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Conserving the Lymphatic Drainage of the Arm Using Axillary Reverse Mapping Procedure in Breast Cancer Patients

Sung Mook Lim, MD, Gwang Hyeon Yoon, MD, Joo Heung Kim, MD, Jee Ye Kim, MD, Hyung Seok Park, MD, Seho Park, MD, Seung Il Kim, MD, Young Up Cho, MD

Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

Axillary lymph node staging is a critical prognostic factor for clinical outcomes in breast cancer patients. The standard approach for axillary lymph node staging in breast cancer patients is axillary lymph node dissection (ALND), which may cause some complications, including ipsilateral upper extremity lymphedema due to a disruption of the ipsilateral upper extremity lymphatic drainage system. Therefore, with the purpose of reducing the incidence of lymphedema, sentinel lymph node biopsy (SLNB) haves been employed to avoid the unnecessary dissection of axillary lymph nodes. With the purpose of minimizing arm lymphedema after axillary staging surgeries in breast cancer patients, the axillary reverse mapping (ARM) technique has been developed to identify and preserve arm drainage system during axillary surgery. Previously, it was considered that preservation of the ARM lymphatics or lymph nodes is not oncologically safe in patients with axillary lymph node metastases. However, recent studies have demonstrated that the ARM procedure is oncologically feasible in clinically node-negative, SLN-positive patients when ARM nodes do not coincide with SLNs. ARM is a feasible technique for identification and preservation of axillary arm lymphatics with an acceptable incidence of SLN crossover and that may prevent lymphedema in SLNB and/or ALND in patients with clinically determined low axillary nodal status breast cancer.

Key Words: Breast carcinoma · Sentinel lymph node biopsy · Axillary reverse mapping · Lymphedema

INTRODUCTION

Prolongation of survival in patients with breast cancer as a result of advancements in the treatment of breast cancer has turned the attention on factors that affect patients' quality of life, such as lymphedema. Lymphedema after breast cancer is characterized by regional swelling, typically in one or both arms, due to excess accumulation of protein-rich fluid in body tissues [1]. Although axillary dissection can be avoided as a result of sentinel lymph node biopsy (SLNB), lymphatic involvement has decreased as a result of early diagnosis, and modern radiotherapy techniques decrease the risk of lymph edema, there is compelling evidence that axillary dissection, morbid obesity, and mastectomy are risk factors that increase the rate of lymphedema [1,2]. Axillary lymph node dissection (ALND) has been highlighted as the most important risk factor for lymphedema in the clinical studies performed to date [3,4]. In the last ten years or so the concept of selecting only the first lymph node draining the breast-the sentinel lymph node, has become commonplace. Current the National Comprehensive Cancer Network (NCCN) guidelines states that minimally invasive surgery should be performed where possible for patients with no evidence of lymph node involvement and this should be by SLNB [5]. SLNB for breast cancer during the last decade has been the most important advance in more than a century in decreasing the morbidity of axillary lymph node surgery.

Data on comparable survival between patients undergoing ALND and those having SLNB alone, has been

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Address for correspondence: **Young Up Cho**, MD, PhD
Department of Surgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2091, Fax: +82-2-313-8289
E-mail: youngup@yuhs.ac

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demonstrated in the Phase III study Z-0011 trial by The American College of Surgeons Oncology Group. This prospective multi-center trial compared overall survival between patients with positive sentinel lymph nodes, randomized to receive either ALND or no further axillary treatment following SLNB. At 1 year, lymphedema was reported subjectively by 13% (37 of 288) of patients after SLNB with ALND and 2% (6 of 268) after SLNB alone ($p<0.001$). There were no significant differences between the two groups for overall survival, disease-free survival, 5 year in-breast or nodal recurrence [6]. Further, with a positive SLNB, an axillary node dissection is still the standard of care.

Recently, with the purpose of minimizing arm lymphedema after axillary staging surgeries in breast cancer patients, the axillary reverse mapping (ARM) technique has been developed to identify and preserve arm drainage system during axillary surgery.

MAIN

Axillary Reverse Mapping (ARM)

1. Concept of Axillary reverse mapping

Mapping the drainage of the arm with blue dye and preserving the identified lymphatics would decrease the likelihood of disruption of the lymphatics draining the arm during ALND or SLNB. The ARM procedure aims to identify and preserve nodes and/or lymphatics draining from the arm, it is hypothesized that there are distinct non-overlapping nodes which drain the arm and the breast respectively [7,8]. This concept has already been tested and validated in a mice model in which two different drainages were shown by a two-color spectral fluorescence lymphangiography [9]. What is important is to either anatomically resect axillary lymph nodes or physiologically remove only the lymph nodes draining from the breast. Because, although the majority of patients has different pathways of lymphatic drainage from the ipsilateral breast and upper limb, in a small minority of patients the drainage pathway is through a common SLN [10]. Anatomically, there are lymphatic interconnections between ARM nodes and SLN. The ARM node could be involved with metastases in patients with extensive lymph node metastases.

In a study of Noguchi et al. [11], in clinically node-positive patients, thereby, the ARM procedures are unsafe. However, a medial lymphatic draining from the breast and a lateral lymphatic draining from the arm may flow separately, unless grossly involved nodes alter the pattern of lymphatic flow. In clinically node-negative patients, ARM nodes are not involved with metastases even in patients with positive SLNs when they do not coincide with SLNs (Separate type). Therefore, the ARM procedure is oncologically feasible in these patients. On the other hand, when ARM nodes are SLN-ARM nodes (Concordance type), ARM lymphatics/nodes within the boundaries of a standard ALND should be resected in SLN-positive patients. Therefore, surgical treatment of the axilla can be individualized on the basis of the axillary nodal status.

2. Axillary reverse mapping procedure

During the ARM procedure, it is necessary to use an injection of a lymphatic tracer into the upper limb to visualize the lymphatic arm drainage. Thompson et al. [7] injected blue dye into the upper inner arm intra- or sub-dermally (Fig. 1). Then, they massaged the injection site and raised the arm until blue lymphatics were observed in the upper extremity, and eleven of 18 (61%) blue lymphatics and/or blue nodes were identified in the axilla proper. In a study of Nos et al. identification blue node rate was 71% (15 of 21) (Fig. 2) [8].

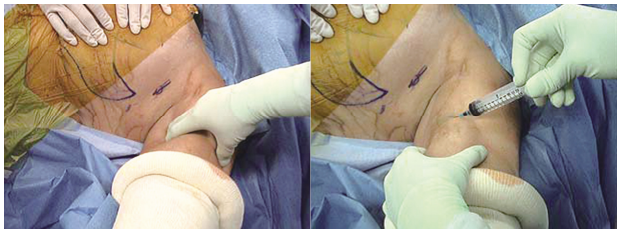


Fig. 1. Blue dye injection into the upper inner arm. Thompson et al. [7]

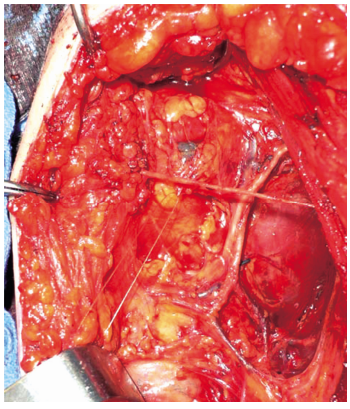


Fig. 2. Identification of a blue node in relation with the lymphatic arm drainage. Nos et al. [8]

Table 1. Methods and Results of ARM during ALND procedure. Noguchi et al. [11]

Methods	Authors	No. of ARM procedure	Identification rates by ARM	Rates of crossover (SLN=ARM node)	Metastatic involvement of resected ARM nodes
Dye	Thompson et al.[7]/2007	18	61% (11/18)	0.0%	0.0% (0/7)
	Nos et al. [8]/2007	21	71% (15/21)	Not reported	0.0% (0/10)
	Rubio et al. [21] /2012	36	83.3% (30/36)	13.3% (2/15)	13% (4/30)
	Connor et al. [22] /2013	57	72% (41/57)	7% (4/57)	15.7% (3/19)
Dye & Isotope	Nos et al. [12]/2008	23	91% (21/23)	Not reported	14% (3/21)
	Tausch et al./2013	143	78.3% (112/143)	Not reported	25% (14/55)
Isotope	Gennaro et al. [13]/2013	60	75% (45/60)	Not reported	No data

3. Oncological safety of Axillary reverse mapping

Nos et al. [12], tried to improve the identification rate of the lymphatic arm drainage (LAD), using a method of isotope and blue dye injection. The radioactive ARM node was detected by using the gamma probe. The ARM nodes were identified in 21 (91%) of 23 patients during ALND (Table 1). Gennaro et al. [13] used only radioisotope for identifying ARM nodes. It does not enable the lymphatic vessels to be visualized as well as blue dye.

When the clinical application of ARM for a patient, we have to concern the oncological safety of ARM is a priority. In case of SLNB, Boneti et al. [14] reported that crossover occurred in only 6 (2.8%) of 218 patients. Other investigators reported concordance rates of 7.2-28% between ARM nodes and SLN [15-18]. Deng et al. [15] revealed that ARM procedure during SLNB may be oncologically safe. In that study, all of possible metastatic ARM nodes were SLN-ARM nodes which certainly be removed as SLN during SLNB and were clear of tumor cells when they did not coincide with SLNs, even in patients with positive SLNs. They could distinguish ARM nodes which did not contain metastasis from that contain metastasis by mapping lymphatic drainage of breast and the ipsilateral arm in a patient at the same time. They observed that all possible metastastic ARM nodes were SLN-ARM nodes. In another opinion, Ponzone et al. [19] performed ARM procedures in 49 breast cancer patients undergoing ALND and they reported that 3 patients with extensive nodal metastatic involvement (i.e., pN2a and pN3a) showed breast cancer metastatic cells in the blue ARM nodes. So they suggested that ARM procedures were not safe in patients with extensive nodal metastatic involvement.

CONCLUSION

The ARM concept is derived from the sentinel lymph node biopsy. The goal of the ARM study was to develop a technique to identify and preserve arm lymphatic drainage, thus decreasing the occurrence of lymphedema associated with staging the axillary lymph nodes in patients with breast cancer. However, a number of problems remain to be resolved in the practical use of the ARM procedure.

Noguchi et al. [17] mentioned about the following issues. One issue is that identification rates of ARM nodes and/or lymphatics were insufficient using blue dye alone. So, several methods of increasing the identification rate have been studied with an isotope, or a blue dye, or fluorescence as tracers.

Another issue is whether the ARM nodes are not involved in patients with axillary lymph node metastases. Thompson et al. [7], as well as Boneti et al. [20], found no cancer cells in the ARM nodes even when the patients had many positive axillary lymph nodes. However, subsequent studies have shown that there is ARM node involvement [12,19].

The other issue is, as mentioned above, whether the SLN draining the breast is the same node as the ARM node draining the upper extremity.

Previously, it was considered that preservation of the ARM lymphatics or lymph nodes is not oncologically safe in patients with axillary lymph node metastases. However, recent studies have demonstrated that the ARM procedure is oncologically feasible in clinically node-negative, SLN-positive patients when ARM nodes do not coincide with SLNs. When ARM nodes do not coincide with SLNs, they are not involved even in SLN positive patients.

ARM is a feasible technique for identification and preservation of axillary arm lymphatics with an acceptable incidence of SLN crossover and that may prevent lymphedema in SLNB and/or ALND in patients with clinically determined low axillary nodal status breast cancer. A larger sample size is needed to determine if

ARM can reduce the incidence of lymphedema in patients undergoing SLNB alone and to confirm the absence of ARM metastases in clinically node negative patients undergoing ALND.

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