Utility of Preoperative Staging of Ipsilateral Axilla with Ultrasound and Guided Needle Aspiration in Early-Stage Breast Cancer—Current Indian Scenario

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Abstract

Clinical assessment of the axilla, especially in early-stage breast cancer, can have a high degree of inaccuracy with over-staging curtailing the use of sentinel node biopsy. Imaging of axilla, using ultrasound ± guided fine needle aspiration cytology (FNAC) can help in better staging. In this study, we aim to compare physical examination and ultrasound of axilla and FNAC and assess their accuracy in preoperative staging of axilla. This was a prospective observational study. Patients with biopsy-proven invasive early-stage breast carcinoma, consenting to be part of the study, underwent ultrasound (US) of ipsilateral axilla with guided FNAC, when indicated and underwent surgery which included complete axillary dissection. Postoperative histopathology was compared to preoperative US and guided cytology (if done), to correlate the latter's efficacy in detecting positive axillary nodes. Clinically, 96% of patients had palpable axillary nodes, though of doubtful significance. On US axilla, 62% had suspicious nodes (guided FNAC was performed). Sensitivity and specificity of US axilla was 90.9% and 60.7%, with sensitivity reaching 100% in patients with > 1 node positive, while that of US + FNAC was 85.7 and 100% respectively. Although all US nodal parameters studied showed positive correlation with final nodal pathology ($p < 0.005$), loss of fatty hilum was the best predictor of metastatic nodal disease. Preoperative ultrasound of ipsilateral axilla ± FNAC helps in better preoperative staging of axilla. Its routine use can help reduce the false positivity of clinical examination and help in avoiding unnecessary axillary dissection and also in better selection of patients for sentinel node biopsy.

Keywords Breast cancer · Fine needle aspiration · Axilla · Axillary ultrasound · Sentinel lymph node biopsy

Introduction

Globally, breast cancer is the second most common cancer. As per the GLOBOCAN 2012 fact sheets, published by International Agency for Research on Cancer (IARC), the estimated new breast cancer cases were 1.67 million in 2012 alone, accounting for 25% of all cancers [1]. In India, it is the most common cancer among women, among most of the cancer registries under National Cancer Registry Program [2].

In breast cancer, of the many prognostic factors, axillary nodal status is one of the most important. Axillary management has seen a lot of changes from the initial radical mastectomy described by Halstead, through the more conservative procedures of sentinel node biopsies to nonsurgical management—axillary irradiation (in select patients). Clinical examination of the primary and axilla is one of the components of “triple assessment;” however, it is subjective and associated with a high degree of inaccuracies. Over-staging or under-staging of the axilla can happen with the use of clinical examination alone, in turn affecting management of the patient. A palpable but indeterminate node in axilla on clinical examination may compromise the routine use of sentinel node biopsy. More objective measures like ultrasound staging of axilla can make preoperative staging more effective. This study was conducted to compare the clinical examination and ultrasound of ipsilateral axilla with guided aspiration cytology (in select cases) with postoperative nodal pathology, to ascertain the accuracy of either of the preoperative assessment.

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Methods

The study was conducted as a prospective study at a tertiary cancer care center. Institute scientific committee and ethics committee approval were obtained prior to the initiation of study. Patients with early-stage breast cancer attending the outpatient clinic, on satisfying the inclusion and exclusion criteria and on consenting to be part of the study, were serially selected.

Inclusion Criteria

- (1) Female patients with early-stage breast cancer (T1,T2, N0, N1, M0) according to *AJCC Cancer staging manual*, 7th edition [3].

Exclusion Criteria

- (1) Patients below 18 years and above 80 years
- (2) Patient not consenting for study
- (3) Patients with previous ipsilateral axillary surgeries (node biopsy/axillary clearance)
- (4) Patients with noninvasive breast cancers
- (5) Patients not fit for surgery or not willing for complete axillary dissection.

All patients underwent routine triple assessment and staging workup. On physical assessment, axilla was noted as having no palpable axillary nodes, palpable but of doubtful significance (indeterminate), and suspicious nodes. After confirmation of invasive malignancy and absence of metastatic disease, patients were subjected to ultrasound of ipsilateral axilla by an experienced radiologist, using 3–12 MHz frequency ultrasound probe (GE Voluson 730 PRO). Each axilla was screened in its entirety to identify the presence of nodes, number and their morphological pattern (presence or absence of fatty hilum, cortical thickness measurement, presence or absence of eccentric cortical lobulations) along with vascularity using color Doppler.

Cortical thickness was measured from the cortical margin till the deepest portion of cortex. Nodes with more than 3-mm cortical thickness were considered positive. The whole node was assessed for presence of cortical lobulations and whether uniformly or eccentrically placed. Nodes with eccentric cortical lobulations were considered positive. The hilar status of the node was assessed and those with loss of fatty hilum were considered positive. Using color Doppler imaging, the vascular pattern was assessed to look for central or peripheral pattern and homogenous or heterogeneous pattern of distribution. Nodes with peripheral vascular pattern or with heterogeneous pattern were considered suspicious of metastasis. These parameters were noted for each node with a maximum of four

nodes being assessed in one axilla. If any node was found to have any one parameter as abnormal, the node was considered suspicious of containing metastasis.

Patients with suspicious node were subjected to fine needle aspiration cytology (FNAC) under ultrasound guidance. In case multiple nodes were found to be suspicious in the same patient, FNAC was performed from the most suspicious node. FNAC was performed using an 18-gauge needle attached to a 10-ml syringe and with real-time visualization of needle within the node. Two to three passes were made, and the aspirate was spread on a glass slide and fixed immediately with a fixative and sent to the pathology department for analysis.

All patients underwent complete axillary dissection surgery with mastectomy/wide excision for the primary tumor. In the postoperative histology, nodal yield, number of positive nodes, level of axilla involved, and presence of perinodal spread were noted and were correlated to the preoperative clinical assessment and ultrasound assessment of axilla and guided FNAC to determine their effectiveness in identifying disease in the axillary nodes. A total of 50 patients were enrolled in the study.

Statistical Analysis

Analysis was performed using statistical software SPSS, Version 17.0. Sensitivity, specificity, positive and negative predictive value, and accuracy were calculated independently for clinical assessment, ultrasound of axilla, and for US with FNAC. Tumor characteristics were compared between the positive and negative nodal groups to identify any difference and their statistical significance using chi-square test. Receiver operating curves (ROC) were drawn for the individual US-detected nodal parameters to identify the best predictor of metastatic disease in node based on the area under the curve.

Results

The median age of the population studied was 46.50 years, with most women in the group of 41–50 years (34%). Forty-six percent of patients were premenopausal, 26% perimenopausal, and 28% being postmenopausal.

On clinical examination of breast, upper outer quadrant was the commonest site of primary in breast (50%), upper inner quadrant being second (28%). On clinical examination of axilla, 96% of patients were classified as indeterminate axilla while 4% were classified as negative.

Based on the primary tumor size and nodal assessment, clinical stage was assigned based on the American Joint Committee on Cancer (AJCC) staging 7th edition manual [3]. Most patients were of stage IIB (84%), stage IIA constituting 10%, and stage I 4%. Six patients had prior excision of the primary tumor.

Ultrasound of ipsilateral axilla identified nodes in 47 of 50 patients. In three patients, no nodes were identified and were considered negative. Median number of nodes identified was 2. Nodal characteristics (loss of fatty hilum, presence of cortical thickness > 3 mm, eccentric cortical lobulations, and altered vascular pattern) (Fig. 1) were documented as described before. The nodal positivity based on the presence of any one of abovementioned features is described in Table 1.

Taking at least one parameter as positive, 31 patients were found to have positive ultrasound axilla. In the rest, though nodes were identified, they were considered negative. Among these US-positive patients, 19 patients had only one suspicious node, 9 patients had 2 suspicious nodes, 1 patient had 3 suspicious nodes, and 2 patients had all 4 nodes being suspicious for metastatic disease. Comparing various tumor-related factors and positivity on ultrasound, location of the primary in the breast, grade of tumor did not show any significant difference while size of the primary tumor was found to be significantly different ($p=0.04$).

All patients with suspicious nodes on US had guided FNAC performed. Twelve patients had positive FNAC indicating presence of axillary nodal metastasis, six had negative FNAC, six had reactive nodes, and in seven patients, the FNAC was inconclusive.

After complete axillary dissection, 22 patients had positive axillary nodes, number of positive nodes ranging from 1 to 24 (Table 2). Among patients with positive nodes, axillary involvement showed a sequential pattern of involvement, with level 1 node involvement seen in all patients with positive nodes and all patients with level 3 involvement having levels 1 and 2 involvement.

Comparing clinical examination with final histopathology, physical examination was inaccurate in 52% of patients. Twenty-six patients who were staged as cN1 based on

Table 1 Nodal characteristics and nodal positivity

Ultrasound nodal characteristic	Number of patients considered to have positive nodes
Loss of fatty hilum	23
Cortical thickness (> 3 mm)	24
Presence of cortical lobulation	19
Altered vascularity on Doppler	19
Positive axilla by ultrasound	31

presence of palpable axillary nodes were pN0 on final histology. The specificity of clinical examination was 7.14% and positive predictive value was 45.8% and accuracy 48%.

Comparing ultrasound staging of axilla with final histology, US was true positive in 20 patients and true negative in 17 patients, and false negative in 2 and false positive in 11 patients. The sensitivity and specificity was 90.0% and 60.7% respectively and accuracy was 74%. Each nodal parameter detected on US was found to have a positive correlation with the final nodal status [(by kappa measurement of agreement), with exact two-sided significance $p < 0.005$ by Pearson chi-square test]. When each of the four nodal parameters detected on ultrasound was compared individually with the final histology, loss of fatty hilum and presence of cortical lobulations had the highest accuracy. Receiver operating curves (ROC) drawn for each of the nodal parameters showed loss of fatty hilum to be the best predictor of nodal metastasis, followed by presence of eccentric cortical lobulations (Table 3).

Assessing the efficacy of ultrasound in identifying nodal metastasis in comparison to the nodal disease burden, ultrasound picked up all cases with more than one node positive and also picked up all patients having perinodal spread. It was false negative in only two patients with one node positive

Fig. 1 **a** Axillary node with loss of fatty hilum. **b** Axillary node with eccentric cortical lobulations and increased cortical thickness. **c** Axillary node with increased homogenous cortical thickness (> 3 mm). **d** Axillary node with nonhomogenous altered vascularity on color Doppler

Table 2 Nodal status on final histopathology

Patients with positive axillary nodes	22
Mean number of nodes dissected	
Total	20.66 ± 7.01
Pathological (p) nodal stage	
pN1 (1–3 nodes positive)	18 patients (81.8%)
pN2(4–9 nodes positive)	0 patients (0%)
pN3(> 10 nodes positive)	4 patients (18.2%)
Perinodal spread present	55.56%

Staging as per AJCC 7th Edition Staging Manual

(both in level 1 in axilla without any perinodal spread) on final histology. Sensitivity was 100% for all patients with more than one node involvement.

Comparing US-guided FNAC (done in 31 patients) and final histology, US FNAC was true positive in 12 and true negative in 10 patients and inconclusive in 7. There were two false-negative FNAC, which were reported as reactive nodes. In both cases, the positive nodes were only in level 1. The overall sensitivity and specificity of US FNAC was 85.7% and 100% with an accuracy of 91.7%.

On follow-up of patients with preoperative US FNAC, at 1 week post procedure but prior to definitive surgery, there was pain associated to the procedure in one patient (3.2%); no patient had any hematoma or other complications.

Discussion

In our study, physical examination of axilla had a sensitivity of 45.8% and specificity of 7.14%. The reported sensitivity and specificity for the same literature ranged from 32.3 to 68% and 62.5 to 97.3% respectively [4–7]. Our results were observed to have a lower specificity rate due to high false positivity (considering mere presence of node as positive). Palpation alone if used as a triage modality for selecting patients for sentinel node biopsy may thus be inaccurate, leading to a lot more number of patients ending up with unnecessary axillary dissection.

Our study detected nodes on ultrasound assessment in 96% of patients. In comparison to this, the studies of Deurloo et al., Damera et al., and Bonnema et al. had a nodal detection rate of 35–62% [8–10]. Analyzing the various tumor-related factors that could influence positivity on ultrasound, we found size of primary tumor to be the only factor to have statistical significance, which was comparable to the results of Mainiero et al. and Baruah et al. [11, 12]. Baruah et al. found that the grade of tumor was a significant factor influencing the outcome of the axillary ultrasound [12]; however, in our study, grade of tumor did not have a significant influence on ultrasound positivity.

Various studies assessing US-based nodal parameters predicting nodal involvement have found loss of fatty hilum to be the best predictor. Abe et al. [13] and Feu et al. [14] noted loss of fatty hilum to be the most specific sign of metastatic node which was also found in our study, having the maximum area under curve on ROC analysis. Considering the cutoff value for cortical thickness to represent metastatic disease, plotting on ROC curve, thickness of > 3 mm was found to have the maximum sensitivity (72.7%) and specificity (71.4%). With a cutoff of 2.3 mm, Deurloo et al. had a higher sensitivity but a lower specificity than our study [8], while Cho et al. using a cutoff ≥ 2.5 mm obtained a sensitivity of 85% and specificity of 78% [15]. It would be ideal to take a cutoff value, as anything more than 2.5–3 mm.

The overall sensitivity and specificity of preoperative US axilla in our study (positivity of any one parameter described above) was 90.9% and 60.7% which compares well with Moore et al. (based on asymmetric cortical lobulations, hyperechoic medullary region, hilum morphology, node shape, peripheral blood flow) [16] and Cho et al. (based on cortical thickness and hilar configuration) [15]. The two studies had reported sensitivity and specificity rates of 81% and 69% and 85% and 78% respectively. Study by Vaidya et al. [7] reported a very high specificity rate (90%) and a low sensitivity rate (69%). Alvarez et al. [17] in their meta-analysis reported a sensitivity and specificity rate of 81.7% and 96.1% using cortical morphological-based assessment of axillary nodes preoperatively.

Using US-guided FNAC in patients with suspicious nodes helped in reducing false positivity and improved specificity from 60.7 to 100%, with an accuracy rate of 74.2%. Moore et

Table 3 Comparison of efficacy of ultrasound nodal parameters

Ultrasound nodal feature	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	Area under the curve (ROC analysis)
Loss of hilum	77.27	78.5	73.91	81.48	78	0.779 ± 0.069
Cortical thickness	72.7	71.42	66.6	76.92	72	0.779 ± 0.069
Cortical lobulations	68.2	85.71	78.9	77.42	78	0.769 ± 0.071
Altered vascularity	63.6	82.14	73.68	74.19	74	0.729 ± 0.075

ROC receiver operating curve

al. [16] also reported an improvement in specificity from 69 to 100% with addition of guided FNAC. Various other studies have also reported 100% specificity with the use of guided FNAC [11, 12, 17].

Efficacy of preoperative US in identifying axillary metastasis was found to have direct correlation with axillary disease burden. In our study, all patients with more than one positive node were correctly identified. Two patients missed on preoperative US were pN1 on final histology (1 positive node). This was also observed by Moore et al. [16] reporting a 100% accuracy in patients with > 3 positive nodes and Bonnema et al. [9] reporting accuracy of 63% for ≥ 4 positive nodes versus 42% for one positive node. Krishnamurthy et al. [18] found that all patients with ≥ 3 positive nodes were correctly diagnosed preoperatively, while for patients with tumor deposit < 0.5 mm, it was 44%. Also noted was the fact that patients with US FNAC-detected nodal metastasis tended to have larger tumor deposits in nodes (9–13 mm) compared to negative US FNAC but positive sentinel node (3–6 mm). This was observed in Van Rijk et al.'s [19] study ($p < 0.001$). Van Wely et al. [20] also confirmed the same in their meta-analysis. Deurloo et al. [8], Baruah et al. [12], and Cyr et al. [21] also noted that micrometastasis and isolated tumor cell-positive patients had poor identification rates in preoperative US. Pilewskie et al. [22] also noted that finding an abnormal node on preoperative axillary imaging was significantly associated with having more than three total positive nodes on final pathology ($p = 0.003$).

Ultrasound-guided FNAC was also found to be a safe procedure as per our study with only one patient reporting localized pain post procedure at 1 week duration and no patients having hematoma or other complications, similar to the complication rates observed by Rikiya Nakamura et al. [23].

Sentinel node biopsy has become standard of care for clinically node-negative axilla. Given the high false-positive rate of clinical examination alone, presence of palpable axillary nodes alone may not be a sole contraindication for sentinel node. Specht et al. [24] in their analysis of conduct of sentinel node in clinically palpable axilla found clinical examination of axilla to have a high rate of inaccuracy (41%) with a false-positive rate of 53%, and concluded that in the presence of negative image-guided FNAC, sentinel node deserves a wider consideration. Given the high false positivity of clinical examination seen in our study and in the literature, it may be a viable and scientifically sound option to consider for US screening on these patients before deciding on sentinel node.

It has also been observed that since ultrasound-guided FNAC has a positive correlation with axillary disease burden, positive preoperative US-guided FNAC can help avoid unnecessary sentinel node biopsy in a clinically node-negative (cN0) axilla, avoiding a two-staged procedure and also reducing the cost burden on the health care system. Various studies [12, 19, 25, 26] report a 7.8–24.7% avoidance of sentinel node

biopsy with routine use of preoperative US $\pm$ FNAC. In a cost/accuracy ratio analysis by Franco Genta et al. [27], use of US with guided FNAC identified 33.3% patients preoperatively, thus avoiding sentinel nodes, and also showed that even though US with FNAC had cost implications, this was outweighed by avoidance of sentinel node biopsy and with immediate axillary dissection.

With the ACOSOG Z0011 trial [28] advocating in favor of avoidance of completion axillary dissection in select patients with < 3 nodal metastasis and also considering the fact that ultrasound $\pm$ guided FNAC-negative patients have a significantly lower disease burden, there is a question on the need for sentinel node biopsy at all in these patients. This is being addressed by SOUND trial by Veronesi et al. [29] and the trial in the USA (NCT01821768) [30], where select patients with negative preoperative axillary US + FNAC are randomized to sentinel node biopsy or observation alone. These trials will thus directly compare the efficacy of preoperative ultrasound with sentinel node biopsy. Amy E Cyr et al. [21] have reported the pilot phase study of the trial—NCT01821768—including 68 patients with early breast cancer and with a median follow-up of 17 months, no recurrences have been noted in either arm. In the sentinel node arm, three patients were found to have positive nodes, one patient with micrometastasis, one with deposit < 2 mm, and third with two nodes having largest tumor deposit measuring 7 mm.

Preoperative staging of ipsilateral axilla in patients with early-stage breast cancer does hold significance, both in patients with palpable but indeterminate nodes and in node-negative axilla. In the former, it can help in identifying true negative patients, who can then benefit from sentinel node biopsy. In the latter scenario, it can identify patients with true positive nodes, thus avoiding need for sentinel node biopsy. The future of axillary management is expected to see further changes with the results of above studies and it is going to give more emphasis to preoperative staging of axilla with US axilla.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. IARC, GLOBOCAN (2012) Fact sheets by cancer. [cited 2017 Sep 7]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2. Chapter10.pdf. [cited 2017 Sep 7]. Available from: http://www.ncrpindia.org/ALL_NCRP_REPORTS/HBCR_REPORT_2007_2011/ALL_CONTENT/ALL_PDF/Chapter10.pdf

3. Edge SB, Compton CC (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17(6):1471–1474
4. Bruneton JN, Caramella E, Héry M, Aubanel D, Manzino JJ, Picard JL (1986) Axillary lymph node metastases in breast cancer: preoperative detection with US. *Radiology* 158(2):325–326
5. Pamilo M, Soiva M, Lavast EM (1989) Real-time ultrasound, axillary mammography, and clinical examination in the detection of axillary lymph node metastases in breast cancer patients. *J Ultrasound Med* 8(3):115–120
6. de Freitas R, Costa MV, Schneider SV, Nicolau MA, Marussi E (1991) Accuracy of ultrasound and clinical examination in the diagnosis of axillary lymph node metastases in breast cancer. *Eur J Surg Oncol* 17(3):240–244
7. Vaidya JS, Vyas JJ, Thakur MH, Khandelwal KC, Mittra I (1996) Role of ultrasonography to detect axillary node involvement in operable breast cancer. *Eur J Surg Oncol* 22(2):140–143
8. Deurloo EE, Tanis PJ, Gilhuijs KGA, Muller SH, Kröger R, Peterse JL et al (2003) Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer. *Eur J Cancer Oxf Engl* 1990 39(8):1068–1073
9. Bonnema J, van Geel AN, van Ooijen B, Mali SP, Tjiam SL, Henzen-Logmans SC et al (1997) Ultrasound-guided aspiration biopsy for detection of nonpalpable axillary node metastases in breast cancer patients: new diagnostic method. *World J Surg* 21(3):270–274
10. Damera A, Evans AJ, Cornford EJ, Wilson ARM, Burrell HC, James JJ et al (2003) Diagnosis of axillary nodal metastases by ultrasound-guided core biopsy in primary operable breast cancer. *Br J Cancer* 89(7):1310–1313
11. Mainiero MB, Cinelli CM, Koelliker SL, Graves TA, Chung MA (2010) Axillary ultrasound and fine-needle aspiration in the preoperative evaluation of the breast cancer patient: an algorithm based on tumor size and lymph node appearance. *AJR Am J Roentgenol* 195(5):1261–1267
12. Baruah BP, Goyal A, Young P, Douglas-Jones AG, Mansel RE (2010) Axillary node staging by ultrasonography and fine-needle aspiration cytology in patients with breast cancer. *Br J Surg* 97(5):680–683
13. Abe H, Schmidt RA, Kulkarni K, Sennett CA, Mueller JS, Newstead GM (2009) Axillary lymph nodes suspicious for breast cancer metastasis: sampling with US-guided 14-gauge core-needle biopsy—clinical experience in 100 patients. *Radiology* 250(1):41–49
14. Feu J, Tresserra F, Fábregas R, Navarro B, Grases PJ, Suris JC et al (1997) Metastatic breast carcinoma in axillary lymph nodes: in vitro US detection. *Radiology* 205(3):831–835
15. Cho N, Moon WK, Han W, Park IA, Cho J, Noh D-Y (2009) Preoperative sonographic classification of axillary lymph nodes in patients with breast cancer: node-to-node correlation with surgical histology and sentinel node biopsy results. *AJR Am J Roentgenol* 193(6):1731–1737
16. Moore A, Hester M, Nam M-W, Brill YM, McGrath P, Wright H et al (2008) Distinct lymph nodal sonographic characteristics in breast cancer patients at high risk for axillary metastases correlate with the final axillary stage. *Br J Radiol* 81(968):630–636
17. Alvarez S, Añorbe E, Alcorta P, López F, Alonso I, Cortés J (2006) Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. *AJR Am J Roentgenol* 186(5):1342–1348
18. Krishnamurthy S, Sneige N, Bedi DG, Edieken BS, Fornage BD, Kuerer HM et al (2002) Role of ultrasound-guided fine-needle aspiration of indeterminate and suspicious axillary lymph nodes in the initial staging of breast carcinoma. *Cancer* 95(5):982–988
19. van Rijk MC, Deurloo EE, Nieweg OE, Gilhuijs KGA, Peterse JL, Rutgers EJT et al (2006) Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. *Ann Surg Oncol* 13(1):31–35
20. van Wely BJ, de Wilt JHW, Francissen C, Teerenstra S, Strobbe LJA (2015) Meta-analysis of ultrasound-guided biopsy of suspicious axillary lymph nodes in the selection of patients with extensive axillary tumour burden in breast cancer. *Br J Surg* 102(3):159–168
21. Cyr AE, Tucker N, Ademuyiwa F, Margenthaler JA, Aft RL, Eberlein TJ et al (2016) Successful completion of the pilot phase of a randomized controlled trial comparing sentinel lymph node biopsy to no further axillary staging in patients with clinical T1-T2 N0 breast cancer and normal axillary ultrasound. *J Am Coll Surg* 223(2):399–407
22. Pilewskie M, Mautner SK, Stempel M, Eaton A, Morrow M (2016) Does a positive axillary lymph node needle biopsy result predict the need for an axillary lymph node dissection in clinically node-negative breast cancer patients in the ACOSOG Z0011 era? *Ann Surg Oncol* 23(4):1123–1128
23. Nakamura R, Yamamoto N, Miyaki T, Itami M, Shina N, Ohtsuka M (2017) Impact of sentinel lymph node biopsy by ultrasound-guided core needle biopsy for patients with suspicious node positive breast cancer. *Breast Cancer Tokyo Jpn* 25:86–93. <https://doi.org/10.1007/s12282-017-0795-7>
24. Specht MC, Fey JV, Borgen PI, Cody HS (2005) Is the clinically positive axilla in breast cancer really a contraindication to sentinel lymph node biopsy? *J Am Coll Surg* 200(1):10–14
25. Rattay T, Muttalib M, Khalifa E, Duncan A, Parker SJ (2012) Clinical utility of routine pre-operative axillary ultrasound and fine needle aspiration cytology in patient selection for sentinel lymph node biopsy. *Breast Edinb Scotl.* 21(2):210–214
26. Diepstraten SCE, Sever AR, Buckens CFM, Veldhuis WB, van Dalen T, van den Bosch MAAJ et al (2014) 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* 21(1):51–59
27. Genta F, Zanon E, Camanni M, Deltetto F, Drogo M, Gallo R et al (2007) Cost/accuracy ratio analysis in breast cancer patients undergoing ultrasound-guided fine-needle aspiration cytology, sentinel node biopsy, and frozen section of node. *World J Surg* 31(6):1155–1163
28. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW et al (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 305(6):569–575
29. Gentilini O, Veronesi U (2012) Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: sentinel node vs observation after axillary UltraSOUND). *Breast Edinb Scotl* 21(5):678–681
30. Axillary ultrasound with or without sentinel lymph node biopsy in detecting the spread of breast cancer in patients receiving breast conservation therapy - Full Text View - [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT01821768) [Internet]. [cited 2017 Sep 11]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01821768>