Journal of Clinical and Medical Images

Research Article ISSN: 2640-9615 | Volume 5

Correlation of Preoperative Axillary Lymph Node Status to Final Histology After Axillary Surgery for Breast Cancer

Tang ELS[1,2*], Chotai N[3,4], Chong BK[3], Sin PY[1], Lee SYS[1], Chan MYP[1], Chen JJC[1], Goh MH[1] and Tan EY[1]

[1]Department of General Surgery, Tan Tock Seng Hospital, Singapore

[2]Department of General Surgery, Woodlands Health Campus, Singapore

[3]Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore

[4]Radlink Diagnostic Imaging Centre, Singapore

[*]Corresponding author:

Tang Ee Ling Serene,
Department of General surgery,
11 Jalan Tan Tock Seng,
Singapore 308433,
Tel: +65 63577807;
E-mail: serene_tang@whc.sg

Received: 13 Nov 2020
Accepted: 08 Dec 2020
Published: 14 Dec 2020

Citation:

Tang ELS. Correlation of Preoperative Axillary Lymph Node Status to Final Histology After Axillary Surgery for Breast Cancer. Journal of Clinical and Medical Images. 2020; V5(4): 1-8

Keywords:

Axillary ultrasound; Breast Cancer; Axillary lymph node biopsy; Sentinel lymph node biopsy; Axillary surgery

1. Abstract

1.1. Introduction: Axillary lymph node(ALN) status is an important prognostic factor for breast cancer. The high accuracy of axillary ultrasound(AUS) has led to several ongoing trials where sentinel lymph node biopsy(SLNB) omission is explored for negative AUS in early breast cancer. We aimed to correlate pre-operative ALN status with final histology. Specifically, we sought to identify factors associated with a false negative AUS.

1.2. Materials & Methods: An 11-year retrospective review of breast cancer patients who underwent surgery between 1st January 2006 and 31st December 2016 at a tertiary Breast Unit, was performed. Ultrasound ALN characteristics, preoperative biopsy findings and final postoperative histology were evaluated. Women with clinically non-palpable axillary nodes were included.

1.3. Results: 1665 breast cancer patients were evaluated. 368 patients had an abnormal preoperative AUS. Axillary metastasis was 18-fold higher in patients with an abnormal AUS (P <0.001, 17.927, 95% CI: 13.493 to 23.820). However, 15.3%(198 of 1297) of those with a normal AUS had axillary metastases. The sensitivity, specificity, positive predictive value and negative predictive value were 58.7%, 92.7%, 76.4% and 84.7% respectively. Loss of fatty hilum and tumour size were independent predictors of ALN metastases.

The low sensitivity of the ALN on preoperative ultrasound may not be sufficiently accurate to determine the true presence of ALN metastasis. 1518 patients underwent an SLNB. 22.1% (336 of 1518 patients) had ALN involvement.

1.4. Conclusion: A normal preoperative axillary ultrasound is insufficient to negate the need for SLNB. SLNB is still necessary for accurate staging and treatment of breast cancer.

2. Introduction

Axillary lymph node (ALN) status is an important prognostic factor for breast cancer and is the main consideration for adjuvant chemotherapy and radiation therapy. Up to 70% of women with early breast cancer have no axillary lymph node metastases [1 ,2]. The status of the axillary nodes at the time of diagnosis impacts the decision for surgery to the nodal basin. The advent of the sentinel lymph node biopsy (SLNB) was practice changing when it was introduced in 1991 [3] and full axillary nodal dissection (ALND) was no longer done as a routine but only in instances where the sentinel lymph node (SLN) was positive for metastases [4]. The Z11 trial has gone a step further to suggest that ALND can be safely omitted when there is limited SLN involvement [5].

At our unit, SLNB is the standard of care for women with no

pre-operative evidence of axillary nodal involvement, with ALND being done when the SLN is positive for metastases or when there is pre-operative evidence of nodal involvement. The axillary nodes are routinely documented on the breast ultrasound done for initial work-up and in the recent years, it has become common practice to obtain histological confirmation of abnormal nodes through a core biopsy. Pre-operative axillary ultrasound (AUS) has been variously reported to have a sensitivity of 65% to 86% and specificity of 75% to 85% in predicting nodal involvement [6, 7] and pre-operative node biopsy has been reported with a sensitivity of 80% and specificity of 98% in detecting nodal metastases [8, 9].

The accuracy of AUS has increased over the years with increasing experience, subspecialisation and refinements in sonography technology. This has led to several ongoing trials (eg. SOUND, INSEMA, BOOG 2013-08) to explore the feasibility and safety of omitting SLNB entirely should the AUS be negative for abnormal nodes in women with early staged breast cancer [10–12]. The safety of such an approach ultimately depends on the accuracy of pre-operative AUS, the frequency and the implications of a missed abnormal axillary node. In this study, we reviewed our experience with pre-operative AUS and node biopsy in women diagnosed and treated at our unit. We correlated pre-operative status of the axillary nodes with that on final histology in order to determine the frequency a false negative AUS and factors associated with it.

3. Materials and Methods

This was a retrospective, single centre study in a tertiary breast unit and included women diagnosed with early breast cancer who underwent breast cancer surgery between 1st January 2006 and 31st December 2016. Women with no clinically palpable axillary nodes and who did not have contraindications for sentinel lymph node biopsy (SLNB) were included. Women with ductal carcinoma-in-situ, metastatic disease, inflammatory breast cancer, tumours involving the skin or chest wall (T4 tumours), tumours involving the nipple-areolar complex, clinically palpable axillary and supraclavicular lymph nodes and women who had received neoadjuvant treatments were excluded.

Ethics committee approval was obtained for this study (DSRB2019/00058). Details of patient demographic profile, breast and axillary ultrasound features, pre-operative axillary nodal biopsy findings and histological analysis of the surgical specimen were collected from the clinical records. Bilateral breast and axillary ultrasound was performed as a routine work-up for women diagnosed at our unit. Breast ultrasound was performed using the Acuson S2000 system (Siemens Medical Solutions, Mountain View, USA) or Toshiba Aplio 80 (Toshiba Inc., Tokyo, Japan). Both machines were equipped with a variable-frequency linear array transducer set at [9–14] MHz. The ultrasound was performed in supine oblique position with the arm above the head while scanning. The breast tumor was assessed for location, distance from nipple, size, morphology and internal vascularity. The AUS generally evaluated level I lymph nodes for features of tumour involvement. Occasionally, level II nodes would also be identified when enlarged. The axillary nodes were considered normal when the following features were present: oval or lobulated shape, smooth and well-defined margins, uniformly thin, hypoechoic cortex having cortical thickness within 3 mm and preserved fatty hilum. Abnormal nodal features included a rounded shape, diffuse cortical thickening more than 3 mm, focal cortical bulge, eccentric cortical thickening, hilar effacement and an irregular capsular surface

Histological confirmation of radiologically abnormal nodes either by fine needle aspiration cytology (FNAC) or core needle biopsy was done according to surgeon discretion. Axillary node core biopsy was generally performed under ultrasound guidance by accredited radiologists at our unit. Biopsy was performed under local anesthesia using a 14G or 18G spring loaded core biopsy needle. An average of 2 to 3 cores was obtained through the abnormal lymph node cortex and sent for the histological analysis. Fine needle aspiration cytology of the axillary lymph node was generally performed by the surgeon, either freehand or under ultrasound guidance. The abnormal axillary lymph node was isolated and aspiration of the targeted lymph node was performed with a 21G needle under aseptic technique. An average of 3 passes were performed and the cytology was smeared on 4 slides; 2 of which are air-dried, and 2 fixed in 95% methylated spirit. These slides were then sent to the cytology lab for cytological analysis.

SLNB was performed by accredited breast surgeons at the time of surgery. Single modality blue dye was used. Under anesthesia, 2ml of Patent V blue dye would be injected beneath the nipple-areolar complex targeting the sub areolar lymphatic plexus. The breast would be massaged for 5 minutes to facilitate diffusion of the blue dye to the axillary nodal basin. The axilla was then exposed and the sentinel nodes at level I would be identified by tracking blue lymphatics draining to a blue node. All blue nodes were removed for frozen section analysis. An average of 3 nodes were removed. The decision to proceed with ALND or otherwise was based on the frozen section analysis. Following frozen section analysis, the entire node would be formalin fixed and paraffin embedded for further histological analysis.

4. Statistics

The presence of abnormal preoperative AUS was correlated with pre-operative axillary node biopsy (if performed) and with the final histology of the axillary nodes at surgery. Correlation analyses were performed using Chi-squared test, t test, and one-way ANOVA, as appropriate, using the Graph Pad Prism version 7 (Graph Pad software Inc., San Diego, CA, USA). Logistic regression to identify independent predictors of axillary lymph node metastases was performed with Stata package release 11.0 (Stata Corporation, Texas, USA). A full model was first created to include all poten-

tially important explanatory variables. At each step, the variable with the smallest contribution to the model was removed, until a final backward stepwise model was obtained. A 2-tailed P value test was used for all analyses, and a value of P <0.05 was considered statistically significant.

5. Results

The study included 1665 women diagnosed with clinically node-negative breast cancer between 1st January 2006 to 31st December 2016. Median age was 58 years (ranging from 25 to 93 years). Distribution of disease stage was as follows: 770 of 1665 women (46.3%) with Stage I, 723 (43.4%) with Stage II, 172 (10.3%) with Stage III disease. Median tumour size was 19 (ranging from 1mm to 120mm), and median tumour grade was 2. Three quarters of tumours (1264, 75.9%) were oestrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive, and 375 (22.5%) were human epidermal growth factor receptor (HER)-2 positive. The majority of tumours were classified as invasive ductal carcinoma, not otherwise specified. Details are included in (Table 1). Slightly more women were treated with mastectomy, with or without reconstruction, compared to wide local excision. A total of 1518 women underwent SLNB, with 341 of these proceeding to a ALND at surgery. In 23 instances, the surgeon proceeded with ALND despite not having a positive SLN documented at surgery; in 19 instances because of non-identification of the SLN and in 5 instances because of palpable non-SLN nodes noted intra-operatively. Nineteen patients with a positive SLN (intra-operative frozen section had been falsely negative) declined ALND and opted for axillary radiation instead.

All women had no clinically abnormal ALN. The majority of women (1297 of 1665, 77.9%) also had no radiological evidence of abnormal nodes, while abnormal nodes were found on AUS in 368 women (22.1%). Abnormal axillary US findings occurred more frequently with larger tumours (P <0.001), ER-negative tumours (P <0.001), and PR-negative tumours (P <0.001) (Table 1). Overall, 28.9% of women (479 of 1665) were found with ALN involvement at final histology. Nodal involvement was confirmed pre-operatively in 131 women and was found at surgery in another 348 women; 336 following ALND done for positive SLNB and 12 following ALND done upfront based on abnormal AUS findings.

Of the 368 patients with abnormal AUS, thickened node cortex was the most commonly reported feature, occurring in 78.5% (289 of 368) of women and it showed a positive correlation with nodal disease (P = 0.044, OR 2.489, 95% CI: 1.073 to 5.772) (Table 2). Loss of fatty hilum, observed in 40.0% (147 of 368) of the women, also showed a strong correlation with nodal disease (P <0.0001, OR 6.236, 95% CI: 3.101 to 12.430) and nodal metastases was confirmed in 80.0% (67 of 84) of ALN biopsies done when loss of fatty hilum was present. In all, more than 90% of women (135 of 147, 91.8%) with loss of fatty hilum were found with nodal metastases, compared to 73.8% (59 of 80) of women with cortical thickening but no loss of fatty hilum. Both loss of fatty hilum and thickened cortex were independent predictors of nodal metastases (P <0.001, OR 11.897, 95% CI: 6.054 to 23.379 and P <0.001, OR 10.201, 95% CI: 7.056 to 14.749 respectively), together with tumour size (P <0.001, OR 1.039, 95% CI: 1.026 to 1.051) and negative ER status (P = 0.018, OR 1.749, 95% CI: 1.102 to 2.776) (Table 3). Seventy-six percent of women (281 of 368) with an abnormal AUS were eventually found with axillary metastases, compared to 15.3% (198 of 1297) of those with a normal AUS (P <0.001, OR 17.927, 95% CI: 13.493 to 23.820). Pre-operative AUS had a sensitivity of 58.7% and specificity of 92.7% in predicting nodal involvement. Positive predictive value was 76.7% and negative predictive value was 84.7% (Table 4). Subgroup analysis of patients with true negative AUS with that of false negative AUS revealed that those with false negative AUS had significantly larger tumour size (P < 0.001), were more likely ER positive (P < 0.004, OR 1.804, 95% CI 1.194 to 2.724) and PR positive (P < 0.003, OR 1.672, 95% CI 1.180 to 2.368), and had more number of ALN metastases on final histology (P < 0.001).

Over the study period, 204 of the 368 women (55.4%) with abnormal preoperative AUS underwent pre-operative node biopsy; 164 via core biopsy and 40 via FNAC. Pre-operative ALN biopsy had a sensitivity of 83.4% and specificity of 100.0% in predicting nodal involvement (Table 5). Positive predictive value was 100.0% and negative predictive value was 64.4% (Table 5). False negative rate of FNAC was 45.2% (14 of 31) while that of core biopsy was 10.8% (12 of 111). Metastatic nodal disease was confirmed pre-operatively in 131 of these 204 patients (64.2%), who subsequently underwent upfront ALND. Nodal biopsy was negative for metastases in the remaining 73 women; 56 of whom underwent SLNB and 16 of whom underwent ALND as decided by the surgeon. Axillary nodal metastases were eventually found at surgery in 26 of these women, giving pre-operative nodal biopsy a false negative rate of 35.6%. Of the 1518 patients with normal AUS findings or a negative node biopsy who underwent SLNB, 336 patients (22.1%) were eventually found to have ALN involvement at surgery. Women with abnormal AUS but a negative node biopsy were still 3 times more likely to have a positive SLNB compared to women with normal AUS (P <0.001, OR 3.073, 95% CI 1.859 to 5.080).

Tumour burden was significantly higher in women with abnormal AUS findings in whom nodal involvement was later confirmed (P <0.001, OR 16.848 and 95% CI 11.914 to 23.826) compared to those with an initial normal AUS (Table 6). Half of those (101 of 198, 51.0%) with normal AUS had only a single involved node, compared to only 32.4% (91 of 281) of those with an abnormal AUS (Table 6). The median number of nodes involved in those with normal AUS was 0, compared to 2 in those with abnormal AUS.

Table 1: Patient demographics and tumour characteristics.

		Abnormal AUS (n = 368)	Unremarkable AUS (n = 1297)	P value
Median Age (years)		57 (27 – 88)	58 (25 – 93)	0.459
Ethnicity				0.406
	Chinese	271	1082	
	Malay	40	89	
	Indian	27	62	
	Others	30	64	
Tumour Histology				0.415
	Invasive Ductal Carcinoma	331	1083	
	Invasive Lobular Carcinoma	22	87	
	Mixed Invasive Ductal and Lobular Carcinoma	9	24	
	Invasive Mucinous Carcinoma	4	62	
	Invasive Tubular Carcinoma	1	14	
	Others	1	27	
Median radiological tumour size (mm)		27 (2 - 130)	20 (2 - 117)	< 0.001
Median pathological tumour size (mm)		25 (0 - 100)	17 (0 - 120)	< 0.001
Tumour ER status				< 0.001
	Positive	235	997	
	Negative	131	297	
Tumour PR status				< 0.001
	Positive	195	864	
	Negative	171	430	
Tumour HER2 status				0.359
	Positive	114	261	
	Negative	240	984	
	Equivocal	12	34	
Tumour stage				0.215
	I	41	729	
	II	192	531	
	III	135	37	
Type of breast surgery				0.163
	Wide Excision	83	557	
	Mastectomy	241	646	
	Mastectomy with reconstruction	44	94	
Type of Axillary Surgery				0.410
	SLNB	83	1094	
	SLNB followed by ALND	138	203	
	ALND	147	0	
Median No. of ALN metastases		2 (0 - 44)	0 (0 - 30)	< 0.001

Univariate analysis between AUS findings and patient demographics and tumour characteristics. Legend- AUS: Axillary ultrasound, ER: oestrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor (HER)-2, SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection, ALN: axillary lymph node.

Table 2: Correlation with ALN pathology.

	ALN metastasis (n = 479)	No ALN metastasis (n = 1186)	P value
Median patient age	57 (27 - 91)	58 (25 - 93)	0.372
Radiological lesion size	26 (2 - 130)	19 (2 - 117)	< 0.001
Pathological lesion size	25 (0 - 100)	16 (0 - 120)	< 0.001

AUS			< 0.001
Abnormal	281	87	
Normal	198	1099	
Loss of fatty hilum			< 0.001
Yes	135	12	
No	78	43	
Thickened nodal cortex			0.044
Yes	231	58	
No	16	10	
Tumour ER status			0.577
Positive	359	873	
Negative	118	310	
Tumour PR status			0.866
Positive	306	753	
Negative	171	430	
HER2 status			0.447
Positive	130	245	
Negative	337	887	
Equivocal	10	36	
Tumour histology			0.512
Invasive Ductal Carcinoma	424	990	
Invasive Lobular Carcinoma	30	79	
Mixed Invasive Ductal and Lobular Carcinoma	14	19	
Invasive Mucinous Carcinoma	6	60	
Invasive Tubular Carcinoma	3	12	
Others	2	26	
Final disease stage			0.380
I	1	769	
II	306	417	
III	172	0	

Univariate analysis between ALN involvement, patient demographics and tumour characteristics. Legend- ALN: axillary lymph node. AUS: Axillary ultrasound, ER: oestrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor (HER)-2.

Table 3: Logistic regression of clinicopathological parameters stratified by axillary lymph node metastases (n = 1579).

	Odds Ratio	Standard Error	P value	95% Confidence Interval
Radiological tumour size (mm)	1.015	0.005	0.003	1.005 to 1.026
Pathological tumour size (mm)	1.039	0.006	< 0.001	1.026 to 1.051
Loss of fatty hilum	11.897	4.101	< 0.001	6.054 to 23.379
Thickened cortex	10.201	1.919	< 0.001	7.056 to 14.749
Negative ER Status	1.749	0.412	0.018	1.102 to 2.776
Negative PR Status	1.308	0.272	0.196	0.871 to 1.965

Legend- ER: oestrogen receptor, PR: progesterone receptor

Table 4: Tabulation of numbers (percentage of the entire cohort) for axillary ultrasound findings with respect to pathological ALN involvement (n = 1665).

Pre- Op ALN Biopsy	LN involvement on final histology (n= 479)	No LN involvement on final histology (n=1186)
Abnormal AUS	281 (16.9)	87 (5.2)
Normal AUS	198 (11.9)	1099 (66.0)

Table 5: Tabulation of numbers of women (percentage) who underwent pre-operative axillary lymph node (ALN) biopsy with respect to nodal involvement on final histology (n = 204)

	Nodal involvement on final histology (n = 157)	Node negative on final histology (n = 47)
Positive Pre-operative ALN biopsy	131 (64.2)	0
Negative Pre-operative ALN biopsy	26 (12.7)	47 (23.0)

Table 6: Extent of ALN involvement with respect to pre-operative AUS findings

No. of ALN involved	Normal AUS Finding (n=1297)		Abnormal AUS Finding (n=368)	
	No ALN metastases (TN) (n=1099)	ALN metastases (FN) (n=198)	No ALN metastases (FP) (n=87)	ALN metastases (TP) (n=281)
0	1099	0	87	0
1	0	101 (51.0%)	0	91 (32.3)
2	0	45 (22.7%)	0	38 (13.5%)
3	0	23 (11.6%)	0	28 (10.0%)
≥4	0	29 (14.7%)	0	124 (44.1%)

6. Discussion

In our study, 29% of women with clinically node negative disease were eventually found with nodal involvement. This included 281 women with an abnormal AUS and 198 women with a normal AUS. We observed pre-operative AUS to have a sensitivity of 58.7% in predicting nodal involvement, which was relatively similar to various reports in the literature ranging from 54% to 67% [13,14]. Thickened nodal cortex and particularly loss of fatty hilum were independently predictors of nodal involvement [6, 13–16]. Not surprisingly, tumour size correlated positively with the likelihood of nodal metastases and we also observed that ER-negative tumours were often found with nodal disease, perhaps an indication of a more aggressive phenotype [17].

Starting from 2012, the practice of obtaining pre-operative biopsy for histological confirmation of sonographically abnormal nodes became more prevalent at our unit. In the last 2 years of the study, more than 90% of those with abnormal AUS had pre-operative histological confirmation. Pre-operative ALN biopsy had high accuracy in determining nodal status, with a sensitivity of 83.4% and specificity of 100.0%. It is now adopted as a routine standard of care in women with abnormal AUS at our unit and has helped guide the decision for SLNB or upfront ALND. Nodal biopsy is now almost always performed via a core biopsy under image guidance, following our experience of the high false negative rates found on FNAC. Other studies have also described high inadequacy rates of fine needle node aspirates, some as high as 46% [18, 19], compared to a false negative rate of 15.3 to 31% reported for image guided biopsies [20, 21].

The pertinent question of today is whether it is safe to omit the sentinel lymph node biopsy in early breast cancer and base the decision for axillary management on clinical and radiological findings [22]. While an abnormal AUS is highly suggestive of nodal involvement, our observation that 22.1% of women with normal AUS or a negative pre-operative ALN biopsy had node-positive disease would imply that almost a quarter of women would be under-staged, and perhaps under-treated, should SLNB had been omitted. The false negative rate of AUS of 41.3% would suggest that SLNB should not be omitted based on a normal AUS. Furthermore, women with abnormal AUS but a pre-operative nodal biopsy that was negative for malignancy remained at risk of a positive SLN. Overall, pre-operative ALN biopsy had a false negative rate of 16.5%, with majority of instances occurring when FNAC was done instead of an image-guided core biopsy.

The prospective randomized INSEMA, SOUND and BOOG 2013-08 trials explore the possibility of omitting even SLNB in women who have normal AUS [10–12]. Our study found that 15.3% of

women with normal AUS have nodal disease. Going by the Z011 trial data, which reported equivalent outcomes when ALND was omitted in limited SLN disease, it could be argued that many of these women would not have benefited from ALND anyway even if SLNB had been done [5]. However, 14.7% of women with normal AUS were found with 4 or more nodes involved and historical studies have reported increased rates of axillary recurrence and poorer breast cancer specific survival when axillary surgery was avoided in early breast cancer [23–28]. One difficulty with omitting SLNB, and to a certain extent ALND, is that the full extent of nodal involvement might not be known. While indications for chemotherapy, targeted therapy are now considered for almost all node-positive cancers, in certain subgroups, such as ER-positive/HER2-negative cancers, the extent of nodal involvement would affect the decision to apply genomic assays like MammaPrint and Oncotype DX, to determine the benefit of chemotherapy [29–31]. From our study, AUS alone would not be able to provide an accurate stratification into N1 or N2 disease.

7. Conclusion

Abnormal AUS features, including thickened node cortex and loss of fatty hilum, increases the likelihood of having metastatic ALN involvement. However, a normal pre-operative AUS, or even a negative pre-operative ALN biopsy, may not be sufficient to negate the need for the SLNB. It is also difficult to determine the extent of nodal involvement based on AUS alone.

References:

1. Stachs A, Gode K, Hartmann S, Stengel B, Nierling U, Dieterich M et al. Accuracy of axillary ultrasound in preoperative nodal staging of breast cancer - size of metastases as limiting factor. Springerplus. 2013; 2: 350.
2. Gerber B, Heintze K, Stubert J, Dieterich M, Hartmann S, Stachs A, et al. Axillary lymph node dissection in early-stage invasive breast cancer: Is it still standard today? Breast Cancer Res Treat. 2011; 128: 613-24.
3. Tanis PJ, Nieweg OE, Valdes Olmos RA, Rutgers EJT, Kroon BBR. History of sentinel node and validation of the technique. Breast Cancer Res. 2001; 3: 109-12.
4. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003; 349: 546-53.
5. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA - J Am Med Assoc. 2011; 305: 569-75.
6. Deurloo EE, Tanis PJ, Gilhuijs KGA, Muller SH, Kroger 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.
7. Bonnema J, Van Geel AN, Van Ooijen B, Mali SP, Henzen-Logmans SC, Schmitz PI, 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.
8. Vidya R, Iqbal FM, Bickley B. Pre-operative axillary staging: Should core biopsy be preferred to fine needle aspiration cytology? Ecancermedicalscience. 2017; 11: 724.
9. Ganott MA, Zuley ML, Abrams GS, Lu AH, Kelly AM, Sumkin JH, et al. Ultrasound Guided Core Biopsy versus Fine Needle Aspiration for Evaluation of Axillary Lymphadenopathy in Patients with Breast Cancer. ISRN Oncol. 2014; 2014: 703160.
10. Gentilini O, Veronesi U. 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. 2012; 21: 678-81.
11. Reimer T, Stachs A, Nekljudova V, Loibl S, Hartmann S, Wolter K, et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (C/IT1-2) in the context of breast conserving therapy: First results following commencement of the intergroup-sentinel-mamma (INSEMA) trial. Geburtshilfe Frauenheilkd. 2017; 77: 149-57.
12. van Roozendaal LM, Vane MLG, van Dalen T, van der Hage JA, Strobe LJA, BoersmaLJ, et al. Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: A Dutch randomized controlled multicentre trial (BOOG 2013-08). BMC Cancer. 2017; 17: 459.
13. Stachs A, Thi A, Dieterich M, Stubert J, Hartmann S, Glass A, et al. Assessment of Ultrasound Features Predicting Axillary Nodal Metastasis in Breast Cancer: The Impact of Cortical Thickness. Ultrasound Int Open. 2015; 01: E19-24.
14. Lee B, Lim AK, Krell J, Satchithananda K, Coombes RC, Lewis JS, et al. The efficacy of axillary ultrasound in the detection of nodal metastasis in breast cancer. Am J Roentgenol. 2013; 200: W314-20.
15. Abe H, Schmidt RA, Kulkarni K, Sennett CA, Mueller JS, Newstead GM. Axillary lymph nodes suspicious for breast cancer metastasis: Sampling with US-guided 14-gauge core-needle biopsy - Clinical experience in 100 patients. Radiology. 2009; 250: 41-9.
16. 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.
17. Ahmed ARH. HER2 expression is a strong independent predictor of nodal metastasis in breast cancer. J Egypt Natl Canc Inst. 2016; 28: 219-27.
18. Kane G, Fleming C, Heneghan H, McCartan D, James P, Trueick R, et al. False-negative rate of ultrasound-guided fine-needle aspiration cytology for identifying axillary lymph node metastasis in breast cancer patients. Breast J. 2019; 25: 848-52.
19. Leenders MWH, Broeders M, Croese C, Richir MC, Go HLS, Langenhorst BLAM, et al. Ultrasound and fine needle aspiration cytology of axillary lymph nodes in breast cancer. To do or not to do?

Breast. 2012; 21: 578-83.

20. Ciatto S, Brancato B, Risso G, Ambrogetti D, Bulgaresi P, Maddau C, et al. Accuracy of fine needle aspiration cytology (FNAC) of axillary lymph nodes as a triage test in breast cancer staging. Breast Cancer Res Treat. 2007; 103: 85-91.
21. Pisano ED, Fajardo LL, Tsimikas J, Sneige N, Frable WJ, Gatsonis CA, et al. Rate of insufficient samples for fine-needle aspiration for nonpalpable breast lesions in a multicenter clinical trial: The Radiologic Diagnostic Oncology Group 5 Study. The RDOG5 investigators. Cancer. 1998; 82: 679-88.
22. Reimer T, Engel J, Schmidt M, Offersen BV, Smidt ML, Gentilini OD. Is Axillary Sentinel Lymph Node Biopsy Required in Patients Who Undergo Primary Breast Surgery? Breast Care. 2018; 13: 324-30.
23. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-Year Follow-Up of a Randomized Trial Comparing Total for the Treatment of Invasive Breast Cancer. English J. 2002; 347: 1233-41.
24. Intra M, Trifiro G, Viale G, Rotmensz N, Gentilini OD, Galimberti V, et al. Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol. 2005; 12: 895-9.
25. Rudenstam CM, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB, Rey P, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: First results of International Breast Cancer Study Group trial 10-93. J Clin Oncol. 2006; 24: 337-44.
26. Martelli G, Boracchi P, Orenti A, Lozza L, Maugeri I, Vetralla G, et al. Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-year results of trial and out-trial patients. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2014; 40: 805-12.
27. Agresti R, Martelli G, Sandri M, Tagliabue E, Carcangiu ML, Maugeri I, et al. Axillary lymph node dissection versus no dissection in patients with T1N0 breast cancer: a randomized clinical trial (INT09/98). Cancer. 2014; 120: 885-93.
28. Wang J, Tang H, Li X, Song C, Xiong Z, Wang X, et al. Is surgical axillary staging necessary in women with T1 breast cancer who are treated with breast-conserving therapy? Cancer Commun. 2019; 39: 25.
29. Cardoso F, Van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016; 375: 717-29.
30. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015; 373: 2005-2014.
31. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018; 379: 111-21.