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## Axillary Reverse Mapping: A Potentially Safe Procedure in Oncology

Behnam Behboudi<sup>a</sup>, Mohamadreza Neishaboury<sup>a, b</sup>, Fezzeh Elyasinia<sup>a</sup>, Massoome Najafi<sup>a</sup>, Ahmad Kaviani<sup>\*a, b</sup>

<sup>a</sup> Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Kaviani Breast Disease Institute, Tehran, Iran

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### ABSTRACT

**Background:** In an attempt to reduce the risk of developing lymphedema following breast cancer surgery, some researchers suggested that by identifying and preserving the lymphatic plexus which drains ipsilateral arm we can minimize the risk of lymphedema. The procedure is known as axillary reverse mapping (ARM). In the current study, we investigated the oncological safety of this technique.

**Methods:** A total of 60 patients who were undergoing axillary lymph node dissection were involved. The indications for axillary dissection were whether clinically node-positive axilla or positive sentinel lymph node biopsy. ARM was performed by injecting 2 ml of methylene blue subcutaneously in the upper and medial part of ipsilateral patients' arm along the intermuscular groove.

**Results:** ARM nodes were identified by means of methylene blue injection in 51(85%) patients (identification rate = 85%). For the subgroup of clinically positive axillary lymph nodes, identification rate was 93.1%, and the corresponding figure was 77.4% for positive SLNB group ( $P = 0.148$ ). Pathological evaluation of harvested ARM nodes demonstrated metastatic involvement in 8(27.5%) and 1(3.2%) patients in clinically positive and SLNB positive groups respectively ( $P=0.026$ ).

**Conclusions:** Based on the findings of this study it seems that ARM could be considered as a safe procedure in patients who are a candidate for ALND when SLNB is positive. In contrast, in patients with clinically positive axillary nodes, there is a considerable risk of tumoral metastasis in ARM nodes.

### Introduction

Recent studies have casted doubt on the short-term efficacy of complete axillary lymph-node dissection (ALND) in oncology patients receiving chemotherapy or axillary radiotherapy.<sup>1-4</sup> Considering the high risk of development of lymphedema after

ALND (up to 77%), sentinel lymph node biopsy (SLNB) is more commonly used to investigate the extent of axillary lymph node involvement.<sup>5, 6</sup> It is noteworthy that several studies aiming at assessment of the long-term side-effects of SLNB have demonstrated an increased risk of development of lymphedema by up to 13%.<sup>7, 8</sup>

With the view of the aforementioned potential complications, efficacy and safety of modified surgical techniques for preservation of axillary lymphatic drainage have been investigated by different studies with the main objective of preventing or at least reducing risk of lymphedema. Recently, several studies have hypothesized that by

**Address for correspondence:**

Ahmad Kaviani, MD  
Address: Kaviani Breast Disease Institute (KBDI), No 3,  
Tavaneer Sq., Tehran, 1434888483, Iran  
Tel: +98 21 88871785  
Fax: +98 21 88871698  
Email: akaviani@tums.ac.ir



differentiating arm lymph nodes from the breast ones and preserving them, the risk of lymphedema may be reduced.<sup>9-11</sup> Accordingly, axillary reverse mapping (ARM) is introduced to distinguish and preserve arm lymph nodes.<sup>12</sup>

This technique is utilized by means of subdermal injection of a blue dye in upper and inner parts of patient's arm, whereby facilitating visualization of lymphatic plexus of the arm during ALND procedure. Although findings of some studies advocate this hypothesis and provide supportive evidence for potential long-term benefits of ARM,<sup>13-</sup><sup>19</sup> the safety of this technique in oncology is still not well elucidated.<sup>11</sup> The term "cross-over" node refers to lymph nodes which receive lymphatic drainage from both the breast and the arm.<sup>20</sup> Therefore, it would be plausible to infer that preserving these nodes leads to an increased risk of recurrence.

The current study was designed to evaluate the metastatic involvement of lymph nodes detected in ARM procedure. The findings of this study could provide information regarding oncological safety of preserving lymph nodes draining the ipsilateral arm in breast cancer patients.

## Methods

### *Patients and study protocol*

This prospective study was designed and conducted at two referral clinics in Tehran, Iran between 2014 and 2016. Patients who were undergoing breast surgery (either mastectomy or breast conservative surgery) with ALND (level I and II nodes) were enrolled in the study. The criteria for performing ALND were as follow: 1) clinically positive lymph nodes or 2) positive SLNB. Subjects were excluded if they had previously received neoadjuvant chemotherapy, hormonal therapy or radiotherapy. Also, pregnant patients and those with known history of allergic reaction to methylene blue were not included. Written informed consent was obtained prior to the enrollment of the subjects and institutional ethical board of Tehran University of Medical Sciences reviewed and approved the study protocol.

### *SLNB procedure*

In patients with clinically negative axillary lymph nodes, SLNB was carried out by injecting radioactive colloid in subareolar plexus. Prior to making any incision in the axillary region of the subjects, sentinel nodes were localized using a hand-held gamma probe. If the sentinel node could not be detected based on radioactivity, then methylene blue was also injected in subareolar plexus and the patient was excluded from performing ARM. If SLN was detectable by gamma probe, patients underwent ARM procedure. Subsequently, sentinel nodes were dissected and sent for frozen section analysis. Dissection of the axillary nodes was performed if the

histopathological assessment of harvested nodes indicated any tumoral involvement.

### *Axillary reverse mapping*

ARM was performed by injecting 2 ml of methylene blue subcutaneously in the upper and medial part of ipsilateral patients' arm along the intermuscular groove. Then the site of injection was gently massaged very smoothly, and patients' arms were elevated for few minutes to enhance lymphatic drainage; and, subsequently, routine prep and drape were done prior to initiation of procedure.

### *Axillary lymph node dissection*

ALND was performed through routine axillary incision unless the patient was planned to undergo mastectomy, in which case ALND was carried out through the incision made for the surgery. The limits of ALND included axillary vein superiorly, anterior serratus muscle as medial limit and latissimus dorsi muscle as the lateral limit. Level I and II axillary nodes were dissected, and after recording of the number of blue nodes (lymph nodes draining arm lymph), and these nodes were harvested and sent for pathologic examination.

### *Pathology*

The blue nodes were labeled as arm nodes; and, ALND harvested axillary nodes were labeled as axillary nodes before being sent for pathologic assessment in separate formalin-filled bottles. The samples then were sent to pathology department and were sectioned at 3-mm thickness along the long axis. If the largest diameter of the lymph node was < 5mm, they were bisected. One section of each node was submitted for hematoxylin and eosin staining.

### *Statistical analysis*

Data analyses were performed using IBM SPSS version 19.0 software. Categorical data were compared between study groups by means of Chi-square or Fisher's exact tests where applicable. However, continuous variables without normal distribution among study subjects were compared using Mann-Whitney U test.

## Results

A total of 60 patients were enrolled in the current study. It was observed that 29 subjects (48.3%) had clinically positive axillary lymph node involvement and 31(51.7%) had positive SLNB. The mean age of the patients was  $48.23 \pm 7.57$  years.

ARM nodes were identified by means of methylene blue injection in 51(85%) patients (identification rate = 85%). For the subgroup of clinically positive axillary lymph nodes, identification rate was 93.1% (27 of 29 patients) and the figure was 77.4% (24 of 31 patients) for positive SLNB group. There was no statistically significant



differences in identification rate between the two groups ( $P=0.148$ )

The median numbers of lymph nodes detected during the procedure were 1 (IQR: 1 – 2) in the clinically positive group and 1 (IQR: 1 – 1.75) in the positive SLNB group ( $P=0.734$ ).

Pathological evaluation of harvested ARM nodes demonstrated metastatic involvement in 8(27.5%) and 1(3.2%) patients in clinically positive and SLNB positive groups respectively. Statistically significant differences were observed when the two groups were compared with respect to positive ARM nodes ( $P = 0.026$ ).

No adverse effect due to injection of methylene blue (e.g. skin necrosis or inflammatory reaction) was observed among study participants.

## Discussion

The aim of the present study was to determine metastatic involvement of lymph nodes identified during ARM. Our findings were consistent with previous studies on feasibility and oncological safety of ARM. We observed the detection rate of 85% for ARM nodes amongst our patients. However, this figure was different depending on the primary indication of ALND and ARM nodes were more commonly detected in the clinically positive group in comparison with those who underwent ALND following a positive SLNB (93.1% vs. 77.4%). The first group demonstrated significantly higher rates of metastatic involvement of ARM nodes (27.5% vs. 3.2%). Previously, several studies have been designed and conducted to evaluate the metastatic potential of ARM lymph nodes. Two points can be considered to be of singular importance regarding their findings: firstly, they reported different identification rates for ARM nodes (ranging from 50% to 91%), and, secondly, the rate of metastasis of the nodes is reported to be ranging from 14% to 43% by different investigators.<sup>13-19</sup> Therefore, it may be concluded that these findings not only cast doubt on the clinical effectiveness of ARM procedure, but also raise serious questions about its safety. The reason for metastatic involvement of ARM nodes is not clear but researchers have proposed that progression of the primary disease is responsible for tumoral metastasis to ARM nodes.<sup>15</sup>

In one study, Ikeda and his colleagues evaluated the oncological safety of performing ARM in a cohort of 60 patients.<sup>21</sup> Consistent with our findings, they reported a higher rate of tumoral involvement of ARM nodes among clinically node-positive patients in comparison with those with a positive SLNB. Moreover, they observed that clinically node-positive patients with extensive axillary metastasis (more than 4 metastatic nodes) comprised the majority of patients with positive ARM nodes. This finding further supports the hypothesis that progression of primary breast cancer may be

responsible for metastasis to ARM nodes. A systematic review of eight ARM studies suggested that in order not to jeopardize the oncological safety of primary surgery, patients with the N1 disease can benefit from procedures which preserve ARM nodes. In contrast, it is demonstrated that harvesting the ARM nodes (plus reappoximating or performing lymphovenous anastomosis) would be a safe treatment option in patients with N2 or N3 disease.<sup>22</sup> Considering the 27.5% of tumoral involvement of ARM nodes among our clinically node-positive patients, results of this study emphasize on the mentioned proposal that this group of patients may not be an appropriate candidate for this technique.

One of the main limitations of the current study was the use of methylene blue for detecting ARM nodes. This dye was chosen due to its availability in our centre. Several reports on inflammatory skin lesions or even skin necrosis after injection of methylene blue has been reported in the literature. Some researchers used isosulfan blue for detection of ARM nodes.<sup>17</sup> It is worth mentioning that none of our patients experienced any adverse effect and identification rate of ARM nodes in our study was similar to those in which isosulfan blue was used for staining ARM nodes.

In conclusion, based on the findings of this study it seems that ARM could be considered as a safe procedure in patients who are a candidate for ALND when SLNB is positive. In contrast, in patients with clinically positive axillary nodes, there is a considerable risk of tumoral metastasis in ARM nodes. Further studies with larger sample size are warranted to elucidate the oncological safety of ARM in the mentioned group of patients.

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