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Utility of Axillary Reverse Mapping (ARM) and Incidence of Metastasis in Arm Draining Lymph Nodes in Patients with Breast Cancer

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Abstract

Objective Lymphedema of the upper limb is the most common complication in patients with breast cancer, who require axillary lymph node (LN) dissection. Proposition of identifying upper limb draining LN and preserving it, during axillary dissection can reduce significant postoperative morbidity, but it has the risk of inadequate oncological resection. This study was planned to find out metastatic rate in axillary reverse mapping (ARM) nodes in our population.

Materials and Methods Lymphoscintigraphy (LSG) was performed using intradermal injection of ^{99m}Tc Sulfur Colloid into ipsilateral second and third interdigital web spaces of hand in patients with breast cancer. Planar, single-photon emission computed tomography-computed tomography images were acquired followed by intraoperative localization of arm draining LNs using Gamma Probe. All identified ARM nodes were dissected and sent for histopathological examination to confirm metastatic involvement.

Results Twenty eligible patients were prospectively analyzed. The identification rate of arm draining LN with LSG was 90% (18/20). Among 14 eligible patients included in the study, ARM node metastasis was seen in two patients. A total of 64 ARM nodes were dissected from 14 patients, 4/64 nodes (2 patients) were positive for metastases (6.25%). Of the six patients excluded from the study, in 1 patient ARM node could not be identified on Gamma Probe, in two cases, it could not be retrieved surgically, in next two cases ARM could not be identified on LSG and remaining one case was removed because of previous surgical intervention.

Conclusion In the current study, LSG showed the identification rate of 90% for ARM nodes in patients with carcinoma breast and metastatic involvement was seen in 6.25% (4/64) of these nodes in 2/14 (14.2%) patients, which is in agreement with previously published data. Oncological safety of preserving ARM nodes needs to be evaluated in the larger population.

Keywords
- axillary lymph node dissection
- axillary reverse mapping
- breast cancer
- lymphedema
- lymphoscintigraphy
- sentinel lymph node

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Introduction

With approximately 1.69 million new cases per annum, breast cancer is the most common cancer of females[1] worldwide and only second behind lung cancer in cancer-related mortality among them. Age-adjusted rate of breast cancer and mortality in Indian females is as high as 25.8 and 12.7 per 100,000 women, respectively. Mortality-to-incidence ratio for breast cancer is as high as 66 in rural areas and 8 in urban areas.[2] For both prognosis (in early stage disease) and treatment (for regional control of disease), accurate lymph node (LN) staging is essential.[3] Surgical resection of the tumor constitutes central modality of breast cancer treatment and modified radical mastectomy (MRM) with axillary LN dissection (ALND) is one of the surgeries being done for breast cancer patients. Among various postoperative morbidities (i.e., lymphedema, infections, seroma, neurologic, and sensory deficits)[4] associated with ALND, major and most widely published morbidity is upper limb lymphedema. Rate of lymphedema with ALND is 6 to 57%.[5–8]

Lymphedema can be defined as "an abnormal, generalized, or regional accumulation of protein-rich interstitial fluid, resulting in edema formation and eventually chronic inflammation with or without fibrosis." It occurs due to diminished lymphatic flow, leading to progressive increase in intraluminal hydrostatic pressure and thus congestion and dilatation of lymphatic vessels. It is a potentially serious complication associated with functional, esthetic, and psychological problems, thereby affecting the postsurgery quality of life of breast cancer patients.[5]

Sentinel LN biopsy (SLNB), a technique introduced by Mortan et al, proposed to identify the first few LN draining the tumor. SLNB is used in patients of breast cancer as a tool to screen patients who can be spared of ALND, thereby reducing the incidence of upper limb lymphedema. However, even with SLNB, the incidence of upper limb lymphedema remains significant at 0 to 13%.[9,10] Approximately 25% patients reported to have connection between the lymphatic drainage of the upper limb and breast.[11] A substantial proportion of the lymph from the subcutaneous tissue of the arm drains into the central axillary nodes and some directly to the anterior and posterior axillary nodes. The later may colocalize with the sentinel node draining from the breast. Colocalization of sentinel nodes of the arm and breast (crossover nodes) is a plausible cause of lymphedema in SLNB.

The main cause of lymphedema is the damage to the upper limb lymphatics during axillary node clearance. Therefore, it is essential to identify these lymphatics and to preserve them is an attractive proposition.[12] This forms the basis of axillary reverse mapping (ARM) in axillary surgery for carcinoma breast patients.[13] By mapping the lymphatic drainage of the arm, using ARM technique, it is feasible to identify upper limb lymphatics and preserve them. Preservation of these lymphatics should consequently prevent the disruption of drainage from the arm and resulting lymphedema thus reducing the morbidity associated with ALND and improving the quality of life.[14] However, there are concerns reported in the literature that preservation of the crossover nodes draining lymph from both arm and breast may result in retained metastasis and inadequate oncological resection.[15]

ARM technique can be performed using blue dye and ^{99m}Tc sulfur colloid lymphoscintigraphy (LSG). ARM using blue dye involves injection along the medial intramuscular crease that allows rapid drainage of dye to the axilla during surgery. It allows direct visualization of arm lymphatics and arm draining LNs during ALND, thus allowing preservation of arm draining LNs and lymphatics.[16] In this prospective study, we aimed to assess the feasibility of ARM technique using ^{99m}Tc sulfur colloid LSG for the identification of upper extremity draining LN and to assess the metastatic rate in ARM nodes by histopathological examination, in our population of Uttarakhand.

Materials and Methods

Study Type and Setting

This study was a prospective, observational study conducted in the Department of Nuclear Medicine in collaboration with Integrated Breast Cancer Clinic of AIIMS, Rishikesh. After getting approval from the Institutional Ethics Committee, patients of early breast cancer (stage I–IIIA, T3 N1 M0) planned for surgery (MRM with ALND) and satisfying inclusion criteria of the study were enrolled from January 2019 to February 2020. Pregnant female or lactating mothers were excluded. Informed consent was obtained from patients before enrolment in the study.

Radiotracer Preparation and Injection Method

Sulfur colloid was tagged with freshly eluted ^{99m}Tc under strict aseptic condition. ^{99m}Tc sulfur colloid was then passed through a 22 µm filter to obtain ^{99m}Tc sulfur colloid of particle size ranging from 100 to 220 nm. One day protocol was followed, that is, injection of radiotracer and imaging was done on the same day of surgery. Following all radiation safety and aseptic precautions, intradermal injection of ^{99m}Tc sulfur colloid (filtered) was given in the second and third web spaces (0.5 mCi/17.5MBq each) of ipsilateral hand of carcinoma breast patient.[17]

Imaging Procedure

Imaging was done using GE NMCT 670 gamma camera with large field-of-view and low energy, high-resolution collimators. Immediately after injection, dynamic (flow) imaging was performed for 60 seconds. Planar (static) imaging was done from 5 minutes onward till 15 minutes followed by delayed imaging at 30 minutes, after injection (if necessary). Spot images were acquired in anterior and posterior views for 2 minutes each using 256×256 matrix size with zoom factor of 1 with approximate pixel size 2.2 (GE NMCT 670 gamma camera). For better localization of arm draining LNs, single-photon emission computed tomography/computed tomography (SPECT/CT) was also done, after visualization of ARM node. SPECT imaging was performed using 128×128 matrix size with 60 projections over 360 degrees and 7 to 10 seconds projection. Low-dose CT scan was done. Raw data

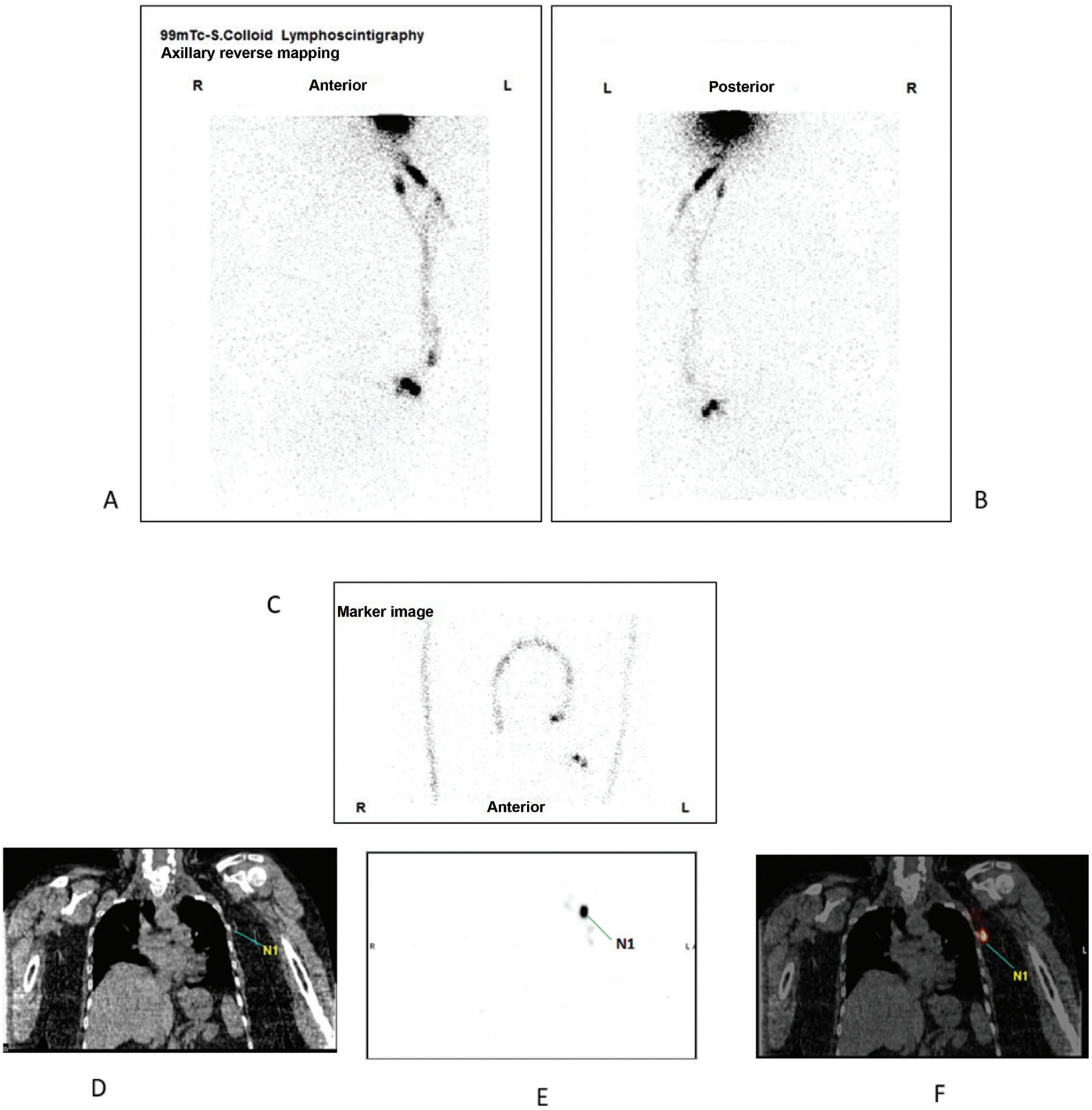

Fig. 1 Lymphoscintigraphy images of a patient with carcinoma left breast, acquired after injection of ^{99m}Tc sulfur colloid (filtered) into the second and third interdigital web spaces of left hand. Anterior (**A**) and posterior views (**B**), marker image (**C**), computed tomography (**D**), single-photon emission computed tomography (SPECT) (**E**), and SPECT/CT (**F**) images showing tracer avid left axillary level I lymph nodes (N1). This patient underwent mastectomy with intraoperative localization of left axillary reverse mapping node. On histopathological evaluation, one of these left arm draining nodes was positive for metastases.

obtained from gamma camera was processed on GE Xeleris work station (►**Fig. 1**). Location of the LN was marked on the skin with a small spot of indelible ink.

Operating Room Procedure

Using gamma camera-based LSG images and intraoperative gamma probe, upper limb draining LNs were localized. Location of arm draining LNs was marked over skin with indelible ink, based on preoperative LSG images. Gamma probe-guided dissection of all hot LNs, showing counts more than 10 times the background counts, was performed. Gamma probe was placed over the active node for confirmation before its excision (*in vivo*) and after excision (ex vivo). Probe was also placed over LN bed to confirm the removal of all hot nodes. Intraoperatively localized hot nodes were considered as ARM nodes, draining the arm. These ARM nodes were segregated and sent in separate containers for histopathological examination.

Statistical Analysis

Data was analyzed using the Microsoft Excel software. Result is given as percentage of patients in which upper extremity draining LN was identified. Percentage of patients in which arm draining LN harbors metastasis is also calculated. The chi-squared test is applied for comparison of proportion of metastatic nodes. A p-value of less than 0.05 is considered statistically significant.

Table 1 Overall distribution of patients

Total number of patients, ARM nodes identified on imaging ($n = 18/20$)			
ARM nodes identified	Not identified on imaging (LSG)	Not identified by gamma probe	Identified by both gamma probe and LSG
18/20	2/20	1/20	17/20
Eligible patients where ARM nodes identified and histopathological examination available ($n = 14$)			
Identified on imaging	Identified by gamma probe	ARM nodes identified (*n*)	ARM Nodes positive for metastasis on histopathological examination
14	14	64	4/64

Abbreviations: ARM, axillary reverse mapping; LSG, lymphoscintigraphy.

Results

A total of 20 patients were studied with a mean age of 48.95 ± 10.13 years (range: 34–71 years). Arm draining nodes with ARM technique were identified in 18/20 patients (identification rate ~90%). Among 20 patients enrolled in the study, 14 eligible patients were considered for final analysis. In 2/6 excluded cases, ARM nodes could not be identified on LSG, and 1/6 patient was excluded because of inability to retrieve arm draining LNs intraoperatively, 2/6 patients were excluded, as pathological specimen of LNs was not sent in separate containers, in busy operating room, so arm draining LNs could not be differentiated from other axillary nodes (►**Table 1**). Remaining ⅙ case was excluded due to previous surgical intervention. Tumor laterality was right sided in six patients and left sided in eight patients, while six patients had clinically palpable nodes in axilla and in eight patients axillary nodes were not palpable.

Out of 14 eligible patients analyzed, 7 patients were treatment naïve, whereas 6 patients received chemotherapy and 1 patient underwent lumpectomy before imaging. In 14 patients, 64 arm draining LNs were identified with average number of ARM node being 4.6 LNs per patient. Out of 14 patients, 2 (14.2%) were found to have metastasis in ARM nodes on histopathological evaluation; however, in 12 of 14 patients, ARM nodes were free of metastasis. A total of 4 out of 64 ARM nodes were found to be positive for metastasis in two patients. Among these two patients with metastases in ARM nodes, one patient had preoperative stage IIB disease with postoperative pathological node status, pN2a, and in this case, only one out of two ARM nodes was positive for metastases. Second patient had preoperative stage IA disease with pathological node status of pN1 mi, and in this case, 3/7 identified ARM nodes were positive for metastasis (►**Tables 2** and **3**).

The current study shows least chance of metastasis in stage IIA patients (0/7 nodes, 0%) whereas stage IIB (1/37 nodes, 2.6%) and stage IA (3/18 nodes, 16.6%) had intermediate risk of metastasis. However, one case with stage IIIA, which is not included in main group due to previous surgical intervention, showed highest probability of metastasis (3/6 nodes, 50%) to ARM nodes.

Pathological node status of harvested ARM nodes was also evaluated in this study. Number of patients belonging to node status pN0, pN1, and pN2 is 8, 3, and 3, respectively, whereas the number of ARM nodes retrieved from them is 41.18 and 5, respectively.

In the current study, considering mean follow-up of 20.6 ± 1.7 months, only 2/13 (15%) patients developed lymphedema following ALND; however, 1/13 patient was lost to follow-up.

Discussion

Concept of ARM was proposed to identify and preserve the upper limb draining LNs during ALND, to reduce the incidence of upper limb lymphedema[14] in patients of carcinoma breast, requiring MRM with ALND. Our study yielded ARM node identification rate of 90% that is comparable to other studies. ARM nodes identification rate of 91, 100, and 100% was reported by Nos et al,[17] Britton et al,[18] and Gennaro et al,[19] respectively, who used only radioisotope as means of identifying ARM nodes. Interestingly, method using combination of

Table 2 Stagewise distribution of patients and retrieved axillary reverse mapping nodes

Stage	Number of patients	Number of patients positive for ARM node metastasis	Number of patients negative for ARM node metastasis	Total number of nodes (out of 64)	Number of ARM nodes positive for metastasis	Number of ARM nodes negative for metastasis
IA	3	1	2	18	3/18	15/18
IB	–	–	–	–	–	–
IIA	2	0	2	7	0/7	7/7
IIB	8	1	7	37	1/37	36/37
IIIA	1	0	1	2	0/2	2/2

Abbreviation: ARM, Axillary reverse mapping.

Table 3 Treatment history of axillary reverse mapping node positive patients

Patient	Number of ARM node positive on histopathological examination	History of previous Treatment	
		Surgery	Chemotherapy
Patient number: 7	1 out of 2	No	No
Patient number: 19	3 out of 7	No	Yes

Abbreviation: ARM, axillary reverse mapping.

blue dye and radioisotope had lower ARM node identification rate of 91, 78, and 93.5%, as seen in studies by Nos et al,[17] Tausch et al,[20] and Yue et al,[21] respectively.

There is risk of incomplete oncological resection, if arm draining LNs are spared during ALND, probably due to existence of crossover nodes. Hence, the oncological safety of sparing ARM nodes is questionable that is also supported by various studies reporting different rates of metastatic involvement of ARM nodes.

Out of 14 included patients in the analysis, two patients (14.2%) were found to harbor metastatic ARM nodes that in turn accounted for 4 metastatic ARM nodes out of total 64 ARM nodes (6.25%). In our study, 6.25% of ARM nodes were harboring tumor metastasis, which is close to previously published data with average metastatic rate reported as 8.1% ranging between 0 and 18%.[22–27] Our results also corroborated with similar study by Nos et al[17] that reported metastatic involvement in 8.8% of ARM nodes. Three patients out of 21 patients had 3 (one in each patients) metastatic ARM nodes among 34 resected nodes. All three patients who were positive for ARM node metastasis had pN3a involvement. The involvement of ARM nodes can be explained by significant axillary tumor burden (10 or more metastatic nodes).[17] Similarly, an Indian study done by Gandhi et al[28] reported metastatic ARM nodes in 5 among 47 (10%) patients. Eighty percent (4/5) patients had pN3 disease, whereas one patient had pN2 disease.

However, in our study, two patients who were having ARM node metastasis had pathological N-stage of pN2a and pN1 mi. Out of these two cases, one was treatment naïve and the other patient received adjuvant chemotherapy prior to ARM had pN stage of pN1 mi. Possible reason of micrometastasis in pN1 mi stage could possibly be due to partial response to chemotherapy and residual disease.

ARM node metastasis is positively related to nodal stage. In patient with N2 or higher metastatic disease, lymph from the breast may flow back into the arm lymphatic drainage[29] that explains the positive ARM node in one of patient in our study. A recent study[29] reported 18.5% (or 5/27) resected ARM nodes were metastatic, of which 2/5 were crossover node in N1 or N2 disease and 3/5 cases were in heavily positive axilla (N2 or N3). If ARM node is not the SLN node, then it is safe to spare such ARM node in N1 disease. However, in N2 or N3 disease, it is best to resect ARM node.[8]

Till date the published data for ARM node metastasis is inadequate to establish oncologic safety of ARM node preservation, mainly due to insufficient sample size, most of them being single center studies or due to the short follow-up period. Thus, to set standards for oncologic safety, large volume multicentric studies are needed.

Limitations of Study

Small sample size with less number of patients in the study is the main limitation to reach a definitive conclusion. Crossover nodes could not be studied since SLNB procedure was not performed in our study. Some of the published reports concluded that all metastatic ARM nodes only occurred in patients who have crossed SLN-ARM nodes.[26] The incidence of SLN-ARM node metastasis ranges from 0 to 32%.[23,24,26,29–31] With such shortcoming in the study, it is difficult to establish the oncological safety of ARM nodes. Patients who received neoadjuvant chemotherapy were also included in the current study. One out of two patients who had positive ARM node in our study received neoadjuvant chemotherapy implying incomplete response to therapy. Partial or full response to chemotherapy may result in ARM node metastasis clearance, leading to false-negative result. Upper limb lymphatics sparing during ALND was suggested to be oncologically safe in case of radiologically complete axillary remission following neoadjuvant chemotherapy.[32]

Conclusion

Feasibility to perform ARM is reasonably fair with identification rate (90%) in our study. Although proportion of patients harboring metastasis in ARM nodes is very high (14.2%) in this study, percentage of ARM nodes having metastasis (~6.25%) is comparable to overall previously reported average rate of arm node metastasis (8.1%; range: 0–18%) in the literature.[22–27] Various limitations of our study, namely small sample size, limited follow-up of patients, and small number of treatment naive patients, made it difficult to establish oncological safety of preserving ARM nodes. Prospective study with larger sample of treatment naïve patients and longer duration of follow-up are required to validate the safety and efficacy of ARM technique.

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Conflicts of Interest
There are no conflicts of interest.

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