Original Article

Eur J Breast Health 2023; 19(3): 229-234
DOI: 10.4274/ejbh.galenos.2023.2023-3-5

Risk Factors Associated With Sentinel Lymph Node Metastasis in Clinically Node-Negative Breast Cancer

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ABSTRACT

Objective: Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in clinically node negative breast cancer. If predictive factors for sentinel lymph node (SLN) metastasis could be identified, it would allow selection of candidates for SLNB and omit axillary surgery in those with the lowest risk of axillary lymph node involvement. The aim of this study was to determine risk factors associated with SLN metastasis in breast cancer patients in Bahrain.

Materials and Methods: Patients with clinically node-negative breast cancer who underwent SLNB at a single institution between 2016 and 2022 were identified from the pathology database. Patients who had failure of localization of SLN, those with bilateral cancers and those treated for a local recurrence were excluded.

Results: A total of 160 breast cancer patients were retrospectively analyzed. Of these, 64.4% had a negative SLNB and 21.9% of all cases underwent axillary dissection. The following parameters emerged as predictors of SLN metastasis in univariate analysis: age; tumour grade; ER status; presence of lymphovascular invasion (LVI) and tumor size. On multivariate analysis, age was not independently associated with the incidence of SLN metastasis.

Conclusion: This study showed that high tumour grades, presence of LVI and large tumour size were all risk factors related to axillary metastasis after SLNB in breast cancer. In the elderly, the incidence of SLN metastasis appeared to be relatively low, providing an opportunity to de-escalate axillary surgery in these patients. These findings may allow for the development of a nomogram to estimate the risk of SLN metastasis.

Keywords: Axillary lymph node dissection; axillary treatment; breast cancer; early breast cancer; sentinel lymph node biopsy

Cite this article as: Abdulla HA, Salman AZ, Alaraibi SJ, Nazzal K, Ahmed SA, Almahari SA, Dhaif A. Risk Factors Associated With Sentinel Lymph Node Metastasis in Clinically Node-Negative Breast Cancer.Eur J Breast Health 2023; 19(3): 229-234

Key Points

- Sentinel lymph node biopsy is the gold standard for axillary staging in clinically node-negative breast cancer patients.
- Identification of predictive factors for sentinel lymph node metastasis may allow de-escalation of axillary surgery in certain patients.
- Previous studies have shown several risk factors and predictive models for sentinel lymph node metastasis, with limited external generalisability.
- This study suggests that sentinel lymph node biopsy can be omitted in elderly patients.

Introduction

Axillary lymph node status is the most important prognostic factor in patients with early breast cancer, particularly for deciding adjuvant therapy (1). Historically, axillary lymph node dissection (ALND) was routinely performed for staging and to achieve local control, irrespective of nodal status, but this was associated with significant morbidity including lymphoedema, impaired shoulder movements and arm sensation (2). Sentinel lymph node biopsy (SLNB) has emerged as an alternative to ALND and is the standard of care for axillary staging in all clinically node negative patients (3). Compared to axillary dissection, SLNB has been shown to be a feasible and reliable method for axillary staging, while avoiding the unnecessary morbidity of an ALND (4, 5). Recently, there has been a trend towards de-escalating axillary surgery and treatment in breast cancer patients, even in the presence of axillary lymph node metastasis, with reduced patient morbidity and without compromising oncological outcomes, as supported by the ACOSOG Z0011, AMAROS and SINODAR ONE trials (6-8).

The underlying pathways of lymph node metastasis remain unclear (9). The incidence of axillary lymph node involvement in those with

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Received: 18.03.2023
Accepted: 29.04.2023
Available Online Date: 03.07.2023

clinically negative lymph nodes undergoing SLNB is approximately 25-33%, meaning that a larger number of patients are being overtreated with increased morbidity, the need for pathologists should intraoperative frozen section be performed with associated prolonged operative time and increased healthcare costs (10-12). If predictive factors for sentinel lymph node (SLN) metastasis could be identified, it would allow the selection of candidates for SLNB and omit axillary surgery in those with the lowest risk of axillary lymph node involvement. Previous studies described several factors, such as age, multifocal disease, tumor grade, location of the tumor, tumor size, lymphovascular invasion (LVI) and receptor status as being associated with axillary lymph node metastasis (9, 11-15). Nomograms have been developed to estimate the risk of SLN metastasis in the Western population (16, 17). However, external validation of these predictive models may be limited due to differences in other breast cancer populations (12). Bahrain has the highest incidence of breast cancer among the Gulf Cooperation Council states and a significant proportion of patients have aggressive tumours compared to Western countries, including younger age, large and high grade tumors, with more than 50% of patients in Bahrain having lymph node metastasis at the time of diagnosis (18). These differences in clinicopathological characteristics of our local population could be attributed to varying genetic and environmental factors, sedentary lifestyle and ineffective screening programmes (19).

The aim of this study was to determine risk factors associated with axillary lymph node involvement in patients undergoing SLNB and to compare the results with the literature in order identify patients that could avoid axillary staging. The study findings may also be used to develop an algorithm for predicting axillary lymph node status in this population in the future.

Materials and Methods

Patients

The study method was reviewed and performed in accordance with our institution's research ethics committee. Patients with clinically node-negative breast cancer who underwent SLNB at our institution between January 2016 and August 2022 were identified from the pathology database and included in the study. Patients who had failure of localization of SLN, those with bilateral cancers and those treated for a local recurrence were excluded. In patients who underwent neoadjuvant chemotherapy, only those who were initially node-negative and remained node-negative were included. In order to determine factors associated with SLN metastasis, the following variables were evaluated: age at diagnosis; tumour location; number of foci; tumor grade; tumor size; histological tumor subtype; LVI; estrogen receptor (ER), progesterone receptor (PR) and human epithelial growth factor receptor-2 (HER-2) status; Ki-67 proliferation index; history of neoadjuvant therapy; and number of SLNs retrieved.

Surgical Technique

The method of performing SLNB in our center involves a dual technique, using both radioactive colloid and blue dye. Subareolar injection of a radioactive (Tc-99m labelled colloid) tracer is performed a few hours preoperatively on the day of surgery. After induction of general anesthesia, isosulfan blue dye is injected into the subareolar region. A hand-held gamma probe and visual inspection for blue dye is used to retrieve the SLN.

Pathological Technique

Histopathologists examined the lymph nodes by frozen section, which was prepared using haemotoxylin and eosin stain and examined microscopically. The frozen section result was communicated to the operating surgeon within 45 minutes. The remaining tissue specimen was fixed in paraffin and slides were prepared for the histopathological examination of permanent preparations postoperatively. Axillary dissection was performed only if macrometastasis was detected in more than two SLNs or there was a single positive SLN in patients who underwent neoadjuvant chemotherapy.

Statistical Analysis

Proportions of SLN metastasis were compared among different groups of patients in terms of patient and tumor characteristics. Statistical comparison was performed using the chi-square test and logistic regression analysis. *P* values less than 0.05 were considered to be significant. Statistical analyses were performed using SPSS software, version 29.0 (IBM Inc., Armonk, NY, USA).

Results

A total of 160 breast cancer patients who fulfilled the eligibility criteria were retrospectively analyzed. Patient clinical and pathological characteristics are summarized in Table 1 and Table 2, respectively. All patients were female. The median age of patients was 53 (range 23-79) years. The majority of cases were left-sided (58.1%), with breast cancer most likely to occur in the upper outer quadrant (48.8%). Most of the patients had a single focus of disease (88.1%). Mastectomy was performed in 52.5% of patients. Invasive ductal carcinoma was the most predominant histological tumor subtype (73.1%). The majority of ductal carcinoma *in situ* (DCIS) tumors were reported to be high grade (80%), while most invasive tumors were grade 2 (51.3%). The mean tumor size was 28.6 mm. For invasive cancers, approximately half of patients had T2 tumors (48.7%). LVI was present in only 20% of cases. The majority of tumors were found to be ER- and PR-receptor positive (79.3% and 73%, respectively). Furthermore, 21.3% of invasive tumors were HER2-positive and 56% of them had high Ki-67 index above 20%. Of the patients with invasive cancer, 18.7% underwent neoadjuvant therapy. The majority of patients (64.4%) had negative SLNB with no further axillary surgery. The median number of SLN retrieved at SLNB was 3 (range 1-5). Of the cohort, 21.9% of cases underwent axillary dissection. In 21 patients (60%) who underwent ALND, no further nodal metastases was identified in the axillary tissue specimen, indicating that the SLNs were the only positive lymph nodes. When univariate and multivariate logistic regression analysis was performed, five predictors of SLN positivity were identified, including age at diagnosis, tumor grade, ER status, presence of LVI and tumor size (Table 3). Although age was associated with a positive SLNB on univariate analysis, it was not an independent risk factor for SLN metastasis on multivariate analysis.

Discussion and Conclusion

The aim of this study was to determine the clinical and pathological risk factors associated with axillary lymph node status in patients undergoing SLNB for breast cancer in a population of women from Bahrain. The following parameters were identified as independent predictors of SLN metastasis on multivariate analysis: Tumor grade; ER status; presence of LVI; and tumor size.

Table 1. Clinical and demographic characteristics of the study population

Age	
Mean	54
Median	53
Range	23–79
Tumour laterality	
Right breast	67
Left breast	93
Tumour quadrant	
Central	16
LIQ[a]	8
LOQ[b]	15
UIQ[c]	34
UOQ[d]	78
Disease focality	
Unifocal	141
Multifocal or multicentric	19
Surgery	
Mastectomy	84
Breast conserving surgery	76
Neoadjuvant therapy	
Yes	28
No	122
Sentinel lymph nodes	
Mean	2.96
Median	3
Range	1–5
Axillary dissection	
Yes	35
No	125

[a]Lower inner quadrant, [b]Lower outer quadrant, [c]Upper inner quadrant, [d]Upper outer quadrant

Table 2. Histological characteristics of the study population

Tumour type	
DCIS[a]	10
IDC[b]	117
ILC[c]	16
Other	17
Tumour grade	
DCIS	
Low	0
Intermediate	2
High	8
Invasive	
Grade I	40
Grade II	77
Grade III	33
Tumour size (in mm)	
≤20	69
>20	91
T-stage	
Tis	10
T1	62
T2	73
T3	15
Lymphovascular invasion	
Present	32
Absent	128
Estrogen receptor status	
Positive	127
Negative	33
Progesterone receptor status	
Positive	116
Negative	44
HER2 status	
Positive	32
Negative	118
N/A	10
Ki-67 index	
≤20%	66
>20%	84
N/A	10
Nodal status	
N0	103
N1	43
N2	8
N3	6

[a]Ductal carcinoma *in situ*, [b]Invasive ductal carcinoma, [c]Invasive lobular carcinoma

LVI is an important factor in breast cancer metastasis, where the process of metastasis is considered to start by lymphangiogenesis, then LVI and finally lymph node metastasis (20). LVI has been described as the strongest independent predictor of nodal involvement (13). This finding was confirmed in the present study. Of our patients with LVI, 56.3% had positive lymph nodes after SLNB. LVI is associated with decreased survival on long-term follow-up, despite absence of nodal disease and it confers an even worse outcome in node-positive patients (9).

It was demonstrated that SLN metastasis was less prevalent in older women (≥60 years) compared to younger patients (<60 years) on univariate analysis. Older women with breast cancer show age-associated changes in the sensitivity to estrogen and usually present with less aggressive tumour biology (12). Our population of older breast cancer patients had smaller and lower grade tumors, which were ER-positive and HER-2 negative. This alteration in estrogen sensitivity

Table 3. Relationship between clinicopathological risk factors and sentinel lymph node metastasis

Age	**Metastasis present**	**No metastasis**	***p* (univariate analysis)**	***p* (multivariate analysis)**
<60	46 (28.7%)	72 (45%)	**0.029**	0.357
≥60	9 (5.6%)	33 (20.6%)		
Tumour side				
Left	32 (20%)	61 (38.1%)	0.564	
Right	23 (14.4%)	44 (27.5%)		
Tumour quadrant				
Upper	33 (20.6%)	79 (49.4%)	0.137	
Lower	11 (6.9%)	12 (7.5%)		
Multifocality or multicentricity				
Yes	5 (3.1%)	14 (8.8%)	0.155	
No	50 (31.3%)	91 (56.9%)		
Surgery				
Mastectomy	30 (18.8%)	54 (33.8%)	0.741	
Breast conserving surgery	25 (15.6%)	51 (31.9%)		
Tumour grade				
Low (grade 1)	15 (9.4%)	25 (15.6%)	**0.018**	**0.011**
High (grade 2-3)	40 (25%)	70 (43.7%)		
Tumour type				
Ductal	43 (26.9%)	84 (52.5%)	0.668	
Lobular	7 (4.4%)	9 (5.6%)		
ER receptor				
Positive	50 (31.3%)	77 (48.1%)	**0.013**	**0.009**
Negative	5 (3.1%)	28 (17.5%)		
PR receptor				
Positive	43 (26.9%)	73 (45.6%)	0.269	
Negative	12 (7.5%)	32 (20%)		
HER2 receptor				
Positive	13 (8.1%)	24 (15%)	0.588	
Negative	42 (26.3%)	79 (49.4%)		
Ki-67 index				
<20%	25 (15.6%)	42 (26.3%)	0.237	
≥20%	30 (18.8%)	58 (36.3%)		
LVI				
Present	18 (11.3%)	14 (8.8%)	**0.006**	**0.003**
Absent	37 (23.1%)	91 (56.9%)		
Neoadjuvant therapy				
Yes	10 (6.3%)	18 (11.3%)	0.516	
No	45 (28.1%)	87 (54.4%)		
Tumour size				
<20 mm	18 (11.2%)	45 (28.1%)	**0.045**	0.214
≥20 mm	37 (23.1%)	50 (31.2%)		
T stage				
T1-T2	48 (30%)	87 (54.3%)	**0.031**	**0.020**
T3	7 (4.37%)	8 (5%)		

and combination of these favorable histological parameters may be contributing factors for the reduced incidence of SLN metastasis in our older patients. In line with recent trends towards de-escalating axillary surgery, our results support the Society of Surgical Oncology Choosing Wisely guideline recommendation against routine SLNB in elderly patients with hormone receptor-positive and HER2-negative breast cancer, as axillary staging does not influence adjuvant therapy or outcomes in these patients (21).

Tumor size has been described as one of the strongest predictive risk factors for SLN metastasis after LVI and is also associated with higher probability of detection of metastasis after axillary dissection (15). This is because larger tumours are more likely to harbor an invasive component with associated LVI (14). Relevant studies have shown that tumor size was positively correlated with lymph node metastasis and our results are consistent with this (9, 13-15). In the present study, compared with smaller tumours (≤20 mm), the risk of SLN metastasis was approximately 1.5 fold greater for tumours larger than 20 mm (26% versus 39%, respectively). In terms of T-stage, the risk for SLN metastasis was 23.6% for T1 tumours, 42.4% for T2 tumours and 50% for T3 tumours. Nevertheless, a proportion of our patients underwent neoadjuvant therapy, which affected the true tumor size and thus it may not be representative of the actual tumor burden (14).

Although there are studies linking high grade tumors with axillary lymph node metastasis (9, 15), other studies have shown no significant association between tumor grade and nodal metastasis (11, 20). In particular, one study found that increasing tumor grade did not predict a higher risk for axillary lymph node metastasis, where grade 3 tumors did not show any increased propensity to spread to regional lymph nodes and any possible over treatment of breast cancer patients on the basis of tumour grade should be discouraged (13). Approximately two-thirds of the patients in our cohort with positive SLN metastasis had high grade tumours, compared to 27% with grade 1 tumors.

ER, PR and HER-2 receptor statuses are important for directing hormonal and targeted therapies in breast cancer management. There is some controversy about the role of molecular markers in predicting axillary lymph node metastasis; some authors reported an association (15), others showed no correlation (11, 17, 22), while one study even showed an inverse relationship (13). In the present study, 60% of patients with ER-positive tumors and 70% of cases with PR-positive tumors did not have axillary nodal metastasis after SLNB. In contrast, only about a quarter of patients with HER-2 positive tumors had nodal metastasis detected after axillary surgery. On formal statistical analysis, only ER status showed a significant association with lymph node involvement.

Study Limitations

There are a few potential limitations of this study. These include its retrospective nature, patients enrolled from a single institution and relatively small sample size. In addition, patients who underwent neoadjuvant chemotherapy were included, which might have affected the results. Therefore, the generalizability of our findings is limited. However, this study is the first from Bahrain to evaluate predictive factors for SLN metastasis. Our results will not change the indications for SLNB. Even patients with high probability of lymph node metastasis are candidates for SLNB, as the majority of these patients can still avoid axillary dissection.

This study showed that high tumor grades, presence of LVI and large tumor size were independent risk factors related to SLN metastasis in clinically node-negative Bahraini breast cancer patients. These findings also suggest that, in the elderly, the likelihood of axillary metastasis after SLNB is relatively low and axillary surgery may be omitted in these patients. Our findings may allow for the development of an algorithm to predict which patients are at high risk for axillary lymph node metastasis. There are ongoing trials evaluating whether SLNB contributes to staging or local control, and the need for surgical staging of the axilla in other patient subgroups may be eliminated by non-invasive measures or observation in the future.

Ethics Committee Approval: The study method was reviewed and performed in accordance with our institution's research ethics committee.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.A.A., A.D.; Concept: H.A.A.; Design: H.A.A., A.D.; Data Collection or Processing: A.Z.S., S.J.A., K.N., S.A.A., S.A.A.; Analysis or Interpretation: H.A.A., A.Z.S., A.D.; Literature Search: H.A.A., S.J.A., K.N., S.A.A.; Writing: H.A.A., A.Z.S., S.J.A., K.N., S.A.A., S.A.A., A.D.

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

Financial Disclosure: The authors declared that this study received no financial support.

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