



The Benefit of Routine Axillary Sonographic Assessment in cN0 Breast Cancer Patients

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ABSTRACT

Objective: Axillary ultrasound (US) is often part of the routine assessment of the clinically negative axilla in primary breast cancer, which determines the extent of axillary surgery to be performed. This study aims to ascertain the burden of disease in the axilla of patients with a normal clinical examination (cN0) but with US detected metastatic axillary lymph nodes.

Materials and Methods: We retrospectively identified 345 female patients who underwent axillary lymph node dissection, following a positive lymph node biopsy, between January 2015 and August 2019.

Eighty-nine of those had a positive biopsy prior to surgery. They were divided into two groups: Those with clinically palpable axillary disease preoperatively, cN1 (n = 41), and those with a normal clinical axillary examination, cN0 (n = 48). We assessed the number of positive axillary lymph nodes dissected in the two groups.

Results: In the cN0 group the mean value of excised disease-positive axillary lymph nodes was 3.6, while in the cN1 group it was 8.0 ($p < 0.01$). However, further analysis showed that 25 patients of the cN0 who had T1/T2 tumors had ≥ 3 positive lymph nodes.

Conclusion: Our study suggests that the presence of clinically palpable axillary lymph nodes appears to be correlated to a higher number of positive lymph nodes. However, in cases of non-palpable sonographically positive lymph nodes there might still be significant axillary disease, even in T1 and T2 tumors. Therefore we still support the routine use of preoperative sonographic assessment of the axilla for early breast cancer.

Keywords: Axilla; axillary dissection; breast ultrasonography; positive lymph nodes; sentinel node biopsy

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Key Points

- Palpable axillary lymph nodes might imply bigger axillary tumor burden.
- In cases of non palpable lymph nodes, there still might be significant axillary disease.
- Routine Sonographic assessment of the axilla in early breast cancer is essential, and might change the management.

Introduction

Axillary lymph node dissection (ALND) has high sensitivity as a technique for the detection of axillary metastatic disease in patients with breast cancer (1). However, it carries an increased risk of complications, such as lymphedema, nerve injury, wound infection, paresthesia and axillary seromas (2, 3).

In 1994 Giuliano et al. (1) showed that sentinel lymph nodes (SLN) were significantly more likely to contain metastasis than non-sentinel lymph nodes removed during ALND.

The sensitivity of sentinel lymph node biopsy (SLNB) for node involvement has been estimated to range between 71% and 100% with a false-negative rate of about 8.4% (4-6). One of the greatest advantages of SLNB is the near total absence of local postoperative complications, and long-term survival is at least equivalent to that after ALND (7-9).

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ALND was the standard of care for patients with SLN metastases until the Z0011 study was published (10). Patients with 1–2 SLN metastases who were planned for lumpectomy and whole breast post-operative radiotherapy were randomized to ALND or no further surgical treatment. Their results showed that axillary relapse after a median follow-up of 6.3 years was 1% in those who received no further axillary surgery.

Although the trial closed early and in spite of criticism of Z0011, it changed the practice of treating the axilla in many institutions worldwide, especially in North America (11).

The AMAROS trial is another study that was published in 2014 and showed that ALND and axillary radiotherapy after a positive SLN provide comparable axillary control for patients with T1-2 primary breast cancer and no palpable lymphadenopathy (12).

The current trend in the treatment of breast cancer is going towards minimizing axillary surgery, and ALND should no longer be considered routine management of the node-positive breast cancer patient (13, 14).

Staging of the axilla begins with a history and physical examination. Patients with impalpable axillary lymph nodes are defined as clinically lymph node negative (cN0).

There are differences in non-operative axillary staging in different parts of the world. European Society for Medical Oncology (ESMO) guidelines considers routine pre-operative axillary ultrasound +/- needle biopsy an integral part of the non-operative axillary staging for patients with non-palpable lymph nodes (14).

In our institution, ESMO guidelines are followed and routine axillary ultrasound (US) is performed as part of the assessment for primary breast cancer. Any suspicious lymph nodes identified on US are biopsied. The decision to proceed with an ALND is based on biopsy results; if the biopsy is positive for cancerous cells then the patient would undergo ALND as part of the primary procedure, whereas if the biopsy is negative then the patient would undergo SLNB first. This approach may mean, as suggested by some studies (15-17) that we are overtreating the axilla in cases where a positive US guided biopsy is due to micrometastasis or in the presence of 1–2 positive lymph nodes only (when the tumor size is T1 or T2), which according to Z0011 and AMAROS, ALND could be avoided without affecting nodal recurrence, disease-free survival, or overall survival (10-12, 18).

Purpose

The purpose of this study was to assess the clinical value and implications of sonographic assessment of the axilla in patients with a normal clinical axillary examination. We aimed to assess whether pre-operative US for cN0 patients, followed by a biopsy of abnormal appearing lymph nodes, leads to over treatment of the axilla.

Materials and Methods

We retrospectively identified 345 female patients who underwent ALND between January 2015 and August 2019 in our institution. The patients were identified using our institution’s surgical operations database. Each patient’s electronic medical records were reviewed and the following data were recorded: patient demographics; pre-operative clinical axillary examination findings; ultrasound findings; tumor size; histology and grade; and ALND pathology results.

Patients who received neo-adjuvant treatment (n = 213), patients who underwent ALND for a positive sentinel lymph node biopsy (n = 40) and patients who underwent ALND for axillary disease recurrence (n = 3) were excluded (Figure 1). Post neoadjuvant patients were excluded, because these patients underwent ALND post neoadjuvant, based on a positive lymph node biopsy prior to treatment, when some of them had complete or partial pathological response and including them would have biased our results.

Eighty-nine patients met the inclusion criteria and had a positive lymph node biopsy prior to surgery. They were analyzed in two distinct groups: those with clinically palpable axillary disease pre-operatively (n = 41), denoted as cN1, and those with a normal clinical axillary examination pre-operatively (n = 48), denoted as cN0 (Figure 1).

The Mann-Whitney non-parametric U test was used to compare ALND pathology results between the two groups.

Results

The patient records of the 89 patients who underwent ALND and met our inclusion criteria were reviewed. Forty-eight patients had ALND in the normal clinical axillary examination group (cN0). The mean number of excised, disease-positive axillary lymph nodes was 3.6 (range: 1–22). Further subgroup analysis showed that 23 of the cN0 patients had ≤2 positive lymph nodes and 25 patients had ≥3 positive lymph nodes. Forty-one cN0 patients had T1/T2 tumor size.

In the clinically palpable lymph node group, 41 patients had ALND. The mean number of excised, disease-positive axillary lymph nodes was 8.0 (range: 0–59). A summary of the data can be seen in Table 1.

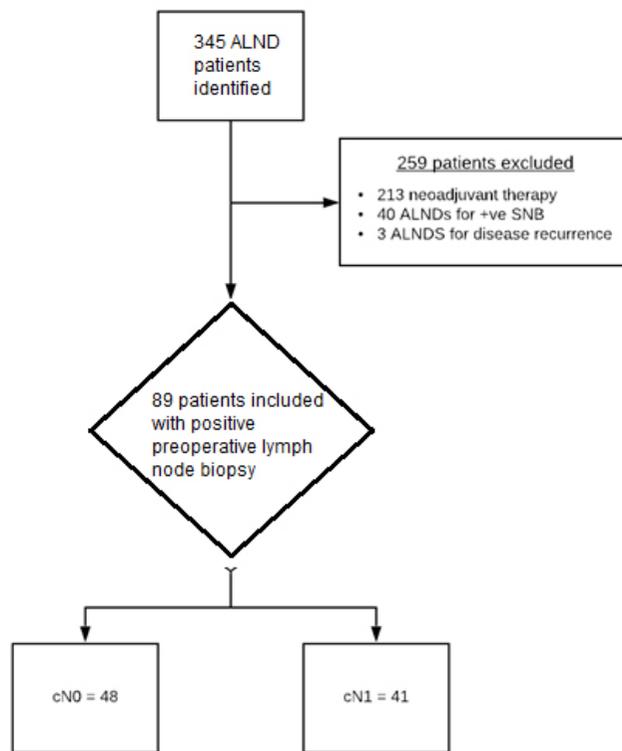


Figure 1. Flow diagram of patients included and excluded from the study

ALND: axillary lymph node dissection; SNB: sentinel lymph node biopsy

Table 1. Demographic and clinico-pathologic characteristics of included patient groups

Characteristics	cN0 group (n = 48)	cN1 group (n = 41)
Mean age in years (range)	59.8 (35–87)	64.2 (41–84)
Tumor histology		
Invasive ductal (IDC)	38	34
Invasive lobular (ILC)	7	5
Other	IDC & DCIS (2) IDC & ILC (1)	IDC & DCIS (2)
Tumor grade		
I	2	0
II	23	18
III	23	23
Mean ALND positive nodes (range)	3.6 (1–22)	8 (0–59)
Median ALND positive nodes	2	4
Tumor		
<2 cm	10	13
2–5 cm	31	19
>5 cm	7	9

ALND: Axillary lymph node dissection; DCIS: ductal carcinoma *in situ*; n: number

The Mann–Whitney test used for our statistical analysis resulted in a *p*-value of 0.008.

Discussion and Conclusion

Axillary lymph nodes status is important in the initial staging of breast cancer as a prognostic factor for overall survival and subsequent management (19, 20). However, there is no consensus regarding the extent of dissection necessary for adequate staging (21). We are living in an era of a paradigm shift from ALND being used as a therapeutic procedure to it being considered a staging procedure only. Updated Ontario Health (Cancer Care Ontario) and American Society of Clinical Oncology (ASCO) guideline algorithm for the management of the axilla in patients with early-stage (clinical stage T1, T2, N0 and N1 breast cancer) recommends SLNB for all patients, including patients with no palpable axillary nodes on physical examination who might have had an US that was equivocal, abnormal, or even biopsy-proven positive (22). However, updated ESMO Guidelines still recommend routine axillary sonographic assessment for all breast cancer patients (23); thus there is still no consensus on this matter.

Our data analysis suggests that the presence of clinically palpable lymph nodes appears to be correlated to a higher number of disease positive lymph nodes retrieved from axillary dissection (mean ALND positive of 8 in cN1 vs. 3.6 in cN0).

However, the number of positive lymph nodes in the cN0 group ranged between 1 and 22. While only 23 patients (48.9%) had two or less positive lymph nodes, the rest 51% (25 patients) had three or more.

This suggests that a significant axillary disease load may be present, even if the axilla is clinically normal on examination. Omitting axillary

US might lead to missed axillary disease left untreated, and its effect on recurrence and survival is unknown.

In conclusion, the presence of clinically palpable lymph nodes in our group of patients was correlated to the axillary tumor load. Nearly half of the patients in our cN0 cohort had two or less metastatic lymph nodes. This might imply that in a certain group of patients with cN0 and a positive, pre-operative, US guided biopsy ALND could be spared, which matches the sixteenth St. Gallen International Consensus Guidelines (24). However, until a large prospective study is done to better define this subgroup of patients, we still support the routine use of pre-operative sonographic assessment of the axilla. Given the relative simplicity of US, lack of radiation, low cost and a relatively accurate means of staging, this seems reasonable, given the lack of definitive evidence either way.

Ethics Committee Approval: The project titled “Breast Cancer Assessment Protocol: Is routine sonographic evaluation of clinically normal axillae necessary?” was registered with our institutional review board at the Royal United Hospital, Bath, U.K. in July 2020 and was given the following ID number: 3434. As per our institutional policy, no ethics approval was required for this type of retrospective review.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.S.; Design: M.K.; Supervision: M.K., S.S., R.S.; Data Collection and/or Processing: M.K., P.S.; Analysis and/or Interpretation: M.K., P.S., S.S., R.S.; Literature Search: M.K.; Writing: M.K., P.S., O.S.; Critical Review: M.K., S.S., R.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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