



A quantitative analysis of tumour characteristics in breast cancer patients with extranodal extension in non-sentinel nodes

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ABSTRACT

Background: The presence of extranodal extension (ENE) is well documented as a predictor of non-sentinel lymph node (NSLN) metastasis. The ACOSOG Z0011 trial (2011) concluded that patients who satisfy criteria including the absence of sentinel lymph node (SLN) ENE can forgo axillary clearance (AC). Currently there are no studies analysing the rate of ENE in NSLN metastasis in which the sentinel node was positive but had no ENE. Determining this incidence will help determine if current paradigms are resulting in residual ENE in NSLN metastasis by forgoing AC based on the Z0011 trial..

Methods: This study determined incidence of ENE at NSLN metastasis in patients with a positive SLN biopsy without ENE in 162 symptomatic breast cancer patients who underwent AC between 2009 and 2014 at Cork University Hospital Breast Cancer Service, a teaching hospital of University College Cork.

Results: Of 965 sentinel node biopsies performed 251 were identified as SLN positive, 162 (64.5%) underwent further AC. Of the 162 patients, 56.8% (92/162) were positive for ENE at SLN, of these 57.6% (53/92) had NSLN metastasis versus 17.1% (12/70) in the ENE-negative group (χ^2 test; $P < 0.001$). On adjusted analysis, ENE at the SLN was a significant predictor of NSLN metastasis (odds ratio [OR] 8.63; 95% confidence interval [CI] 3.26–22.86; $P < 0.001$). The incidence of NSLN-ENE in patients without SLN-ENE was 1/70 (1.4%) compared with 33.7% (31/92) in patients who had ENE at the SLN (χ^2 test; $P < 0.001$).

Conclusion: ENE at the SLN is an independent predictor of NSLN involvement; its absence significantly reduces the likelihood of ENE in NSLN metastasis..

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1. Introduction

Sentinel lymph node biopsy (SLNB) has largely replaced axillary lymph node dissection as the standard of care in the surgical

staging of the axilla in patients that are clinically node negative [1,2]. This shift from axillary lymph node dissection (ALND) was largely influenced by the publication of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial. Z0011 concluded that omitting ALND in favour of SLNB alone in patients with limited metastasis undergoing breast conserving surgery and systemic therapy did not result in statistically significant differences in disease free survival or overall survival [1]. However, patients with

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gross extranodal extension were excluded from the trial leading to the continuation of ALND as the standard of care in these patients.

In light of the Z0011 findings the American Society of Clinical Oncology (ASCO) published updated recommendations reflecting the Z0011 results [3]. Consequently certain patients are increasingly omitting ALND in favour of SLNB thus avoiding the added morbidity of an ALND [4]. Indeed, following the widespread implementation of Z0011 a subset of patients are forgoing axillary clearances and may unwittingly be leaving ENE behind in their non-sentinel lymph nodes. Consequently, it is possible certain patients with more advanced diseases are being undertreated.

Currently, there is a scarcity of literature reporting the incidence of extranodal extension in non-sentinel lymph nodes when the sentinel node was positive but did not display extranodal extension.

2. Methods

We conducted a retrospective cohort study of consecutive patients with breast cancer who underwent axillary clearance following a positive sentinel node biopsy at Cork University Hospital (CUH), a single large academic centre with a combined screening and symptomatic, breast subspecialty service between January 1, 2009, to December 31, 2014. Clinicopathologic data was collected from the prospectively kept breast oncology research database. Data regarding specific tumour characteristics was obtained from the surgical pathology database to evaluate for both predictive and prognostic parameters. This study was approved by the Clinical Research Ethics Committee of the Cork teaching Hospitals.

Sentinel node biopsy was performed on clinically node negative breast cancer patients (cN0), determined by clinical examination. Fine needle aspiration or core needle biopsy was used to confirm the presence of metastasis in suspicious lymph nodes. Sentinel node biopsy was performed using ^{99m}Tc -labeled sulphur colloid and in some circumstances blue dye injection. Lymph nodes with radioactivity and/or blue dye uptake were regarded as sentinel

nodes and were submitted for pathological analysis. All histological specimens were sliced at 2 mm interval and evaluated using the following protocol: 3 consecutive sections at a thickness of 3 μm and stained with haematoxylin & eosin (H&E), AE1/AE3 immunohistochemistry and H&E respectively. All cases were reported by a specialized breast pathologist. Staging was determined using the American Joint Committee on Cancer AJCC TNM system. The Nottingham Histological Score System was used to determine grade.

During the study period 1417 symptomatic patients with invasive disease were identified, of these 965 underwent SLN biopsy resulting in 251 patients identified as sentinel node positive. Within this cohort, 162 patients underwent axillary lymph node dissection as a second procedure following evaluation of characteristics in the sentinel node. Clinicopathologic data collected included age, adjuvant therapy, tumour morphology, histological grade, pathological tumour size, lymphovascular invasion, oestrogen receptor (ER) expression, progesterone receptor (PgR), human epidermal growth factor 2 (HER2) status, number of SLN metastases, number of involved sentinel nodes, non-sentinel node metastases, SLN extranodal extension and NSLN extranodal extension. ENE was defined as the extracapsular growth of tumour cells, invasion of perinodal fat or extranodal location of tumour cells.

Statistical analysis was performed using IBM, SPSS statistics V20. Unadjusted analysis was performed using χ^2 tests for categorical variables and unpaired 2-tailed *t*-test for continuous variables. Adjusted analysis was performed using logistic regression analysis to adjust for multiple covariates to determine if any variables alone or in combination could predict non-sentinel node metastasis. Odds ratios [OR] and confidence intervals [CI] were calculated in both uni- and multivariate analysis and are presented within. Statistical significance was evaluated at a $p < 0.05$ level.

3. Results

Nine hundred and sixty-five symptomatic patients with invasive breast cancer were identified between 2009 and 2014, 251 (17.7%)

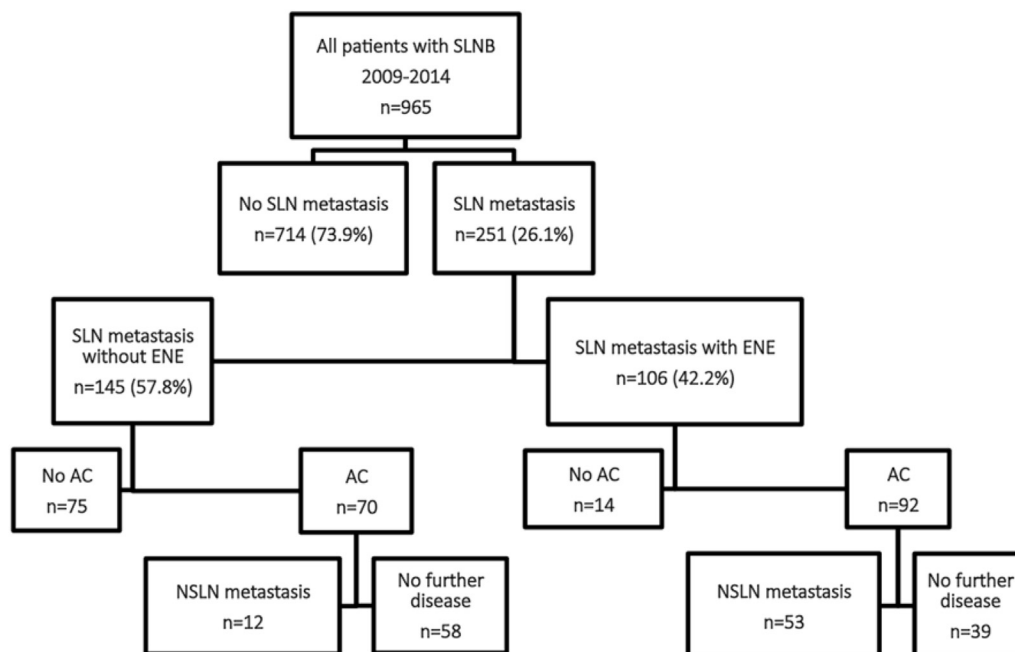


Fig. 1. Patients with breast cancer undergoing sentinel lymph node dissection from 2009 to 2014.

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