardless of the axillary clinical evaluation. We could not evaluate the body mass index for every patient as it was retrospective review and not all these data were well documented in the patients' notes.

Patients with *in situ* carcinoma were excluded from the study. 88.3% of our patients had early-stage breast cancer (T1 and T2). All patients were discussed in breast MDT. Patients with negative axillary examination on US were subjected to SLNB. Final histology results were compared with the US findings. True positive, false positive, true negative, and false-negative values were identified. We concluded sensitivity rate of 59.6%, specificity rate of 95.1%, positive predictive value of 87.5%, and negative predictive value of 80.2, with an overall accuracy rate of 82.2%. Our accuracy rate was higher than figures published by Kochler *et al*., and Nori *et al*.[20,23]

Numerous factors may have contributed to the false negative results in our study including patients' factors like obesity and the degree of shoulder movement. The radiographer's level of experience could also be a significant factor. The size of the LNs as well as the type and grade of the tumor may have an impact on the outcomes.

To improve the results of AUS, US-guided biopsy of the axillary nodes has been introduced. The indications for needle biopsy were different between different studies. Although in some studies only abnormal looking LNs on US were biopsied,[13,29-31] in other studies, all nodes were biopsied regardless of its size or appearance on sonography.[21,32,33] The use of US-guided biopsy has increased the specificity rate, which reached as high as 100%; however, the sensitivity rate was reduced. Core biopsy was found to be more sensitive than fine-needle aspiration in detecting metastasis, according to some studies.[34,35] In our study, all abnormal looking LNs on US scan, were biopsied. Ultrasound-guided core biopsy was the standard procedure in our patients for the assessment of any abnormal looking LN. Of all suspicious criteria, increased cortical thickness and loss of the fatty hilum were the most common indicators for biopsy. Thirty-two patients with abnormal looking nodes on US had US-guided core biopsy; four of them did not have any metastatic disease as confirmed also after the SLNB.

The results of our study may have some limitations. First, the number of the included patients was relatively small (128 patients). Second, the level of experience of the radiologist performing the AUS or the variability of the ultrasound device could have affected the results. Third, we could not compare the LN characteristics with the intraoperative pathological findings.

Conclusion

Although US is a useful technique for axillary staging in breast cancer patients, it should not be used to definitively identify axillary lymph involvement. Many factors may contribute to the variable sensitivity and specificity rates of US between different centers. To improve the diagnostic

accuracy of US, additional studies with a larger population and intra-operative US would be recommended for comparison of the characteristics of each LN detected with pathological finding of the same LN.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 2016;17:43-6.
2. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. [Last accessed on 2022 Mar 25].
3. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, *et al.* Sentinel-lymph-node biopsy as a staging procedure in breast cancer: Update of a randomised controlled study. Lancet Oncol 2006;7:983-90.
4. Warmuth MA, Bowen G, Prosnitz LR, Chu L, Broadwater G, Peterson B, *et al.* Complications of axillary lymph node dissection for carcinoma of the breast: A report based on a patient survey. Cancer 1998;83:1362-8.
5. 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;11:927-33.
6. 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;8:881-8.
7. Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: A meta-analysis. Breast Cancer Res Treat 2010;120:441-7.
8. Cheng J, Ren C, Liu G, Shui R, Zhang Y, Li J, *et al.* Development of high-resolution dedicated PET-based radiomics machine learning model to predict axillary lymph node status in early-stage breast cancer. Cancers (Basel) 2022;14:950.
9. Morawitz J, Bruckmann NM, Dietzel F, Ullrich T, Bittner AK, Hoffmann O, *et al.* Comparison of nodal staging between CT, MRI, and [(18) F]-FDG PET/MRI in patients with newly diagnosed breast cancer. Eur J Nucl Med Mol Imaging 2022;49:992-1001.
10. Farrell TP, Adams NC, Stenson M, Carroll PA, Griffin M, Connolly EM, *et al.* The Z0011 trial: Is this the end of axillary ultrasound in the pre-operative assessment of breast cancer patients? Eur Radiol 2015;25:2682-7.
11. Ahmed M, Jozsa F, Baker R, Rubio IT, Benson J, Douek M. Meta-analysis of tumour burden in pre-operative axillary ultrasound positive and negative breast cancer patients. Breast Cancer Res Treat 2017;166:329-36.
12. Wockel A, Festl J, Stuber T, Brust K, Krockenberger M, Heuschmann PU, *et al*, Interdisciplinary screening, diagnosis, therapy and follow-up of breast cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) - part 2 with recommendations for the therapy of primary, recurrent and advanced breast cancer, Geburtshilfe Frauenheilkd 78 (11) (2018) 1056 -1088.
13. Bedrosian I, Bedi D, Kuerer HM, Fornage BD, Harker L, Ross MI, *et al.* Impact of clinicopathological factors on sensitivity of axillary ultrasonography in the detection of axillary nodal metastases in patients with breast cancer. Ann Surg Oncol 2003;10:1025-30.
14. Ditsch N, Untch M, Kolberg-Liedtke C, Jackisch C, Krug D, Friedrich M, *et al.* AGO recommendations for the diagnosis and treatment of patients with locally advanced and metastatic breast cancer: Update 2020. Breast Care (Basel) 2020;15:294-309.
15. Bruneton JN, Caramella E, Héry M, Aubanel D, Manzino JJ, Picard JL. Axillary lymph node metastases in breast cancer: Preoperative detection with US. Radiology 1986;158:325-6.
16. Yang WT, Chang J, Metreweli C. Patients with breast cancer: Differences in color Doppler flow and gray-scale US features of benign and malignant axillary lymph nodes. Radiology 2000;215:568-73.
17. Abe H, Schmidt RA, Sennett CA, Shimauchi A, Newstead GM. US-guided core needle biopsy of axillary lymph nodes in patients with breast cancer: Why and how to do it. Radiographics 2007;27 Suppl 1:S91-9.
18. Topal U, Punar S, Taşdelen I, Adim SB. Role of ultrasound-guided core needle biopsy of axillary lymph nodes in the initial staging of breast carcinoma. Eur J Radiol 2005;56:382-5.
19. Alvarez S, Añorbe E, Alcorta P, López F, Alonso I, Cortés J. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: A systematic review. AJR Am J Roentgenol 2006;186:1342-8.
20. Koehler KE, Ohlinger R. Sensitivity and specificity of preoperative ultrasonography for diagnosing nodal metastases in patients with breast cancer. Ultraschall Med 2011;32:393-9.
21. Bonnema J, van Geel AN, van Ooijen B, Mali SP, Tjiam SL, Henzen-Logmans SC, *et al.* Ultrasound-guided aspiration biopsy for detection of nonpalpable axillary node metastases in breast cancer patients: New diagnostic method. World J Surg 1997;21:270-4.
22. Podkrajsek M, Music MM, Kadivec M, Zgajnar J, Besic N, Pogacnik A, *et al.* Role of ultrasound in the preoperative staging of patients with breast cancer. Eur Radiol 2005;15:1044-50.
23. Nori J, Vanzi E, Bazzocchi M, Bufalini FN, Distante V, Branconi F, *et al.* Role of axillary ultrasound examination in the selection of breast cancer patients for sentinel node biopsy. Am J Surg 2007;193:16-20.
24. Yang WT, Ahuja A, Tang A, Suen M, King W, Metreweli C. High resolution sonographic detection of axillary lymph node metastases in breast cancer. J Ultrasound Med 1996;15:241-6.
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;55:976-82.
26. Rotim T, Kristek B, Turk T, Kretić D, Perić M, Pušeljić I, *et al.* Measurable and unmeasurable features of ultrasound lymph node images in detection of malignant infiltration. Acta Clin Croat 2017;56:415-24.
27. Shah AR, Glazebrook KN, Boughey JC, Hoskin TL, Shah SS, Bergquist JR, *et al.* Does BMI affect the accuracy of preoperative axillary ultrasound in breast cancer patients? Ann Surg Oncol 2014;21:3278-83.
28. Choi YJ, Ko EY, Han BK, Shin JH, Kang SS, Hahn SY. High-resolution ultrasonographic features of axillary lymph node metastasis in patients with breast cancer. Breast 2009;18:119-22.
29. Sapino A, Cassoni P, Zanon E, Fraire F, Croce S, Coluccia C, *et al.* Ultrasonographically-guided fine-needle aspiration of axillary lymph nodes: Role in breast cancer management. Br J Cancer 2003;88:702-6.
30. Damera A, Evans AJ, Cornford EJ, Wilson AR, Burrell HC, James JJ, *et al.* Diagnosis of axillary nodal metastases by ultrasound-guided core biopsy in primary operable breast cancer. Br J Cancer 2003;89:1310-3.
31. Deurloo EE, Tanis PJ, Gilhuijs KG, Muller SH, Kröger R, Peterse JL, *et al.* Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer. Eur J Cancer 2003;39:1068-73.
32. de Kanter AY, van Eijck CH, van Geel AN, Kruijt RH, Henzen SC, Paul MA, *et al.* Multicentre study of ultrasonographically guided axillary node biopsy in patients with breast cancer. Br J Surg 1999;86:1459-62.
33. Kuenen-Boumeester V, Menke-Pluymers M, de Kanter AY, Obdeijn IM, Urich D, Van Der Kwast TH. Ultrasound-guided fine needle aspiration cytology of axillary lymph nodes in breast cancer patients. A preoperative staging procedure. Eur J Cancer 2003;39:170-4.
34. Houssami N, Ciatto S, Turner RM, Cody HS 3rd, 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;254:243-51.
35. Rautiainen S, Masarwah A, Sudah M, Sutela A, Pelkonen O, Joukainen S, *et al.* Axillary lymph node biopsy in newly diagnosed invasive breast cancer: Comparative accuracy of fine-needle aspiration biopsy versus core-needle biopsy. Radiology 2013;269:54-60.