

Oncological Safety of Axillary Reverse Mapping in Patients With Clinically Node-Negative Breast Cancer

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Research Article

Keywords: Oncological safety, patients, ARM, SLN

Posted Date: May 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-501178/v1>

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Abstract

Background

Axillary reverse mapping (ARM) was developed to preserve the lymphatic drainage from the upper arm during sentinel lymph node (SLN) biopsy or axillary lymph node dissection (ALND). However, the oncological safety of ARM has been controversial.

Methods

Patients with clinically negative nodes (cN0) underwent SLN biopsy and ARM. SLNs were identified using blue dye and radioisotope, and ARM nodes were traced using the fluorescent method. Patients with positive SLN underwent the standard ALND. After surgery, they were followed up for more than three years.

Results

A total of 507 patients with cN0 breast cancer were enrolled between May 2009 and November 2017. SLNs were identified in 499 (98%) of 507 patients, and ARM nodes were identified in 159 (31%) patients in the SLN field. The crossover rate of SLN-ARM nodes was 28%. Among 95 patients with positive SLNs, 70 patients underwent conventional ALND. ARM nodes were identified in 65 (93%) of those patients in the ALND field. The mean number of removed ARM nodes was 7.2 (range 0–25) in patients who underwent the standard ALND. Although ARM nodes were involved in 18 of 65 patients, the involved ARM nodes were the same SLNs identified in 14 (78%) patients. Since SLN-ARM nodes should be removed, ARM nodes were involved only in 4 (5.7 %) patients after SLN biopsy.

Conclusions

ARM nodes were not infrequently involved in patients with positive SLNs, but they were most often SLNs. Therefore, conservative ALND with ARM is oncologically acceptable in patients with positive SLN.

Introduction

Axillary reverse mapping (ARM) was introduced to prevent arm lymphedema by preserving the lymphatic drainage from the upper arm during sentinel lymph node (SLN) biopsy or axillary lymph node dissection (ALND) [1, 2]. However, the ARM technique in ALND has not been widely accepted due to little evidence to support the hypothesis that the lymphatic drainage of the arm and the breast are separate [1, 2].

Anatomically, lymphatics are interconnected between the lymph nodes draining the breast and the nodes draining the upper extremity [7, 8]. Several clinical studies indicated that the ARM nodes are involved in a significant proportion of cases and coincide even with the SLNs [9]. Nevertheless, it has been suggested

that ARM node involvement occur only in patients whose ARM nodes are SLN-ARM nodes [11, 12]. Thus, the oncological safety of the ARM procedure has not been considered controversial [3, 4, 5, 6]. Even in the era of the Z0011, ALND is still required in patients who do not meet the Z0011 criteria for no further axillary treatment after SLN biopsy or when there is evidence of residual axillary disease after neoadjuvant chemotherapy (NAC) [10]. Therefore, it is necessary to confirm the oncological safety of the ARM procedure during ALND.

In general, ARM nodes have been identified by using blue dye [1, 2]. However, dual mapping using blue dye and radioisotope is accepted as a standard method for SLN identification. Therefore, a fluorescence method using an invisible near-infrared fluorescence imaging system has been introduced for the ARM node identification [9]. The fluorescent imaging technique is highly sensitive for identification of ARM nodes [3], and allows assessment of the correlation between the blue and hot SLN and fluorescent ARM nodes. In 2016, a recent ARM experience at our institute was reported, including 292 ARM procedures [3]. The purpose of this study was to evaluate whether it is oncologically safe to preserve ARM nodes in patients with positive SLN who underwent ALND.

Patients And Methods

(1) Patients

We retrieved data from our prospectively maintained database on patients with clinically node-negative (cN0) breast cancer who underwent an SLN biopsy and ARM procedure at our hospital between May 2009 and November 2017. Patients with clinically positive nodes (cN+) and those who received preoperative chemotherapy (NAC) were excluded. All patients signed written informed consent regarding SLN biopsy, ALND and ARM as approved by the Clinical Investigation and Ethics Committees of the Kanazawa Medical University Hospital prior to surgery and they were followed up for more than three years after surgery.

(2) Surgical procedures

Blue and hot SLNs were identified by dual mapping with subareolar injection of blue dye and peritumoral injection of the radioisotope. The SLN biopsy procedure has been described elsewhere [3]. All blue and hot nodes were categorized as SLNs and removed, and suspicious palpable nodes, which were neither blue nor hot, were considered palpable SLNs and removed. ARM nodes were identified using fluorescence method. The ARM procedure also has been described previously [3]. Just before surgery, briefly, 0.1 ml (0.25 mg) of indocyanine green (ICG) (Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan) was injected subcutaneously in the ipsilateral upper extremity, and the injection site was massaged until fluorescent lymphatics were observed near the axilla by using the Photo Dynamic Eye (PDE) of Hamamatsu Photonics Co., Ltd (Hamamatsu, Japan). During surgery, PDE was used to identify fluorescent nodes which were considered ARM nodes. Then, partial mastectomy or total mastectomy with or without immediate breast reconstruction was performed, according to the size or extent of breast cancer and the choice of the patient. Standard ALND was performed in patients with positive SLNs, except for patients

who were scheduled to receive NAC and those who met with the Z0011 criteria. ARM nodes and lymphatics were resected within the boundaries of conventional ALND in patients with positive SLN.

(3) Histopathological examination of SLNs and ALNs

Excised blue and hot SLNs and palpable SLNs were sent for intraoperative pathological examination. They were sectioned at 2-mm intervals unless the lymph node itself was < 5 mm, in which case they were bisected. Sections of SLNs obtained during surgery were frozen, followed by cutting of permanent sections and routine hematoxylin and eosin (H&E) staining. After surgery, dissected axillary lymph nodes (ALNs) including ARM nodes were bisected and histologically examined with H&E staining. When SLNs as well as ALNs contained macrometastases or micrometastases, they were considered positive. When containing no metastases or isolated tumor cells, they were considered negative [13].

(4) Follow-up and measurement of upper extremities

Postoperatively, adjuvant hormonal therapy or chemotherapy was performed, according to the subtype and axillary nodal status of breast cancer and the patient's choice. Patients undergoing partial mastectomy received whole-breast irradiation. A physical examination, mammography, echography and computed tomography were performed six months after surgery and then annually thereafter. All of the patients were followed up for more than three years. Both distant recurrences and loco-regional recurrences were recorded. Arm circumference measurement of both arms was performed for patients who complained of ipsilateral arm or had a sign of arm swelling at physical examination. Lymphedema was defined as a difference in arm circumference of more than 20 mm between the affected and contralateral arms.

Results

A total of 507 patients with cN0 breast cancer were enrolled between May 2009 and November 2017. The characteristics of patients and tumors are shown in **Table 1**. Surgical procedures and the results are summarized in **Table 2**. Two hundred forty-four patients underwent a partial mastectomy and another 244 patients underwent total mastectomy with or without breast reconstruction. The remaining 19 patients had no mastectomy because they were scheduled to receive NAC. All of the patients underwent SLN biopsy with the ARM procedure. The SLN identification rate was 98% and the mean number of identified SLNs was 2 (range 1–9). SLNs were histologically positive in 95 (19%) of 499 patients. On the other hand, the ARM node identification rate was 63% in the SLN field, suggesting that the ARM pathway was located on a deeper layer than the SLN field in the remaining patients. Subsequently, 70 (74%) of 95 patients with positive SLNs underwent ALND. The remaining 25 patients did not undergo ALND because they were scheduled to receive NAC or met with the Z-0011 criteria. The ARM node identification rate was 93% in ALND field, and the mean number of removed ARM nodes was 7.2 (range 0–25) in patients who underwent conventional ALND.

The relationship between the SLNs and ARM nodes was evaluated. The blue and hot SLNs were the same fluorescent ARM nodes identified in 140 patients (crossover type) (**Fig. 1a**). The blue and hot SLNs were close to the ARM nodes but not the same ARM nodes in 19 patients (close type) (**Fig. 1b**). In the remaining 340 patients, blue and hot SLN was not ARM node (separate type) (**Fig. 1c**). The crossover rate of SLN-ARM nodes was 28%. When the close type and the separate type were classified as non-crossover type, 140 (28%) patients were classified as crossover type and 359 patients (72%) as non-crossover type. Interestingly, the rate of positive SLN was 19% in both crossover and non-crossover types (**Table 3**). Although 70 of 95 patients with positive SLNs underwent ALND, SLNs alone were involved in 14 (58%) of 24 crossover type patients and 38 (83%) of 46 non-crossover type patients. In other words, additional nodal metastases at ALND were found in 10 (42%) crossover type patients and 8 (17%) non-crossover type patients. Although the crossover type had more additional nodal metastases than the non-crossover type, the difference did not reach statistical significance ($0.05 < p < 0.1$). On the other hand, ARM nodes were involved in 18 (16%) of 70 patients, but the involved ARM node was the same SLN identified in 14 (78%) of 18 patients. When excluding positive SLN-ALN nodes, the ARM node was involved only in 4 (5.7%) of 449 patients (**Table 3**).

After surgery, they were followed up for more than three years. Four patients died of breast cancer, 21 patients were alive with recurrence, and 3 patients died of other diseases. Ipsilateral axillary recurrence was found in 4 patients (0.9%) after SLN biopsy alone and 2 patients (2.9%) after ALND. While 15 (21.4%) of 70 patients who underwent conventional ALND developed lymphedema, only 3 (0.7%) of 429 patients who underwent SLN biopsy alone developed lymphedema. All of these patients were the crossover type. The incidence of lymphedema in the ALND group was significantly higher than that in the SLN biopsy group ($p < 0.01$). (**Table 4**).

Discussion

Axillary lymph node dissection (ALND) is associated with postoperative morbidities, including arm lymphedema, shoulder dysfunction, seroma, paresthesia and discomfort. Particularly, arm lymphedema is a serious complication and a high risk of lymphedema has been used as an argument against ALND. Currently, however, ALND can be avoided not only in patients with negative SLN but also in those with a few positive SLNs undergoing partial mastectomy with whole-breast irradiation [14] or total mastectomy with axillary irradiation [15]. Nevertheless, SLN biopsy does not completely eliminate the risk of lymphedema. Several studies have reported that the incidence of lymphedema is higher than anticipated, ranging from 2–7% [16, 17, 18]. Moreover, postoperative radiation would not be preferable in patients who underwent total mastectomy with breast reconstruction using implants because of the increased risk of capsular contraction and reconstruction failure [19]. Thus, ALND is still indicated in patients who do not meet Z0011 or AMAROS criteria for no further axillary surgery after SLN biopsy or when there is evidence of residual axillar disease after NAC [10].

The ARM procedure is introduced to map and preserve the lymphatic drainage from the upper arm and reduce the risk of lymphedema [1, 2]. Although ARM is generally performed using blue dye, fluorescent

dye can also be used as an alternative to blue dye for ARM procedure. Several centers have reported using fluorescent imaging technique for ARM [3, 20, 21, 22, 23]. The fluorescent imaging technique is highly sensitive for identifying ARM nodes [3]. The identification rates of ARM nodes are higher in the fluorescent method than in the dye method, and more ARM nodes are identified using the fluorescent method than using the dye method [20, 21, 22]. Nevertheless, the identification rates of ARM nodes are very different between the ALND field and the SLN field, suggesting that the majority of lymphatics draining the upper extremity may be located deeper than the SLNs [3, 9, 21].

A triple mapping technique using blue dye, radioisotope and fluorescent dye helps identify the SLN and ARM nodes simultaneously and assess their correlation and metastatic burden [9]. In the present study, the crossover rate between SLN and ARM nodes was 28%, whereas crossover was seen only in 3.8% of the SLN biopsy and 5.6% of ALND in a study by Tummel, et al. [4]. The crossover rates are much higher in several studies using fluorescence than in those using dye [3, 4, 20, 21, 23]. Although these studies did not agree with the hypothesis that the lymphatic drainage of the arm and the breast are separate [1, 2], crossover of SLN-ARM nodes is the main reason for ARM node involvement in patients with positive SLN [9, 11, 12, 24]. Since SLN-ARM nodes should be removed, the additional rate of involved ARM nodes after SLN biopsy was only 5.7%, which is consistent with the study by Tummel, et al. [4]. Thus, the rate of involved ARM nodes after SLN biopsy was acceptably low. It may be concluded that conservative ALND with ARM is oncologically acceptable in patients with positive SLNs.

In this study, approximately 20% of patients who underwent ALND developed lymphedema. In the ALND, we resected ARM lymphatics and nodes within the boundaries of a conventional ALND in patients with positive SLNs, while sparing fatty tissue and lymphatics over the axillary vein as possible. Although all ARM nodes in ALND were similarly taken to prove no involvement of ARM nodes early in a study of Tummel, et al. [4], however, later benign-appearing ARM nodes were otherwise preserved. Consequently, only 6.5% of patients developed lymphedema. When conservative ALND with ARM is indicated, therefore, the preservation of benign-appearing ARM nodes, except for SLN-ARM nodes, may be essential to minimize arm morbidity [10, 25].

Although patients with cN+ were excluded in this study, NAC is currently administered for them with the aim of achieving a nodal pathological complete response and de-escalating axillary surgery. Subsequently, patients who become cN0 after NAC are eligible for SLN biopsy and ALND can be avoided in patients with negative SLN after NAC. However, ALND is the current standard management for patients with any viable tumor cells in the SLN after NAC [26]. Therefore, a conservative ALND with ARM may be potentially indicated in those patients after NAC. Further studies are needed.

Conclusions

A triple mapping technique using blue dye, radioisotope and fluorescent dye is useful to identify the SLNs and ARM nodes simultaneously and assess their correlation and metastatic burden. In this study, ARM nodes were involved in 26% of patients with positive SLNs, but they were most often SLNs. The crossover

rate between SLNs and ARM nodes was 28%, higher than in those using dye. Since SLN-ARM nodes should be removed, however, the rate of additionally involved ARM nodes was only 5.7% after SLN biopsy. Therefore, conservative ALND preserving ARM nodes is oncologically acceptable in patients with positive SLNs.

Declarations

CRedit authorship contribution statement

Masakuni Noguchi: Conceptualization, Writing - review & editing. Masafumi Inokuchi: Investigation. Miki Noguchi: Investigation. Emi Morioka: Investigation.

Conflicts of interest

None of the authors have any financial or personal relationships with other people or organization that could inappropriately influence (bias) this work.

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Tables

Due to technical limitations, table 1,2,3,4 is only available as a download in the Supplemental Files section.

Figures

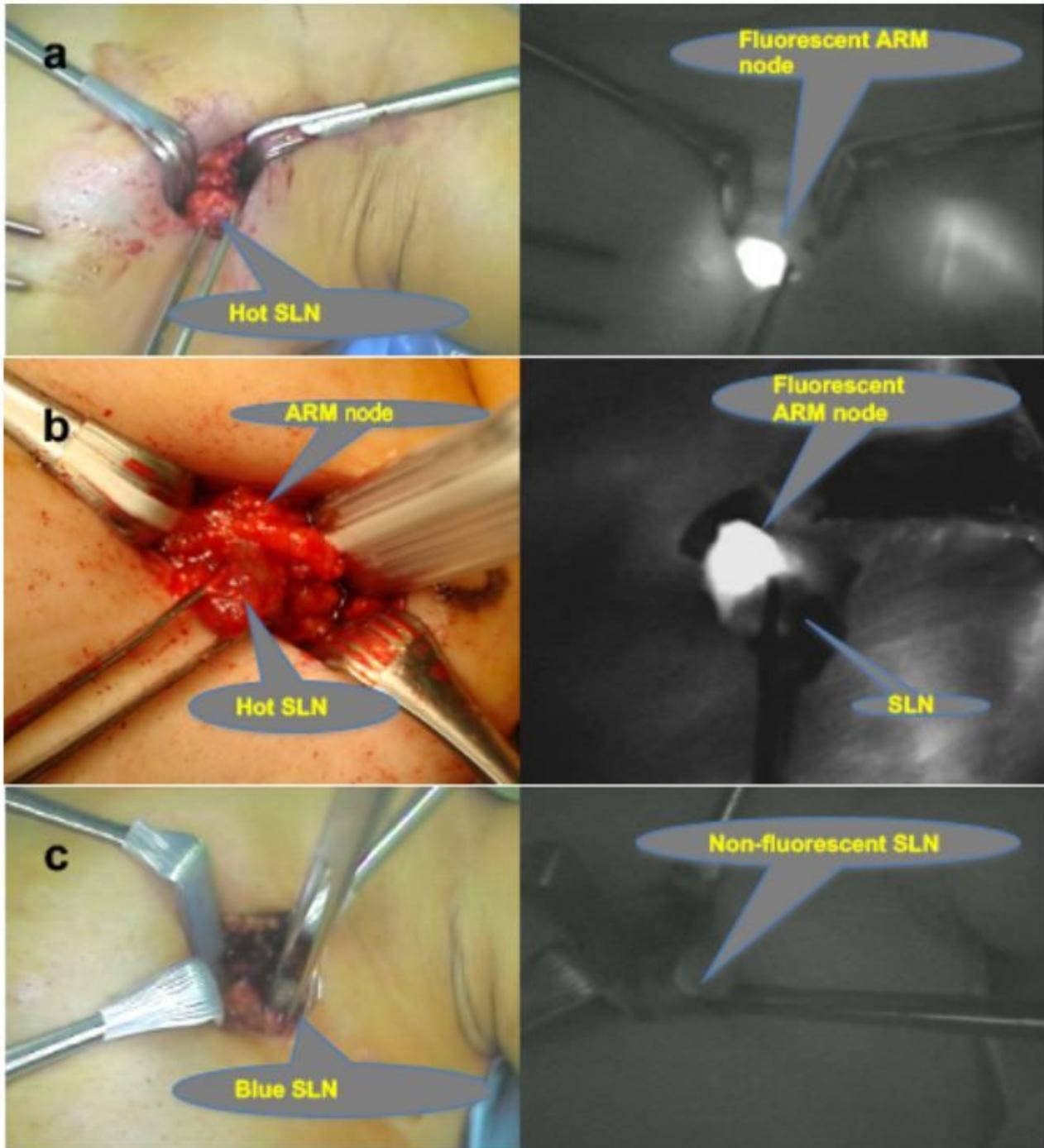


Figure 1

(a) Crossover type: A hot SLN is the same as fluorescent ARM node (Left: operative view; Right: fluorescence image) (b) Close type: Hot SLN is close to ARM node but not the same as ARM node (Left: operative view; Right: fluorescence image) (c) Separate type: A blue and hot SLN is not a fluorescent ARM node. No fluorescent node is observed in the SLN field (Left: operative view; Right: fluorescence image)

Supplementary Files

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