



Can Preoperative Ultrasonography and MRI Replace Sentinel Lymph Node Biopsy in Management of Axilla in Early Breast Cancer—a Prospective Study from a Tertiary Cancer Center

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Abstract

Although SLNB is a less invasive procedure in detecting axillary lymph node metastases (ALNM) in early breast cancer; still, it carries some complications like lymphedema and in addition, performing SLNB requires surgical skills, technical knowledge, presence of facility like preoperative sentinel lymphoscintigraphy, and availability of hand-held gamma probe for intraoperative assessment. We calculated the relative diagnostic strength of preoperative axillary USG and MRI and compared with of SLNB for detection of ALNM in early breast cancer and assessed whether MRI and USG could accurately predict axillary LN status, potentially replacing SLNB. We evaluated 40 cases of clinically node-negative early breast cancer with preoperative axillary USG and MRI and subsequently subjected to SLNB. The sensitivity, specificity, PPV, NPV, and accuracy of axillary USG were 62.5%, 96.88%, 88.33%, 91.18%, and 90% respectively (p value < 0.001). The sensitivity, specificity, PPV, NPV, and accuracy of MRI in detection of ALNM were 75%, 93.75%, 75%, 93.75%, and 90% (p value < 0.001). The sensitivity, specificity, PPV, NPV, and accuracy of combined USG and MRI in detection of ALNM were 87.5%, 90.63%, 70%, 96.67%, and 90% respectively (p value < 0.001), which are comparable to previous study series. The diagnostic performance of combined approach of axillary USG and MRI is promising, as the NPV of combined USG and MRI is approaching the NPV of the SLNB in detecting ALNM. Based on above findings, if axillary LNs are found nonsuspicious in preoperative axillary USG and MRI, further axillary dissection may be avoided, and if found suspicious, then ALND may be directly proceeded avoiding SLNB in between.

Keywords Sentinel node biopsy · USG breast · MR mammography

Introduction

Axillary lymph node (LN) status is an important prognostic factor for breast cancer patients, and it provides information for further treatment decisions. In the past, axillary lymph node dissection (ALND) was performed in all patients to both establish axillary LN status and treat metastatic LNs. However, because ALND can cause significant complications including nerve injury, lymphedema, and shoulder morbidity, sentinel LN biopsy (SLNB) has been evolved in past two

decades and has become the standard procedure for the assessment of axillary LN status [1].

The first attempts to avoid ALND was documented with the National Surgical Adjuvant Breast and Bowel Project B-04 trial which demonstrated that ALND had no survival advantage over observation in clinically node-negative breast cancer [2]. Since then, several studies have been performed to address the same issue.

The concept of SLNB was first introduced to patients with breast cancer by Giuliano et al. in 1994 [3]. Moving to a minimally invasive approach with this technique has substantially reduced the morbidity and mortality of the patient. The National Surgical Adjuvant Breast and Bowel Project Trial protocol B-32 (NSABP B-32) used the combination of blue dye and radioisotopes to compare SLNB and ALND to SLNB alone with axillary dissection being performed only for positive sentinel lymph nodes (SLN). The results of this study showed that the

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SLN could be identified in 97% of cases with a false-negative rate (FNR) of 9.8%. After 8 years of follow up, there were no significant differences reported in overall survival (OS), disease-free survival (DFS), and regional control across both groups. [4]

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial set off an explosion in the field which reported no benefit in clearing axillary nodes when there was involvement of up to two SLNs, and there was a very low axillary recurrence rate in patients not receiving completion ALND (0.9% after 6.3 years of follow-up). [5] Although the results of this trial has been criticized for various reasons, but based on its results, the American Society of Clinical Oncology (ASCO) stated that clinicians should not recommend ALND for women with early-stage breast cancer who have one or two SLN metastases and will receive breast conservation surgery (BCS) with conventionally fractionated whole-breast radiotherapy. [6]

However, the weaknesses and critiques raised to ACOSOG Z-0011 trial led several researchers to design the ongoing POSNOC [7], SENOMAC [8], SINODAR ONE [9], and BOOG 2013–07 [10] trials which may give the clear idea in future about the best modality of treatment to axilla after positive SLNB in early breast cancer.

The low axillary burden detected in SLNB (up to 2) has a little prognostic value as further ALND has no survival advantage. Then the rationale of doing SLNB in low burden axilla in early breast cancer is being questioned. To solve this, SOUND trial is ongoing based on the concept that axillary surgery is not required in early breast cancer with T1 lesion, if the axilla is found to be negative on ultrasound and guided FNAC for suspicious LNs [11].

Although SLNB is less invasive compared with ALND, short-term complications still occur in approximately 25% of patients. The incidence of arm lymphedema is seen in approximately 8% of patients [12]. In addition, performing SLNB requires surgical skills, technical knowledge, presence of facility like preoperative sentinel lymphoscintigraphy, and availability of handheld gamma probe for intraoperative assessment.

Multiple nonsurgical methods have been studied with variable success to predict LN involvement in early breast cancer namely physical examination of axilla, digital mammography, ultrasonography (USG), CT scan, PET scan, and MRI [13–15].

The aim of our study was to find the relative diagnostic strength of axillary USG, MRI, and SLNB for detection of axillary lymph node metastases (ALNM) in early breast cancer and to assess whether MRI and USG could accurately predict presence of ALNM, potentially replacing SLNB.

Materials and Methods

We present the results of a prospective study conducted at BLK Cancer Centre from 2016 to 2018. The study consisted of women with early breast cancer with clinically negative axilla planned for primary surgery (Breast Conservation Surgery or Modified Radical Mastectomy) with preoperative histological documentation of carcinoma breast. All patients underwent preoperative evaluations with MRI and axillary USG. Patients with clinically palpable lymph nodes, those who received preoperative chemotherapy or endocrine therapy were excluded from this study. Other exclusion criteria included patients with ductal carcinoma in situ, prior history of axillary surgery or treatment, recurrent axillary disease, and metastatic breast cancer.

All patients were subjected to thorough history taking, complete physical examination, and relevant blood investigations. B-mode ultrasound was conducted to determine the axillary lymph nodes status. Suspicious lymph node was defined as lymph node >0.5 cm in diameter, a length/width ratio <1.7, absence of hilum, heterogeneous thickening of the cortex, and increased peripheral blood flow.

MRI was performed by using a 1.5-T system with a dedicated breast coil with patients in prone position. The axillary lymph nodes were evaluated with pre- and post-contrast images according to Kvistad et al. [14]. Any abnormal lymph nodes were recorded as suspicious. Criteria for LNs considered abnormal on MRI included size more than 10 mm, rounded shape, eccentric cortical hypertrophy, or abnormal signal intensity enhancement on T1-weighted images.

A patient-labeled negative axilla by clinical examination or suspicious on imaging modalities (USG and/or MRI) underwent a SLNB during surgery using both technetium-99 m sulfur nanocolloid and 1% isosulfan blue dye. A completion level I and II ALND was performed, if SLNB was found to be positive on frozen section examination or not visualized intraoperatively. No further axillary clearance was carried out if SLNs were negative on frozen section examination. Those cases reported negative sentinel lymph node on frozen section and found positive (N1macro) on final HPE, were subjected to delayed completion axillary lymph node dissection.

The data was summarized comparing between groups with Fisher's exact test. Quantitative variables were written in terms of mean \pm sd and compared using Mann-Whitney test. Sensitivity and specificity were calculated to assess the usefulness of various procedures in comparison to histopathology. A *p* value <0.05 was considered statistically significant. The data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 software.

Table 1 Average number of SLN detected intra-op

No. of SLN detected intra-op	<i>n</i>	%
1	3	7.89%
2	17	44.74%
3	14	36.84%
4	4	10.53%
TOTAL	38	100%
Mean ± sd	2.54	± 0.78

Results

We evaluated 40 cases of clinically node-negative early breast cancer with preoperative axillary USG and MRI. Mean patient age was 55.05 years (range 33–75 years). The tumors were located in upper outer quadrant in 55% cases, upper inner quadrant in 22.5%, lower outer in 7.5%, lower inner in 12.5%, and 2.5% cases in the central quadrant. Axillary LNs were found suspicious in 15% cases (6/40) and 20% cases (8/40) in axillary USG and MRI respectively. Out of 40 cases, three cases underwent total mastectomy with SLNB and rest underwent breast conservation surgery with SLNB. SLNB was performed using both Tc 99 m-sulfur colloid and isosulfan blue dye with a detection rate of 95% and FNR of 2.63%. In two cases, SLN was not visualized intraoperatively (Table 1). Only six cases out of 38 patients with SLNB showed positive LN metastases on final histopathological examination from which one case was found negative on frozen section and reported positive in final HPE examination.

Out of eight positive cases, only one case had T1 (< 2 cm size) lesion and the rest had T2 tumors. However, there was no statistically significant ($p > 0.05$) relationship found between T1 and T2 with positive LNs on final histopathology. We calculated the relationship between number of SLNs detected intraoperatively with positive LNs in final histopathology, which was not found statistically significant ($p > 0.05$).

In our study, the sensitivity, specificity, PPV, NPV, and accuracy of axillary USG were 62.5%, 96.88%, 88.33%, 91.18%, and 90% respectively (CI 95%, p value < 0.001) (Table 2). The sensitivity, specificity, PPV, NPV, and accuracy of MRI in detection of axillary lymph node

metastasis were 75%, 93.75%, 75%, 93.75%, and 90% (CI 95%, p value < 0.001) (Table 3). The sensitivity, specificity, PPV, NPV, and accuracy of combined USG and MRI in detection of axillary lymph node metastasis (ALNM) were 87.5%, 90.63%, 70%, 96.67%, and 90% respectively (CI 95%, p value < 0.001) (Table 4).

Discussion

More than 15 years ago, SLNB was introduced in the management of clinically node-negative breast cancer patients to assess the status of axillary LNs. Recent studies have shown negative SLNB in up to 74% of patients in a general breast cancer population [16]. In this study, 32 cases (84.2%) were found negative for lymph node metastasis out of 38 cases detected in SLNB.

Ever since the National Surgical Adjuvant Breast and Bowel Project (NSABP B-04) trial, the need for ALND for clinically node-negative patients has been questioned. After ACOSOG Z0011 and IBCSG 23-01 results, it was suggested that completion ALND could be safely omitted in patients with 1–2 positive metastatic SLNs. Despite the fact that nodal metastases remained in situ, omitting completion ALND after positive SLNB did not result in inferior regional recurrence rates, DFS, and OS.

Prior to 2011, a role for preoperative staging was to detect at least one positive axillary LN. If it was detected, the patient would skip SLNB and receive ALND. However, this was invalidated by the ACOSOG Z0011 study in 2011 and replaced by a new paradigm. With the new paradigm, a role for preoperative LN staging is to detect multiple abnormal LNs (three or more positive LNs, which would suggest exclusion from the 2011 criteria). Therefore, assessing the whole axilla is now more important than to detect a single suspicious LN with USG in its limited field of view. Because the whole axilla can be covered by MRI, technically all axillary LNs should be surveyed with MRI. Hence, the present study was conducted to evaluate the role of two modalities vis a vis USG and MRI to assess their sensitivity, specificity, and accuracy in identifying pathologically positive lymph nodes, and this could be improved when evaluated in combination.

Table 2 Diagnostic accuracy of axillary USG

HPE →	Positive		Negative		<i>p</i> value	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa
	<i>n</i>	%	<i>n</i>	%							
USG axilla ↓											
Suspicious	5	62.50	1	3.12	< 0.001	62.50%	96.88%	83.33%	91.18%	90.00%	0.655
Nonsuspicious	3	37.50	31	96.88							
TOTAL	8	100	32	100							

Table 3 Diagnostic accuracy of MRI

HPE →	Positive		Negative		<i>p</i> value	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa
	<i>n</i>	%	<i>n</i>	%							
MRI axillary ↓											
Suspicious	6	75.00	2	6.25	<0.001	75.00%	93.75%	75.00%	93.75%	90.00%	0.688
Nonsuspicious	2	25.00	30	93.75							
TOTAL	8	100	32	100							

Axillary USG is a portable and simple test that is routinely used preoperatively to evaluate lymph node involvement. The sensitivity and specificity of axillary USG for the detection of ALNM were 61% and 82% respectively, based on a meta-analysis of 31 studies. [11] Van Rijk et al. [17] reported that the sensitivity, specificity, PPV, and NPV were 35%, 82%, 53%, 68%, and 64%, respectively, using 726 breast cancer patients who had no palpable axillary LNs, and the rate of ALNM in this group was 21% only. In several studies, the sensitivity and specificity of axillary USG for the detection of metastatic LNs have been reported as 49–87% and 56–97%, respectively. When combined with USG-guided fine needle aspiration or core needle biopsy, the values were 31–63% and 95–100%, respectively [18]. In our study, the sensitivity, specificity, PPV, NPV, and accuracy were 62.5%, 96.88%, 88.33%, 91.18%, and 90% respectively (95% CI, *p* value < 0.05), which are comparable to the previously reported series. Advantages of USG for LN evaluation include detailed assessment with a high-frequency transducer in both planes and assessment of blood flow with color Doppler imaging. However, disadvantages of USG include operator dependence, limited accessibility for viewing deep LNs, and questionable reproducibility of images.

For breast cancer evaluation, MRI is currently the best study to show anatomy in relation to pathology. In addition, MRI allows evaluation of internal mammary and complete visualization of entire axilla with a comparison of contralateral axilla. The downside to the use of MRI is availability, cost, and patient's physical restrictions (claustrophobia, kidney function, implanted metal objects in some patients). Nonetheless, MRI has increasingly been used for breast cancer evaluation with a reported broad sensitivity range for detecting axillary metastasis as 36–78% and specificity 93–100% [13, 14]. Harman et al. reviewed prior studies and

estimated sensitivity and specificity of MRI for the diagnosis of metastatic axillary LNs as 90% (95% CI 78–96%; range 65–100%) and 90% (95% CI 75–96%; range 54–100%) respectively [19]. In the present study, the sensitivity, specificity, PPV, NPV, and accuracy of MRI in the detection of ALNM were 75%, 93.75%, 75%, 93.75%, and 90% (95% CI, *p* value < 0.001).

Hiroyuki Abe et al. compared MRI and USG for axillary lymph node staging in breast cancer patients in an observer-performance study and found no statistically significant differences in sensitivity, specificity, PPV, or NPV between MRI and USG. The specificity of USG, MRI, and combined USG and MRI were 81%, 79%, and 92% respectively, and the PPV of USG, MRI, and combined USG and MRI were 58%, 59%, and 77% respectively. So, there were statistically significant improvements in specificity and PPV from either MRI or USG alone to combined MRI and USG [20]. In the present study, the sensitivity, specificity, PPV, NPV, and accuracy of combined USG and MRI in detection of ALNM were 87.5%, 90.63%, 70%, 96.67%, and 90% respectively (95% CI, *p* value < 0.001). There was statistically significant higher sensitivity and NPV in combined USG and MRI in comparison to either USG or MRI alone.

SLNB is reported to have a sensitivity of approximately 93–95%, and a specificity of 100% [21, 22]. A meta-analysis showed a FNR of 8.61% (95% CI 8.05–9.2%) of the SLNB and the calculated NPV of the SLNB in a patient group with a prevalence of 40% of axillary metastasis equals to 94.5% [23]. In our study FNR of USG, MRI, and combined USG use - MRI, were 37.5%, 25%, and 12.5% respectively.

Previously, other non-invasive techniques considered to exclude axillary metastases were axillary physical examination (PE), axillary USG, and PET/CT. However, these

Table 4 Diagnostic accuracy of combined USG and MRI

HPE →	Positive		Negative		<i>p</i> value	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa
	<i>n</i>	%	<i>n</i>	%							
US and MRI axillary ↓											
Suspicious	7	87.50	3	9.38	<0.001	87.50%	90.63%	70.00%	96.67%	90.00%	0.714
Nonsuspicious	1	12.50	29	90.63							
TOTAL	8	100	32	100							

methods lack sensitivity and NPV. Sensitivity was 25–35.5% for PE, 43.5–72.3% for axillary USG and 56–62.7% for PET/CT. The NPV was 81.7% for PE, 81.6–83.3% for axillary USG and 79.1% for PET/CT, concluded that the diagnostic performance of these techniques was insufficient to exclude lymph node metastases and omit SLNB. [24, 25]

We aimed to determine whether US, MRI or combined modalities could sufficiently exclude axillary lymph node metastasis, thereby replacing SLNB, consequently eliminating the risk of its morbidity. For this purpose, we focused on the sensitivity and NPV, as we are mainly interested in the exclusion of axillary metastases in order to omit SLNB. Therefore, the NPV should at least be non-inferior to the NPV of SLNB. In our study, NPV of axillary USG or MRI alone was found less than that of SLNB. But in combined axillary USG and MRI, the results are promising, as the NPV is approaching to that of SLNB.

Although SLNB is less invasive compared with ALND, it is still associated with some morbidity including lymphedema, pain, paresthesia, decreased arm strength, and shoulder stiffness. Sixty percent of newly diagnosed clinically node negative early breast cancer patients are pathologically node negative and consequently do not benefit from SLNB. When comparing the cost of combined USG and MRI with SLNB procedure, USG and MRI may cost around Rs 15,000, whereas SLNB adds cost of Rs 20,000 to 25,000 to the surgery cost including cost of presurgical scintigraphy, intraoperative SLNB procedure, and cost of frozen section examination. Secondly, there is an unavailability of frozen section technique, gamma probe, and nuclear medicine department everywhere which limits the widespread use of the SLNB procedure.

Though USG is a simple and widely available procedure but has disadvantages of operator dependence and limited accessibility for viewing deep lymph nodes. MRI is costly and also not available everywhere. So, these imaging modalities can be used subject to the availability and expertise to interpret properly.

Limitations of this study are short sample size and single center study.

Conclusions

In the present study, the diagnostic performances of MRI and USG for assessing ALNM are lower than the diagnostic performance of SLNB. However, the diagnostic performance of the combined approach of axillary USG and MRI is promising, as the NPV of combined USG and MRI found noninferior than the NPV of the SLNB in detecting ALNM.

Theoretically, a non-invasive technique with a higher sensitivity and NPV than SLNB in detection of ALNM can replace SLNB. Based on above findings, combined axillary

USG and MRI may exclude axillary lymph node metastasis, potentially replacing further axillary dissection and consequently eliminating the risk of axillary morbidity in future.

However, the high false-negative rates of combined modalities may limit its application in clinical settings. Large-scale, multicenter studies should be conducted to further explore these findings.

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