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Role of axillary ultrasound in the evaluation of early breast cancer in the era of Z0011: Time to redefine?

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ABSTRACT

Introduction: Ultrasound with concurrent histology of abnormal axillary lymph nodes has revolutionized the treatment of patients with breast cancer. By identifying nodal metastases, patients can avoid a two-stage axillary procedure. However, the results of the American College of Surgeons Oncology Group Z0011 trial indicate that a certain group of patients may have been over-treated with axillary dissection. Our aim was to analyze the nodal burden of patients identified by axillary ultrasound and to determine the proportion of patients who could have foregone axillary dissection incorporating Z0011 trial.

Methods: A retrospective analysis of patients with diagnosed breast cancer who underwent direct axillary dissection was performed. Based on nodal metastases patients were categorized into 'extensive' and 'minimal' groups and studied. Demographics and tumor characteristics were analyzed and eligibility for the Z0011 study was determined.

Results: All 1745 patients diagnosed with breast cancer underwent axillary ultrasound from April 2009 to March 2015. Of these, 197 patients had histology-proven nodal metastases and underwent direct axillary lymph node dissection. One hundred and twenty-one patients (61.4%) had extensive and 76 patients (38.6%) had minimal nodal metastases. Of the latter, 23 patients (11.7%) fulfilled the Z0011 criteria.

Conclusion: This study demonstrated that a large proportion of patients had minimal nodal involvement (38.6%), in contrast to the results published in the literature. In addition, a significant number of patients could have avoided axillary dissection (11.7%) based on the Z0011 criteria. Hence our study encourages to redefine the role of axillary ultrasound to avoid unnecessary axillary dissection.

Key points:

1. Axillary ultrasound is performed in all patients diagnosed with breast cancer.

2. Axillary ultrasound findings do not correlate with histological burden of nodal disease.

3. Role of axillary ultrasound needs to be redefined to avoid unnecessary axillary dissection.

Key words: Ultrasonography; Cytology; Metastasis; Breast Cancer; Lymph nodes

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Introduction

Axillary ultrasound combined with fine needle aspiration cytology (FNAC) or core biopsy (CB) has established its role as an accurate tool for identifying axillary nodal metastasis. This procedure identifies approximately 50% of nodal involvement pre-operatively [1]. In the United Kingdom, axillary ultrasound is customarily performed for all patients diagnosed with breast cancer, as recommended by the National Institute for Health and Care Excellence (NICE) [2]. If nodal involvement is detected by a combination of ultrasound and FNAC/CB, direct axillary lymph node dissection (ALND) is performed.

If axillary ultrasound is unable to identify nodal metastatic disease, sentinel lymph node biopsy will be performed as the gold standard for staging of axillary disease [3–4]. ALND is then recommended as a separate procedure if the sentinel node biopsy yields a positive result [5–6]. Axillary ultrasound therefore facilitates patients to undergo a direct single stage axillary dissection rather than this two-stage procedure. This reduces patient morbidity and generates financial benefits for the healthcare system [7]. However, axillary ultrasound may prove to be a double-edged sword, leading to an over-treatment of axillary disease associated with its significant morbidities [8–9]. This is because various studies have demonstrated that the sentinel lymph node

was the only positive lymph node in 40–60% of patients [10–11] and also nomograms have been validated to identify patients who are at risk of non-sentinel lymph node metastasis [12–14]. More importantly, the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial published earlier in 2011 and recently updated in 2017 suggest that a subgroup of patients can safely avoid ALND after positive sentinel lymph node biopsy [15–16]. In this trial, patients with a tumor size less than 5 cm who also had one or two positive sentinel nodes (without matting or extra nodal extension) were treated with breast-conserving surgery and whole breast irradiation. This study had a median follow up of 9.25 years and found no difference in the overall survival [15] or locoregional recurrence [16] in patients who did or did not undergo axillary lymph node dissection after a positive sentinel lymph node biopsy. Despite some limitations [17–18], this study is the best available evidence to date with long term follow up, supporting the avoidance of ALND in a sub-group of patients [19–20].

The primary aim of our study was to assess the axillary nodal burden from the histopathological findings of direct ALND and classify them into patients with minimal nodal involvement (≤ 2 positive nodes) and extensive nodal involvement (> 2 positive nodes). This study also aimed to identify which of our patients could have safely foregone ALND based on the findings of the Z0011 trial. Overall, we hoped to find features which may be predictive of minimal or extensive nodal involvement by analyzing the differences in tumor characteristics and outcomes between the two groups.

Material and methods

Patients with primary breast cancer between April 2009 and March 2015 were identified from the surgical database of our hospital and retrospectively analyzed. Our departmental policy was to perform axillary ultrasound on all patients with suspected breast cancer. Radiologists with an interest in breast, as well as trained clinical specialists, performed the axillary ultrasounds. Lymph nodes were deemed suspicious if they were multiple and large (> 1 cm), with eccentric or more than 2 mm cortical thickening and replacement or loss of the fatty hilum.

Suspicious nodes identified using axillary ultrasound were sampled using FNAC or CB, at the operator's discretion. Histopathological assessment of nodal samples was then performed using hematoxylin and eosin staining and an immunohistochemical profile was then generated upon identification of metastatic disease. Patients with axillary nodal metastatic disease underwent direct ALND, accompanied by wide local excision (WLE) or mastectomy as deemed clinically appropriate.

Details regarding positive nodal disease from FNAC/CB following axillary ultrasound and further ALND were obtained from histopathological reports. Demographics and tumor characteristics were identified from multi-disciplinary discussions and clinical letters were used to follow-up significant events.

Histopathological data collected were size, type and grade of tumor, multifocality, lymphovascular invasion, HER2 status and the presence of estrogen and progesterone receptors. The number of nodes removed during ALND were recorded as well as the number of positive nodes to categorize into 'minimal' and 'extensive' groups.

We then identified which of these patients could have safely foregone axillary lymph node dissection based on the Z0011 criteria. This included patients who underwent breast conserving surgery for a tumor size less than 5 cm, had ≤ 2 positive nodes from axillary dissection without matting and extra-nodal extension and were treated with adjuvant whole breast irradiation. Patients who underwent preoperative neo-adjuvant treatment and who had a mastectomy as the definitive treatment were excluded.

Statistical analyses

All analyses were conducted with The Graph Pad software (Prism version 5). For numeric data, values are expressed in median with percentages and Chi squared analyses or a Fisher's exact test were used to assess differences in patient and tumor characteristics between those with minimal nodal involvement (≤ 2 positive nodes) and extensive nodal involvement (> 2 positive nodes). A p value of ≤ 0.05 was considered significant.

Results

A total of 1745 patients were diagnosed with operable breast cancer between April 2009 and March 2015. Of these, 269 patients underwent direct ALND for axillary nodal metastases. Ten patients had undergone axillary dissection for recurrent breast cancer and were excluded. Twenty patients were excluded from the study because there were no clear indications for ALND in place of sentinel lymph node biopsy. Biopsies were not performed in 14 patients due to technical reasons, although these patients were highly suspicious for nodal metastases from axillary ultrasound. Three patients had an axillary dissection based on an abnormality in another modality of imaging (CT, MRI and mammogram). Another four patients had axillary dissection based on

suspicion of nodal metastases intraoperatively. Twenty-one patients had benign findings on FNAC/CB, but still received axillary dissection due to high suspicion from axillary ultrasound and were thus excluded.

In total, seventy-two patients were excluded from the study, and the remaining 197 patients with definitive diagnosis of axillary nodal metastases on ultrasound and FNAC/CB who underwent direct ALND were ultimately considered eligible for the study as shown in Table 1.

The median age of the patients was 62 years (range, 23–92). All except one patient were female. Eighty-five patients (43.1%) had breast-conserving surgery, while 112 patients (56.9%) underwent mastectomy. The median pathological tumor size was 24.5 mm (range, 5–130 mm). Fifty six of the 197 patients (28.4%) had T1 tumors, and 119 patients (60.4%) had T2 tumors. Seventeen patients (8.6%) had a tumor greater than 50 mm, while multifocal disease was detected in 12 patients (6%). Invasive ductal carcinoma was the predominant tumor upon final pathology (172 patients, 87%), while invasive lobular carcinoma was observed in 23 patients (12%). Other pathologies were noted in two patients (medullary carcinoma).

Grade 3 disease was found in 136 patients (69%), 57 patients had grade 2 and only four patients had grade 1 disease. Lymphovascular invasion was present in 103 patients (n = 193, 53.4%). The majority of patients were estrogen receptor (ER) positive (155, 78.7%), while 55 (27.9%) were HER2 positive. Thirty-six patients (18.3%) were ER positive/HER2 positive, while 23 patients (11.7%) were triple negative.

Of the 197 patients, FNAC was diagnostic in 92 patients (C5 – 85; C4 – 5; C3 – 2), and a core biopsy confirmed metastases in the remaining 105 patients (B5 – 104; B4 –1). The median number of lymph nodes excised during axillary dissection was 15 (range, 4–35), and the median number of positive nodes was 3 (range, 0–31). Five patients had no positive nodes upon axillary dissection. Within this group of patients, 76 patients (38.6%) had two positive nodes or less from ALND (minimal nodal metastases), and 121 patients had more than two positive nodes (extensive nodal metastases). The characteristics of these groups of patients are outlined in Table 1.

There was no significant difference observed between the two groups in terms of age, type of surgery, tumor size, morphology, estrogen receptor status, HER2 status and multifocality. Differences in tumor grade, progesterone and triple-negative receptor status were borderline but not significant. However, the presence of lymphovascular invasion was significant in patients with extensive nodal metastasis ($P < 0.001$).

The median follow-up was 4.6 years. A total of 15 patients died during follow up; eight from the minimal

Table 1. Characteristics of patients who had axillary clearance and grouped into minimal nodal and extensive nodal metastases

Patient characteristics	≤ 2 Positive lymph nodes (n = 76)	> 2 Positive lymph nodes (n = 121)	p value
Age			
Median (Range)	62 (23-90)	62 (33–92)	0.44
< 50 years	15 (19.7%)	32 (26.4%)	
50–69 years	37 (48.7%)	49 (40.5%)	
= / > 70 years	24 (31.6%)	40 (33.1%)	
Type of surgery			
Breast conserving	38 (50.0%)	47 (38.8%)	0.14
Mastectomy	38 (50.0%)	74 (61.2%)	
Tumor size in mm			
Median (Range)	23 (5–60)	26 (8–130)	0.31
< 20 mm	23 (30.3%)	33 (27.3%)	
20–30 mm	35 (46.0%)	44 (36.4%)	
> 30 mm	18 (23.7%)	39 (32.2%)	
Morphology of tumor			
Ductal carcinoma	70 (92.1%)	102 (84.3%)	0.08
Lobular carcinoma	5 (6.6%)	18 (14.9%)	
Other types	1 (1.3%)	1 (0.8%)	
Tumor Grade			
Grade 1	3 (3.9%)	1 (0.8%)	0.29
Grade 2	23 (30.3%)	34 (28.1%)	
Grade 3	50 (65.8%)	86 (71.1%)	
ER* status			
Negative	17 (22.4%)	25 (20.7%)	0.86
Positive	59 (77.6%)	96 (79.3%)	
PR status**			
Negative	37 (48.7%)	49 (40.5%)	0.30
Positive	39 (51.3%)	72 (59.5%)	
Her2* Status**			
Negative	57 (75%)	85 (70.2%)	0.52
Positive	19 (25%)	36 (29.8%)	
Triple Negative			
No	65 (85.5%)	109 (90.1%)	0.37
Yes	11 (14.5%)	12 (9.9%)	
Multifocality			
No	70 (92.1%)	115 (95%)	0.54
Yes	6 (7.9%)	6 (5%)	
Lymphovascular invasion			
No	52 (68.4%)	51 (42.1%)	0.001
Yes	24 (31.6%)	66 (54.5%)	
Not recorded	0	4	
Mortality follow up 4–5yrs			
Dead	8 (10.5%)	7 (5.8%)	0.27
Alive	68 (89.5%)	114 (94.2%)	

*ER – Estrogen Receptor
**PR – Progesterone Receptor
***Her2 – Human Epidermal Growth Factor Receptor

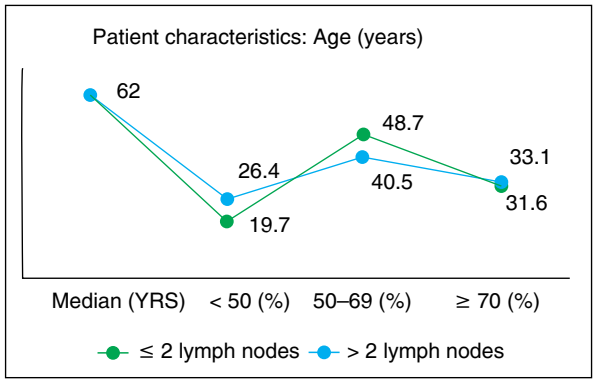

Figure 1. Patient characteristics: distribution with respect to age

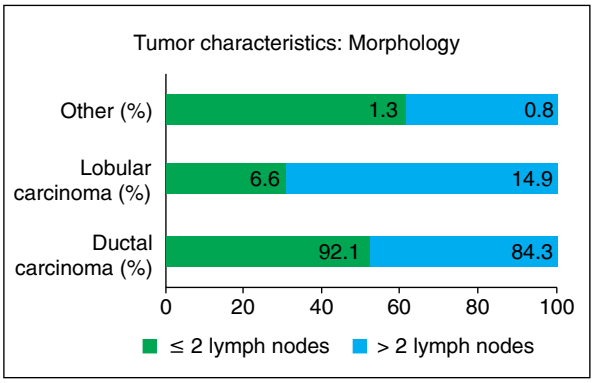

Figure 4. Tumor characteristics: distribution with respect to tumor morphology

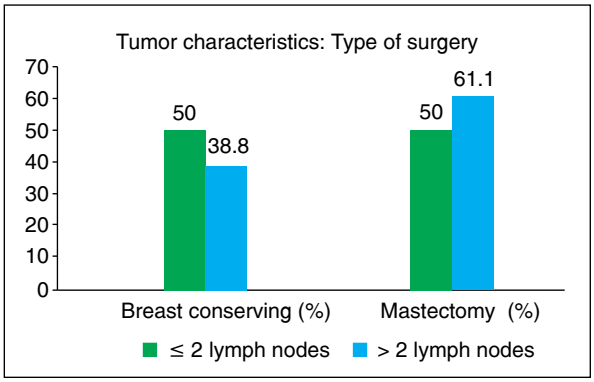

Figure 2. Tumor characteristics: distribution with respect to type of surgery

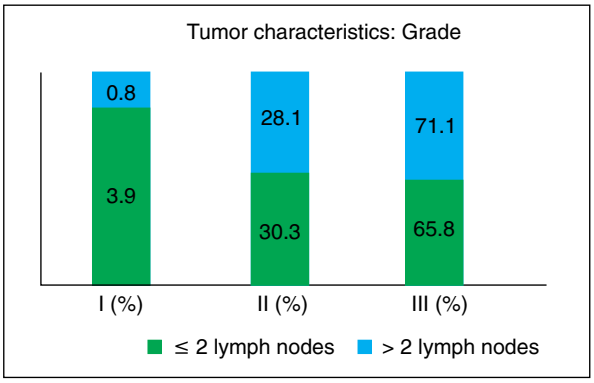

Figure 5. Tumor characteristics: distribution with respect to grade of tumor

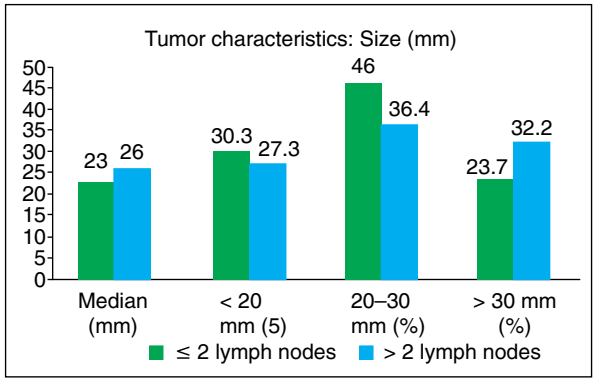

Figure 3. Tumor characteristics: distribution with respect to size of tumor

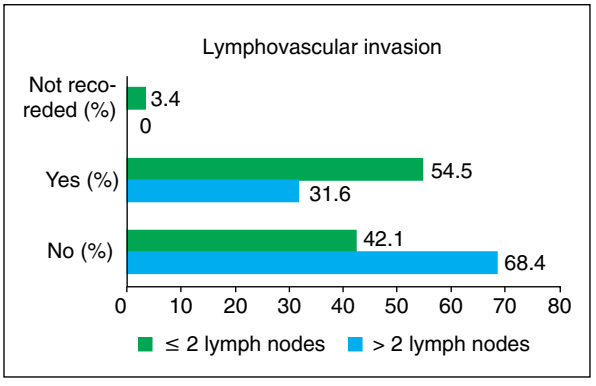

Figure 6. Tumor characteristics: distribution with respect to presence of lymphovascular invasion

nodal group and seven from the extensive nodal group with an overall survival rate of 89.5% and 94.2%, respectively. There was no statistical significance between the two groups in terms of survival.

Patients with minimal nodal involvement were potentially eligible for the Z0011 study. Of these, 53 patients were excluded as they did not meet the criteria, the predominant cause being mastectomy as the definitive

breast surgery. The remaining 23 patients (11.7%) satisfied the criteria for the Z0011 study, and could therefore have been spared axillary lymph node dissection.

Discussion

With advancement in technology and expertise in image interpretation, ultrasound has become a significant preoperative tool in the evaluation of nodal disease.

Studies have shown that high-resolution ultrasound can detect nodal metastases in breast cancer with a sensitivity and specificity ranging from 50–70% and 90–97.2%, respectively [21]. In conjunction with cytology/histology, the literature demonstrates increase in sensitivity and specificity to 80–90% and 100%, respectively, when conducted by experienced radiologists [22–23].

The improvement in ultrasound examination suggests that the chance of finding axillary metastases will increase. This means that more patients who would have otherwise had a sentinel lymph node biopsy will instead be subjected to ALND with its associated morbidity.

In our study, there were no significant differences observed when comparing the tumor characteristics between the two groups. The exception was lymphovascular invasion, which was predictive of patients with extensive nodal metastases. This histopathological factor needs to be taken into consideration while deciding on ALND following positive sentinel node biopsy regardless of the number of positive nodes.

There was no significant difference in overall survival between patients with minimal and extensive nodal metastasis. It is difficult to be certain whether the comparable survival rate achieved translates from both groups receiving ALND or being a simple chance finding needs to be determined.

Previous studies have predominantly shown a high axillary nodal burden in patients identified from axillary ultrasound [24–26]. However, in contrast, our study showed that more than one third of patients had minimal node involvement (38.6%). These findings are in concurrent with the results obtained by Boland et al. [30], who also reports 38.6% of patients had less than three positive nodes from ALND. Selection bias may account for the high axillary nodal burden documented in the literature. Verheuvel et al. [24] explained that axillary ultrasound was performed by general radiologists who were not specialized in breast cancer and Caudle et al. [25] reported that, from 2010, sentinel node-positive patients did not undergo axillary dissection and were excluded from their study. Reyna et al. [26] reported that axillary ultrasound was selectively performed for T2 or larger tumors since 2007 and that T1 tumors were evaluated according to the preference of the surgeon or clinical suspicion. These findings might explain the high axillary nodal burden documented in the literature. Therefore, based on our study, patients with clinically early-stage breast cancer do not have a significant axillary burden of disease when they were identified by axillary ultrasound with cytology / histology. Similar findings were observed by Cools et al. [27], who reports that patients with ultrasound guided biopsy do not harbor more nodal metastases than who are not subjected to it. Recent meta-analysis by Muneer et al. [28] concurred that 43% of patients with positive sentinel lymph node biopsy (SLNB) were subjected to unnecessary ALND.

Based on the findings of the Z0011 trial, a significant number of patients would have avoided direct axillary dissection (11.7% over a period of six years) if they had undergone a sentinel lymph node biopsy rather than an ultrasound guided FNAC/CB. This is twice the number quoted in study by Boland et al. [29] likely due to more than half the number of patients undergoing mastectomy in their group.

Additional detail provided on ultrasound, such as the number of nodes involved and radiographic features of these nodes may further help to identify the patients who would benefit from a direct axillary lymph node dissection and those patients who should receive sentinel lymph node biopsy. Pilewskie et al. [30] stated that 68% of patients with more than one abnormal lymph node on ultrasound axilla have more than or equal to three nodal metastases on ALND. Further research, looking at the correlation between radiographic data and axillary disease burden, may further help to clarify the patients who would be candidates for sentinel lymph node biopsy. Radiologists should also be encouraged to clearly report the abnormalities detected on ultrasound axilla in the light of future studies.

The limitations of our study include biases acquired from retrospective analyses and difficulty in reading ultrasound reports. This is because of absence of precise documentations on ultrasound findings of the axilla in relation to number of lymph nodes as there is tendency to perform biopsy once abnormal node is identified. Although the sample size of our study is relatively small, it strongly advocates that more than one third of patients had low-volume nodal metastases, questioning the need for ALND in all patients with ultrasound guided biopsy proven nodal metastases.

Further prospective studies with novel concepts are required to fully ascertain the sub-group of patients who can forego axillary lymph node dissection. This could be by proceeding directly to SLNB without ultrasound guided biopsy for patients with single abnormal node or by clipping the node after positive biopsy and performing SLNB along with excision of clipped node rather than ALND. Therefore, in the era of Z0011, the role of axillary ultrasound needs to be redefined to avoid unnecessary axillary dissection.

Conclusions

Ultrasound with concurrent histology of abnormal axillary lymph nodes is currently treated with direct ALND and can avoid two stage surgical procedure. However, our study shows that more than one third of these patients were over-treated and could have spared ALND. Hence the role of ultrasound axilla in early breast cancer needs to be redefined.

List of Abbreviations:

FNAC	Fine Needle Aspiration Cytology
CB	Core Biopsy
NICE	National Institute for Health and Care Excellence
ALND	Axillary Lymph Node Dissection
ACOSOG	American College of Surgeons Oncology Group
WLE	Wide Local Excision
HER2	Human Epidermal Growth Factor Receptor 2
ER	Estrogen receptor
PR	Progesterone Receptor
SLNB	Sentinel Lymph Node Biopsy

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