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Assessment of the axilla in women with early-stage breast cancer undergoing primary surgery: a review

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Abstract

Sentinel node biopsy (SNB) is routinely performed in people with node-negative early breast cancer to assess the axilla. SNB has no proven therapeutic benefit. Nodal status information obtained from SNB helps in prognostication and can influence adjuvant systemic and locoregional treatment choices. However, the redundancy of the nodal status information is becoming increasingly apparent. The accuracy of radiological assessment of the axilla, combined with the strong influence of tumour biology on systemic and locoregional therapy requirements, has prompted many to consider alternative options for SNB. SNB contributes significantly to decreased quality of life in early breast cancer patients. Substantial improvements in workflow and cost could accrue by removing SNB from early breast cancer treatment. We review the current viewpoints and ideas for alternative options for assessing and managing a clinically negative axilla in patients with early breast cancer (EBC). Omitting SNB in selected cases or replacing SNB with a non-invasive predictive model appear to be viable options based on current literature.

Introduction

Breast cancer was the most common cancer in Australia in 2020, with 18,909 new cases [1]. 85% of these were diagnosed at stage 1 or 2, where surgical management plays a central role. Ideally, surgery should treat the breast and axilla in a single-stage operation. It should give the best chance of breast preservation, cosmesis and maintenance of quality of life without compromising cure. Surgical management of the axilla has evolved from radical axillary dissection to relatively simpler SNB.

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Current methods of axilla management

Axillary lymph node dissection (ALND)

ALND in node positive EBC

Traditionally, ipsilateral ALND has been integral to breast cancer surgery. Halsted's paradigm of the stepwise progression of the disease formed the basis of this approach [2]. ALND is considered the standard of care in people with clinically node-positive breast cancer undergoing primary surgery, though its role is not proven by level-one evidence. Increasingly, clinically node-positive disease will be treated with neoadjuvant systemic treatment in modern practice. Limiting axillary surgery to SNB and targeted axillary dissection is now acceptable once nodal disease responds completely, clinically and radiologically.

ALND in node negative EBC

ALND is no longer the standard of care in clinically node-negative EBC. It is widely agreed that no clear evidence

exists to prove that axillary dissection imparts a survival advantage in node-negative disease [3–5]. However, it may be important for locoregional control. Axelsson et al., based on "The Danish Breast Cancer Cooperative Group" register, report a better axillary recurrence-free survival in node-negative low-risk patients when ten or more nodes are removed by axillary dissection [6]. The NSABP B- 04 trial concludes that half of all patients with clinically occult axillary nodal metastasis will develop clinically relevant axillary recurrence without axillary dissection. These findings support the view that ALND helps to improve regional control [3, 4, 7–10]. However, this improvement in regional control does not improve overall survival [3].

Although the therapeutic role of axillary dissection has been challenged, axillary node status is still one of the strongest independent predictors of disease-free and overall survival [11–13]. ALND accurately identifies nodal metastasis if at least ten lymph nodes are removed. ALND then provides crucial prognostic information [14–17]. Extent of nodal disease is related to outcome. Although 83% of node-negtive patients survive five years, microscopic metastasis in the lymph node alone causes a significant reduction in the disease-free interval [18, 19]. Only 28% of women survive long-term when more than 13 nodes are positive [20]. Extra-nodal extension is also a marker of poor prognosis [21]. These pieces of information form the basis for selecting appropriate adjuvant treatment.

SNB

SNB was introduced as a less invasive targeted option to obtain the required prognostic information and has become the standard of care in patients with clinically and radiologically node-negative early breast cancer. Krag et al. described the sentinel node technique (first in melanoma and later in breast cancers), and Giuliano and many others later validated it in node-negative breast cancers [22, 23]. Sentinel nodes can be identified in more than 95% of cases with a false negative rate of less than 6–10% and overall accuracy of over 96% [24–29]. Prognostic estimation and treatment decisions can be accurately made based on sentinel node status as it reflects the true axillary status [23, 30]. The axillary recurrence rate is less than 1% after a negative SNB.

Arguments for improvement of current methods of axilla management

The adverse effects of ALND are substantial. Lymphedema (14%), limited shoulder/ arm motion (28%), and neuropathic pain (31%) are some of the main consequences of ALND [31].

Several shortcomings of SNB-based management of the axilla have been noted. The morbidity of SNB, even though better than axillary dissection, is still substantial. Up to 7% of patients suffer arm pain and swelling at the end of 2 years. Lymphoedema, intercostal brachial neuralgia, and shoulder stiffness are seen among many patients after SNB [32–36]. All these symptoms result in a substantial reduction in the quality of life in many cancer survivors [37]. Allergic reactions to blue dye often used to detect the sentinel node occur in 0.7% of all SNB procedures [38]. The accuracy of SNB depends on the number of lymph nodes examined. It is estimated that four lymph nodes may be optimal [39]. NSABP B32 suggested that at least two nodes are necessary to reduce the false-negative rate [38]. Removing just one sentinel lymph node may be associated with a higher recurrence rate [40, 41]. Failure in identifying the sentinel node occurs in 2% of surgeries [42].

Mammographic screening has resulted in a shift in the stage of breast cancer diagnosis [43]. Screen-detected cancers will have a lower chance of node positivity [44]. Two-thirds of patients undergoing SNB will have a negative result and hence be considered subject to unnecessary overtreatment as there is no benefit in removing uninvolved axillary nodes [38, 45–47].

Even when the sentinel node is found to be positive, further axillary surgery is no longer mandatory. More than 60% of patients with SNB-positive disease will have no further disease in the axilla and, therefore, will be subjected to over-treatment if the policy of completion axillary dissection is followed [25, 48, 49]. In patients with early breast cancer undergoing breast-conserving surgery, a finding of up to two positive sentinel nodes does not need to be automatically followed by axillary dissection [50, 51]. Similarly, axillary radiation is adequate for mastectomy patients to treat a positive axilla [52, 53]. Four studies found no survival advantage in performing axillary dissection in this group [54–57]. Similar to the low regional recurrence rates seen in the undissected axilla after negative SNB, those with untreated axilla but positive SNB also show satisfactory regional control [46, 58]. Current evidence favours no axillary dissection in clinically node-negative, SNB-positive early breast cancer [59, 60]. Systemic therapy is usually recommended for SNB-positive patients, and these treatments are not often altered by the number of nodes (except in selected phenotypes and clinical scenarios), further negating the need for completion ALND [61]. ALND may be omitted if the risk of nodal metastasis is less than 5% [62]. No further axillary treatment is needed, even if one or more micrometastases are detected in the SNB [57]. Various studies of patterns of care have demonstrated a decline in the rate of axillary dissection in the last decade, even when underlying trial criteria are not fulfilled [63]. Certainly, in selected circumstances (premenopausal women, those with cancers of non-luminal phenotype), the information

Table 1 Alternative strategies for the management of clinically negative axilla in Early Breast Cancer

No SNB
SOUND Trial [71]
BOOG 213-08 [37]
INSEMA [8]
Tucker et.al [75]
Choosing wisely [76]
Radiological assessment
USS
MRI
PET scan
Predictive models
Clinical
Radiomics
Molecular characteristics of the tumour
Combined

from SNB or subsequent ALND may be critical; however, in a large number of EBCs, this may be found redundant.

From this information, we can conclude that a positive SNB leads to many decision-making challenges and potentially substantial overtreatment. A positive SNB is often a moment of anguish in a patient's breast cancer journey. Further axillary surgery following SNB causes the emotional and physical trauma of a second operation. It leads to delay in the commencement of adjuvant treatment and increased complications and long-term sequelae [64].

Systemic therapy is not entirely decided by SNB status [62, 65–67]. Biological properties of the primary tumour dictate the type of systemic treatment. The risk of recurrence predicted by the SNB status is becoming less critical in this decision-making [68]. In fact, the INSEMA trial estimated that 99% of all patients enrolled in the trial (T1-2 CN0 cancers) could have their systemic treatment planned without the need for SNB [8]. If adjuvant management decisions are made regardless of the nodal status, SNB is unnecessary [69, 70]. There is also increasing evidence that axillary treatment or assessment is unnecessary in early EBC in elderly patients [4, 9, 71, 72]. Redundancy of the information gained by the SNB procedure has prompted many investigators to look for alternative methods of axillary management in EBC.

NSABP 04, Z0011 and IBSCG23-01 trials showed us the same findings: leaving behind clinically occult lymph node metastasis does not significantly increase regional recurrence or decrease survival [37]. A non-invasive alternative to SLNB, which will predict node negativity with sufficient accuracy and give similar prognostic information, will be most desirable in such low-risk cases [73]. A reliable, non-invasive estimate of axillary tumour burden could replace SNB, as ALND is not recommended in cases with less than two positive axillary nodes [74].

Table 2 Strategies for the selective omission of SNB

Recommendations/ study	Group selected for management without SNB
SOUND Trial [71]	T1, any age, BCS with RT, Negative axilla USS
BOOG 213-08 [37]	T1-2, age > 18, BCS with RT, Negative axilla USS
INSEMA [8]	T1-2, age > 18, BCS with RT, c/I N0
Tucker et.al [75]	T1-2, age > 18, BCS with RT, Negative axilla USS
Choosing Wisely [76]	> 70 years old with hormone-positive, HER2 negative, T1N0

BCS Breast-conserving surgery, RT Radiotherapy

A modest estimate is that every second patient with early breast cancer could benefit from even a selective omission of SNB [8]. Cost savings and workflow efficiency improvements accompanying the omission of SNB are also substantial.

Alternative strategies for axillary management:

Many Alternative options for axillary management are reported in the literature. (Table 1)

Selective omission of axillary assessment

Four randomised controlled trials are underway that look at omitting SNB in selected groups of patients. (Table 2) While the SOUND trial only includes patients with tumours less than 2 centimetres, the other three include both T1 and T2 tumours. These studies will examine the effectiveness of managing EBC without SNB in selected groups of patients. At a median follow-up of 5.7 years, the SOUND trial has found the omission of SNB is not inferior in terms of distant disease-free survival to SNB [77]. The Choosing Wisely recommendation developed by the Society of Surgical Oncology and subsequent ASCO guidelines on the management of axilla recommends that SNB is not required routinely in hormone-positive early breast cancer in women over 70 years of age.

Radiological evaluation of axilla

Dedicated radiological evaluation of the axilla using ultrasound scans (USS), Magnetic resonance Imaging (MRI), and Positron Emission Tomography (PET) has been attempted. Axillary USS is very specific but lacks the negative predictive value required to replace SNB [78, 79]. Many modifications of axillary USS have been suggested with improvements in reported results. Preoperative localisation of the sentinel node using contrast-enhanced USS (CEUS) and biopsy of suspicious nodes has been attempted as one of the strategies to replace SNB. A systematic review showed a pooled sensitivity of 54% and specificity of 100% in identifying positive axillary nodes by this technique [80]. Adding shear wave elastography to conventional ultrasound improves the accuracy but is still inferior to the CEUS results [81]. A dedicated MRI assessment may have the required

Table 3 Predictive models for Sentinel node status

Model	Clinical characteristics						Histological characteristics					Molecular characteristics							USS features of lymph nodes		
	Age	Menopausal status	Race	Location	Palpable primary	T	Histological type	LVI	Grade	Multifocality	Margins	ER	PR	Her2	Ki67	Nm-23	Kiss-1	S phase	Transverse diameter	Cortical thickness	Hilum
Bevilacqua	+			+		+	+	+	+	+		+	+								
Carmichael	+			+	+	+	-	+	+												
Chen K###	+			+		+	+	+	+			-	-	+							
Chen JY (Shanghai Model)	+			+		+	+	+													
Chadha##	-					+		+	-									-			
Ahlgren#						+															
Laurentiis++++						+	+	+		+											
Barth+++					+	+		+	+												
Choong++	+					+		+	+												
Mustafa	+					+			+												
Reyal+	+					+		+				+		+							
Kolarik ****	+			+		+	+	+	+	+		+	+	+	+						
Xie F		+				+						+	+	+		+	+				
Fehm T													+	+	+						
Qiu SQ						+			+			+							+	+	+
Ravdin	+					+							+					+			
Silverstein					+	+		+	+												
Takada*	+					+			+					+					+		+
Olivotto	+				+	+	+	+			+										
Gann	+	+		+		+	+		+			+	+					+			
Chua ***					+	+		+		+											
Viale						+	+	+		+			+								
Chagpar **	+				+	+		+													

Table 3 (continued)

Model	Clinical characteristics					Histological characteristics				Molecular characteristics						USS features of lymph nodes		
	Age	Menopausal status	Race	Location	Palpable primary	T	Histological type	LVI	Grade	Multifocality	Margins	ER	PR	Her2	Ki67	Nm-23	Kiss-1	S phase	Transverse diameter	Cortical thickness	Hilum
Greer		+				+	+	+													
Chen W	+			+		+	+	+	+												

*AI-based model using Alternating Decision Tree (AD Tree).

** Two separate models: one with LVI and one without LVI; palpable tumour is a predictor when LVI is not included.

*** In clinically node-negative patients, the risk factors were palpability of the primary tumour, grade, LVI, and multifocality.

**** Preoperative and postoperative models. The postoperative model is accurate, while the preoperative model is not. In addition to the factors listed, the model also included the hospital operated and BMI.

+ Molecular subtypes approximated using ER, and PR is one of the factors.

++ Used a special statistical method- "MEE"; and instead of nuclear grade, nuclear pleomorphism was used.

++Model specifically looks at T1 tumours.

+++ Tumour type is classified into three based on grade and histological subtypes. Irregular borders and nipple inversion are two other specific factors in this model (altogether, six factors in the model).

Tumour size and clinically palpable node are the only factors. SPF or ER, PR status did not contribute.

Model for T1 Tumours.

Separate models for prediction of node positivity and pN2-3 status.

T Primary tumour size, ER Oestrogen receptor, PR Progesterone receptor, HER2 Human Epidermal Growth Factor 2, AI Artificial intelligence, LVI Lymphovascular invasion, MEE maximum entropy estimation, SPF S phase fraction

negative predictive value and sensitivity. However, it has yet to be validated in large studies [82]. PET (using FDG PET/CT) has also shown a high specificity. However, it is widely agreed that better sensitivity and diagnostic performance are needed to adopt this test as an alternative to SNB [83]. Radiological assessment of the axilla with all these advanced imaging techniques appears promising but is not a viable stand-alone alternative to SNB.

Prediction models

Clinicopathological models

Non-invasive estimates of axillary nodal status based on characteristics of the primary lesion (clinical, radiological, histopathological, and molecular) and the appearance of the axilla (clinical and radiological) have been attempted by many researchers. One such method is a nomogram developed by Bevilacqua et al. from the Memorial Sloan Kettering Cancer Centre, incorporating nine commonly estimated clinicopathological parameters of the primary tumour to predict the chance of sentinel node positivity in early breast cancer patients [84]. Sentinel node status can be predicted with an accuracy of 73% uing this nomogram. Similar prediction models for sentinel node status based on the clinicopathological and radiological parameters have been reported by many others [12, 36, 62, 65, 73, 84–103]. Predictive models for sentinel node status estimation incorporating various combinations of preoperative features are summarised in Table 3. Patani et al. in 2007 reviewed available literature on predictive factors of axillary disease [104] and concluded that these methods have yet to be found reliable enough to replace formal assessment of the axilla by SNB. Table 4 summarises the most commonly used and validated clinicopathological models and their reported accuracy. Overall, all these models have similar accuracy.

Radiomics models

One of the new avenues in modelling is artificial intelligence (AI) and machine learning to improve the accuracy of predictive models. AI can be used on standard clinicopathological datasets to improve the accuracy of outcome prediction. Radiomics is the method of extracting "features" related to the geometrical or physical properties of the tissue represented in a standard image using pattern-recognising algorithms. These "features" are translated into a set of numbers representing the physical properties of the lesion and may reflect its biological properties. AI can then analyse radiomics-based features extracted from standard imaging modalities to predict the outcome of the lesion under evaluation [105]. Radiomics has been applied to mammograms, tomograms, ultrasound, computerised tomography, PET, and MRI scans. Table 5 summarises the available radiomics models in sentinel node prediction. Researchers have found that this approach

Table 4 Validated clinicopathological models in use and their accuracy

Model	Variables	Reported AU ROC	External validation
MSKCC	Age, T, LVI, location, multifocality, histologic type and grade, ER and PR	0.754	Yes
MDACC [112]	Age, T, LVI, location, multifocality, histologic type, Triple negative status	0.808	Yes
Paris	Age, T, LVI, Subtype	0.72	Yes
Shanghai	Age, T, LVI, location, histologic type	0.758	Yes

can predict sentinel node status more accurately than the existing clinicopathological models [106–111].

Genomic models

Current advances in molecular and genetic aspects of breast cancer have opened new insights into tumour behaviour and prognosis. Genomic data has revealed characteristic gene amplification patterns associated with different breast cancer subtypes [137, 138]. These cancer subtypes, which are not identifiable by regular histological examination, strongly relate to prognosis and tumour behaviour. Commercially available tests based on this principle, such as the "Oncotype Dx recurrence score" (validated for estimating systemic recurrence risk), have been found to predict locoregional recurrence [139]. These molecular subtypes of breast cancer can be approximately identified based on the expression of receptors (ER, PR and HER2) and the proliferation marker Ki 67 [140]. Such classification has been found to help predict tumour behaviour, including axillary lymph node metastasis. HER2 /NEU overexpression is related to the risk of axillary metastasis [141]. Progesterone receptors and S-phase fraction can significantly contribute to the prediction of nodal involvement [12]. A recent meta-analysis has found that MMP expression is associated with an increased risk of lymph node metastasis [142]. MAM, LRP, MDR1, Nup88, CXCR4, VEGF, COX2, and PIK3R5 are other genes associated with the risk of lymph node metastasis [143–151]. Low expression of the "nm 23 gene" is also associated with the risk of nodal metastasis [152, 153]. Primary tumour miRNA signature is predictive of nodal status as are alterations of tumour cell-surface glycosylation and tumour neo-angiogenesis [154–156]. A recent review by Cavalli et al. concluded that molecular markers identified on the primary tumour can potentially replace sentinel node-based assessment of the axilla [157]. Fehm et al. express a similar view. Tumour biology detected on the core biopsy of the primary tumour will help estimate a high-risk phenotype and risk of nodal involvement, hence the need for axillary dissection [73].

Table 5 Models using radiomics for prediction of sentinel node status classified based on the imaging modality used

USS
Lee [113]
Lee [114]
Gao [115]
Zha [116]
Yu [111]
Qiu [117]
USS and Shear Wave elastography
Jiang [118]
USS by automated breast volume scanning
Wang [119]
MMG
Tan [110]
Yang [109]
CESM
Mao [120]
PET Scan
Song [83]
Cheng [121]
CT scan
Zhang [122]
MRI
Qiu [123]
Wang [124]
Shan [125]
Wang [126]
Yu [127]
Yu [128]
Chen [129]
Song [130]
Obeid [131]
Li [132]
Liu [133]
Tan [134]
Zhang [135]
Han [107]
Zhang [136]
Mao [120]

CESM Contrast Enhanced Spectral Mammography

Conclusion

Sentinel node-based management of the axilla has served well for the management of early breast cancer, and to date, alternative axillary assessment strategies have failed to produce any impact. However, SNB has potential side effects and a reported false negative rate of 6–10%, and SNB has no effect on disease-free or overall survival. Based on the available research evidence, an alternative to SNB can be developed based on clinical, radiological and genomic data. As completion axillary dissection is

no longer recommended for patients with less than two nodes involved with cancer, a non-invasive model to predict the number of involved nodes could be valuable in de-escalating axillary management. It is also likely that these models, even if they don't accurately predict nodal status in all cases, may accurately predict prognosis, will have the same value as that of the nodal status in prognostication, and hence can replace SNB in most patients with EBC.

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JJ and ML prepared the manuscript.JJ prepared the tables. SS and CS reviewed and corrected the manuscript.

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Data availability
Data will not be shared as this is a descriptive review, and there is no primary data to share other than the references.

Declarations

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Competing interests
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