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ORIGINAL ARTICLE – BREAST ONCOLOGY

# Identification and Preservation of Arm Lymphatic System in Axillary Dissection for Breast Cancer to Reduce Arm Lymphedema Events: A Randomized Clinical Trial

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## ABSTRACT

**Background.** Controversy in axillary reverse mapping in axillary lymph node dissection (ALND) possibly results from incomplete recognition of the arm lymphatic system (ALS) and its compromise to oncological safety. The iDEntification and Preservation of ARm lymphaTic system (DEPART) technique facilitates complete identification of ALS; therefore, its use may decrease the occurrence of arm lymphedema. This study aimed to examine the arm lymphedema rate, locoregional recurrence, and feasibility to perform DEPART in ALND.

**Methods.** Patients from February 2013 to October 2017 from two tertiary referral centers were randomly assigned to two groups. In the study group, indocyanine green and methylene blue (MB) were utilized to identify arm sentinel nodes, and 0.1 ml MB was injected into the arm sentinel nodes to reveal the subsequent-echelon nodes and lymphatics. Gross arm lymph nodes were examined by intraoperative partial frozen section and were removed if positive. Arm lymphedema, local recurrence, regional recurrence, and distant metastasis were recorded at different follow-up examinations.

**Results.** Arm sentinel nodes were identified in 573 (83.2%) patients. Subsequent-echelon nodes and lymphatics were visualized in 558 (97.4%) patients. Metastatic arm nodes were identified in 38 (6.8%) patients. The arm lymphedema rate was 3.3% (18/543) in the study group versus 15.3% (99/648) in the control group ($p < 0.001$) after 37-month median follow-up. Regional recurrence showed no difference between the two groups (1.4% and 1.2%, respectively) ($p = 0.392$).

**Conclusions.** DEPART can benefit breast cancer patients who undergo ALND, reducing the arm lymphedema rate without adversely affecting the morbidity of regional recurrence.

The advent of sentinel lymph node biopsy (SLNB) has revolutionized surgical management of axilla in breast cancer patients, avoiding complete axillary lymph node dissection (ALND) in selected patients. However, for breast cancer patients with clinically node-positive axilla (CN+), ALND is still the standard of care but is associated with substantial morbidity, including debilitating arm lymphedema, shoulder dysfunction, paresthesia, and discomfort.[1] It has been hypothesized that damaged arm lymphatic drainage in the axilla is responsible for the increased arm lymphedema rate.[2,3] According to the assumption that the upper extremity and the breast each has its own discrete pathways of lymphatic drainage in the axilla,[4] Thompson developed a new technique, namely

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axillary reverse mapping (ARM), to identify and preserve the lymphatic drainage of the upper extremity.[2,3] Compared with standard ALND, ARM plus ALND can reduce the rate of arm lymphedema to some degree.[5,6]

However, arm lymphedema is not completely eliminated with the application of the ARM technique in ALND. This shortcoming may be partially due to insufficient recognition of arm lymph nodes.[7] The number of ARM nodes identified was 1–1.7 using blue dye, 1.6–7.2 using fluorescence, and 1.3–4.8 using isotope in previous studies that employed the ARM technique in ALND.[8] A ten-human-cadaver study of arm lymphatic drainage mapping by Suami et al.[9] concluded that most lymph vessels flow into 1–3 main lymph nodes. Pavlista et al.[10] injected lipiodol into the dorsal side of the hand of nine healthy people to visualize the arm lymphatic drainage, revealing a similar phenomenon with lymph from the arm being drained by 2–4 main afferents and then entering 1–2 nodes. Usually, the recognized dominant nodes are the first draining nodes, that is, arm sentinel nodes. Presumably, the ARM nodes identified employing the ARM technique in previous studies are the arm sentinel nodes, which is part of the complete arm lymphatic system (ALS). This finding may explain the 5.9–24% morbidity of arm lymphedema after ARM plus ALND.[11,12]

ARM has not been adapted worldwide or placed into routine clinical use because of its uncertain oncological effect in long-term follow-up. In addition, ARM's positive impact on quality of life has not been established in large series. As interconnections between arm and breast lymphatic drainage have been confirmed in previous studies,[13–15] whether to spare ARM nodes has been a moot point. The number of arm lymph nodes recognized using the ARM technique is considered inadequate. Our institution refined the ARM procedure and developed a new definition, iDEntification and Preservation of ARm lymphaTic system (DEPART), attempting to preserve the complete ALS in the axilla basin. A randomized clinical trial was launched to compare ALND plus DEPART versus ALND alone, aiming to examine the rates of arm lymphedema and locoregional recurrence (LRR) and the feasibility of sparing ALS in ALND.

## PATIENTS AND METHODS

### *Patients*

This study was a prospective randomized trial at two tertiary referral academic medical centers, viz. Tongji Hospital of Huazhong University of Science and Technology and Zhongnan Hospital of Wuhan University, from February 2013 to October 2017. The inclusion criteria were the following: (1) patients aged 18 years or older with $T_{1–3}$ invasive breast cancer; (2) clinically node-positive breast cancer, defined as positive on preoperative axillary palpation, ultrasound examination, and computed tomography (CT) scan with contrast; (3) patients who underwent mastectomy with a positive sentinel lymph node (SLN); (4) patients who underwent breast-conserving surgery (BCS) containing more than two positive SLNs; (5) no neoadjuvant chemotherapy (NAC); (6) no previous history of breast cancer. The medical ethics committees of the two institutions approved routine use of the DEPART procedure for this study, which was registered at the Chinese Clinical Trial Registry (ChiCTR1800014247). All patients signed written informed consent regarding ALND and DEPART. After verifying eligibility, the data manager randomly assigned patients to ALND plus DEPART (study group, or group 1) or ALND alone (control group, or group 2) by random number generation using SPSS software before surgery. The probability of committing a type I error was bilaterally set at an $\alpha$ value of 0.05 and committing a type II error at a $\beta$ value of 0.20. The estimated value of the study group lymphedema proportion was 6.0%,[16] and that of the control group was 16% (1-year arm lymphedema rate after ALND by the surgeon prior to the trial). Based on these criteria, including a 10% loss to follow-up and 90% detection rate of ALS in the study group, 600 patients needed to be enrolled in each group. The primary outcome was occurrence of arm lymphedema. The secondary outcome was locoregional recurrence or distant metastasis.

### *SLNB*

For 719 patients with clinically node-negative axilla (CN–), 0.5 ml (5 mg) methylene blue (MB) (H32024827, Jichuan Pharmaceutical Corporation, Taixin, China) was intradermally injected into the areolar region with a 32-gauge needle after induction of general anesthesia to identify sentinel lymph nodes (SLNs).

### *Surgical Techniques of DEPART*

In the study group, 1 ml (2.5 mg) indocyanine green (ICG) (H20045514, Weicai Pharmaceutical Corporation, Liaoning, China) was intradermally injected into the internal bicipital sulcus of ipsilateral arm. The presence of ICG in the body was detected using the Photodynamic Eye (PDE) of Hamamatsu Photonics Co., Ltd. (China) and visualized on a monitor. Withdrawing the lamp, the course of subcutaneous lymphatic vessels was visualized on the monitor by firmly pressing the injection site. Navigated by ICG fluorescence, the course of intradermal lymphatic channels could be delineated on the skin (Fig. 1a). Then,

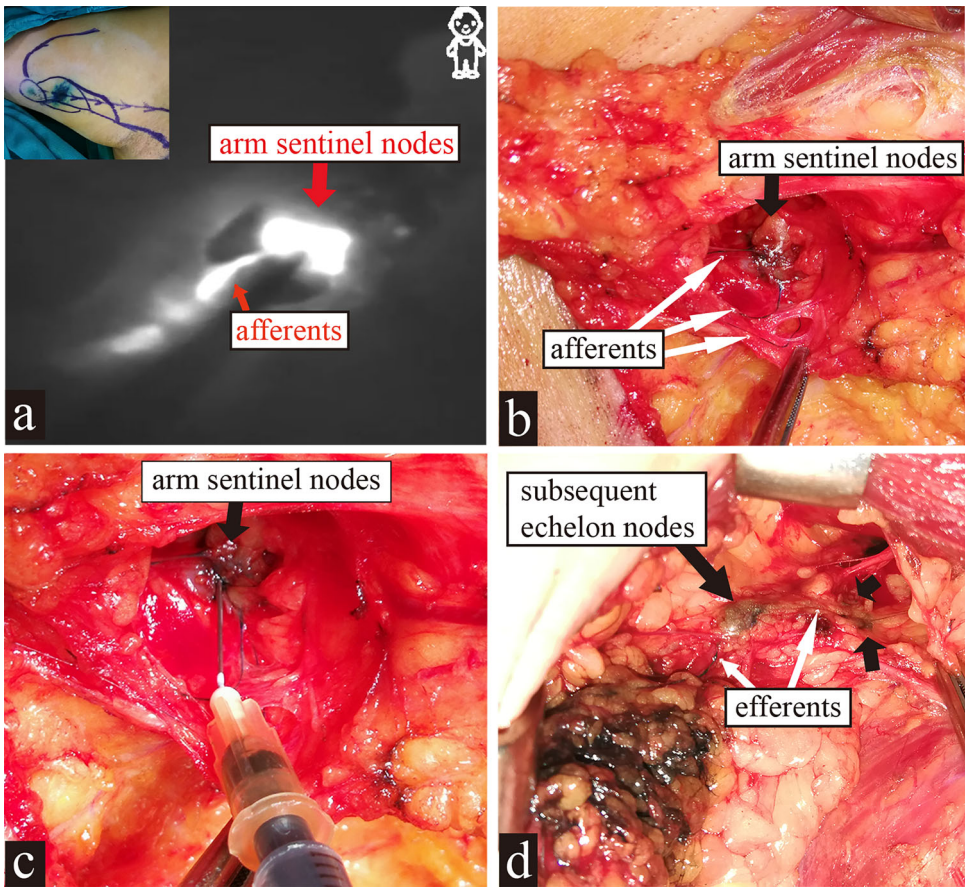


**FIG. 1** Procedure for identification and preservation of arm lymphatic system in vivo (right axilla). **a** Intradermally injecting indocyanine green and methylene blue in the internal bicipital sulcus of ipsilateral arm to identify arm sentinel nodes, corresponding fluorescent image on infrared camera imaging (red arrow). **b** In vivo photograph of arm sentinel nodes and afferent lymphatics. **c** Carefully injecting 0.1 ml methylene blue into the arm sentinel nodes. **d** Subsequent-echelon nodes (black arrow) and efferent lymphatics (white arrow) were revealed in Berg's level II or III

1 ml MB was intradermally injected into the site near the previous injection.

During axillary dissection, blue-stained arm sentinel nodes could be recognized by navigation of the fluorescent channels (see Supplementary Video 1, which shows navigation of the ICG fluorescence image) and were carefully dissected between the structures of the axillary vein and the second intercostal brachial nerve. The identified arm sentinel nodes were carefully injected with 0.1 ml MB using a 1-cc syringe with a 32-gauge needle (Fig. 1c). MB could then flow from the nodes along several lymphatic channels toward the infraclavicular nodes. Subsequent-echelon nodes and lymphatics were identified (Fig. 1d). SLNs were removed after the identification of the arm sentinel nodes and the procedure of MB injection. When patients who underwent mastectomy harbored positive SLNs or patients who underwent BCS had more than two positive SLNs, ALND was performed subsequently. All discernible arm lymphatics and lymph nodes were preserved, except that gross arm lymph nodes (major axis larger than 10 mm or node firm on palpation) were sent for immediate partial frozen section (pFS) to determine their resection during ALND. The operating surgeon (G.W.) had been trained in advance on using the PDE and had operated on more than 20 patients according to the DEPART protocol before participating in the trial.

*ALND*

In total, 874 patients with CN+ axilla and 480 patients with positive SLNs were randomly assigned to two groups. In the control group, ALND was performed with complete resection of at least Berg's levels I and II. Resection of level III was performed only in cases with gross disease in level II and/or III.

*Pathology*

We retrospectively evaluated the status of arm lymph nodes in 29 patients with CN+ axilla using DEPART technique before the trial. The positive predictive value (PPV) among intraoperative fine-needle aspiration cytology (FNAC), touch imprint cytology (TIC), and pFS were compared in the removed arm lymph nodes, as well. pFS was done by taking a quarter of the node and sending it for frozen section.[17] The metastatic status of arm lymph nodes was defined as macrometastasis (> 2 mm). A total of 132 arm lymph nodes were removed in 29 patients, among

which 28 gross nodes were separately sent for pathological examination. The PPV of FNAC, TIC, and pFS was 100%, 87.5%, and 100%, respectively. None of the 104 arm lymph nodes without gross disease harbored metastasis. Considering the satisfactory PPV and the function integrity of the node, pFS was administered to assess metastasis of gross arm lymph nodes in this trial.

Removed SLNs were sent for immediate FS analysis by two pathologists. All retrieved axillary lymph nodes were processed for routine hematoxylin and eosin (H&E)-stained sections. Diameter of the primary tumor, estrogen receptor (ER) and progesterone receptor (PR) status, and human epidermal growth factor receptor-2 (HER-2) status were also assessed immunohistochemically as part of routine pathology examination.

### *Assessment of Lymphedema*

Volumetric measurements of both arms were performed in two groups to evaluate occurrence of lymphedema. A clear glass cylinder filled with tepid water was employed to measure differences in volume of the affected and control upper extremities. The upper extremity was marked at 12 cm proximal to the medial epicondyle. Meanwhile, patients were asked a standard questionnaire (Supplement 2, *Quick*DASH questionnaire) consisting of 11 questions to reliably evaluate the physical function and symptoms of the arm.[18] A difference in volume between the arms $> 10\%$ was defined as lymphedema. Additionally, any physical therapy for arm swelling was recorded.

### *Follow-Up*

All of the patients were measured by the volumetric method at baseline before surgery and at follow-up every 3 months after surgery in the first year, every 6 months in the second and third year, and annually thereafter at reexaminations. Distant metastasis, locoregional recurrence, disease status, or cause of death were recorded by regular follow-up. Time from the first participant enrolled to last participant registered was included in the follow-up time.

### *Data Collection and Statistical Analysis*

Demographic characteristics, tumor–node–metastasis (TNM) stage, and number of axillary lymph nodes in the two groups were collected. TNM staging was performed using the American Joint Committee on Cancer (AJCC) staging manual, 7th edition. Systemic therapy was recommended according to clinical guidelines. Continuous variables were compared between the groups using non-parametric tests. The positive rates of the two groups were compared by the Chi square or Fisher's exact test, if appropriate. Two-sided $p$ values $< 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS statistical software, version 20.0 for Windows.

## RESULTS

### *Patients*

A total of 1656 patients eligible for the study were accrued from February 2013 to October 2017. Sixty-three patients terminated their participation before surgery; 40 of them withdrew consent, 13 canceled surgery and transferred to another hospital, and 10 changed treatment plans. ALND was not performed on 239 patients who underwent mastectomy with negative SLNs. The remaining 1354 patients were randomized into the study group ($N = 689$) or control group ($N = 665$). The CONSORT diagram for the trial is shown in Fig. 2, and baseline characteristics of participants are presented in Table 1. Arm sentinel nodes could not be identified during ALND surgery in 116 (16.8%) patients of the study group, and these 116 patients were thus excluded. Arm lymphatic channels and subsequent-echelon nodes were visualized with injection of MB in 558 (97.4%) cases in the study group. Hence, the total identification rate of complete ALS was 81.0% (558/689). The mean number of arm sentinel nodes, subsequent-echelon arm lymph nodes, and total arm lymph nodes was 2.0 (1, 3), 5.8 (3, 8), and 7.6 (5, 11), respectively (Table 2).

Age ($p = 0.993$), histological type ($p = 0.237$), TNM stage ($p = 0.131$), body mass index (BMI) ($p = 0.214$), and type of breast surgery ($p = 0.262$) were similar between the two groups (Table 1). The most common chemotherapeutic agents used in both groups were anthracycline- and taxane-based combination chemotherapy regimens. According to the National Comprehensive Cancer Network (NCCN) guideline, regional nodal radiation was conducted in patients with one or more positive axillary nodes in 2017. In 2013–2016, axillary radiation was conducted in patients with four or more positive axillary nodes and patients containing one positive axillary node with high risk factors ($p = 0.151$). Resection of level III was performed in 15 (2.8%) patients in the study group and 21 (3.2%, $p = 0.631$) patients in the controlled group owing to gross disease in level I/II.

### *Pathology*

pFS was done in 59 patients with palpable arm lymph nodes, 38 (38/558, 6.8%) of whom were confirmed to have macrometastasis. Thus, the abnormal arm lymph nodes

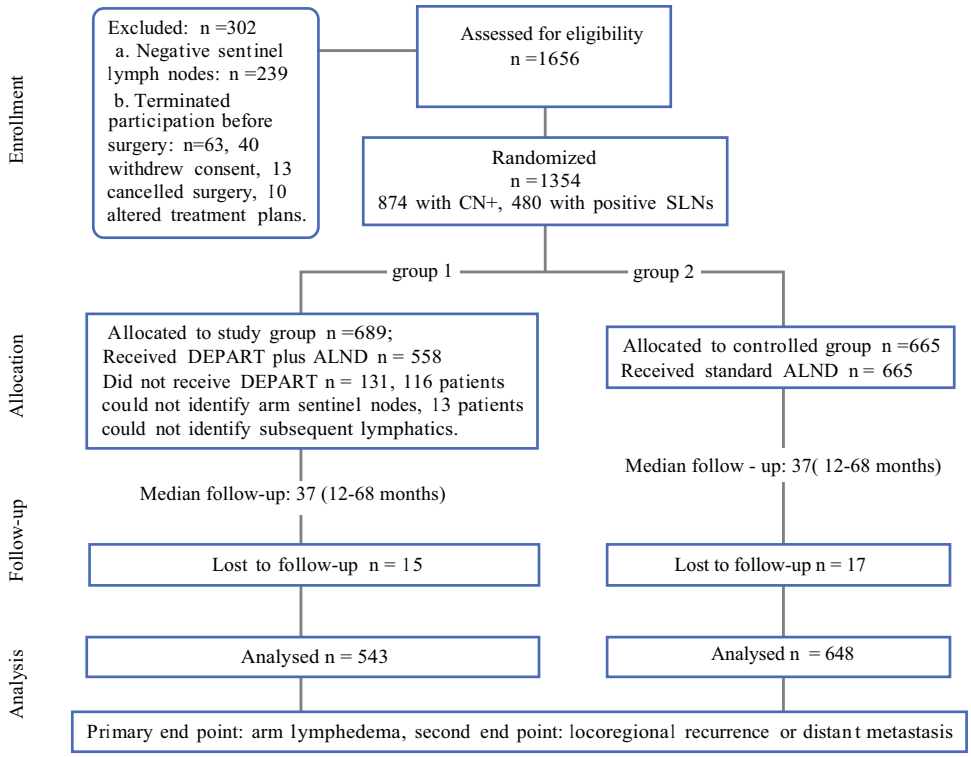


**FIG. 2** CONSORT diagram for the trial. *CN+* clinically node-positive axilla, *SLN* sentinel lymph node biopsy, *DEPART* iDEntification and Preservation of ARm lymphaTic system, *ALND* axillary lymph node dissection

were removed, while the remaining normal nodes were spared during the surgery. After surgery, 11 (28.9%) of the 38 patients with positive arm nodes were confirmed to be $pN_3$ stage, while 13 (34.2%) patients were in $pN_2$ stage and 14 (36.8%) patients were in $pN_1$ stage.

### *Arm Lymphedema*

Thirty-two patients were lost to follow-up, 15 in the study group and 17 in the controlled group. Median 37-month follow-up for lymphedema was available in the remaining patients. Of the available lymphedema data, 3.3% (18/543) of patients undergoing ALND plus DEPART and 15.3% (99/648) undergoing ALND had objective lymphedema measured by the volumetric method. Subjective arm lymphedema was reported in 6.1% (33/543) of patients in the ALND plus DEPART group and 16.0% (104/648) of patients in the ALND group. Objective and subjective arm lymphedema rates at different follow-ups are presented in Supplementary Fig. 3.

### *Recurrence*

There was no significant difference in the median 37-month regional recurrence rate between the two groups, while the arm lymphedema rate was significantly different ($p < 0.001$). In the study group, 5.0% (27/543) developed distant recurrence, and 2.9% (18/543) only developed LRR. Of them, 8 (1.5%) involved an axillary recurrence. Of the 648 patients on whom the DEPART procedure was not performed, 30 (4.6%) developed distant metastasis and 17 (2.6%) had locoregional recurrence only; 9 (1.4%) of them had axillary recurrence. The first reported site of treatment failure for patients is presented in Table 3.

## DISCUSSION

The objective of this study is to examine the effect of DEPART, a surgical approach that attempts to preserve the ALS when performing ALND in patients with breast cancer. This technique is based on but differs from the ARM technique, which has been described in several other studies, as it attempts to visualize the second- and third-echelon arm lymph nodes and not only the first one or two lymph nodes to which the lymph of the arm drains. To reveal arm lymphatic drainage, ICG and MB were utilized to identify arm sentinel nodes, and 0.1–0.2 ml MB was injected to the nodes subsequently. The mean number of total arm lymph nodes was 7.8, ranging from 5 to 11. During the surgery, the gross arm nodes were examined by intraoperative pFS and removed when positive for metastasis. The metastasis rate of arm lymph nodes was 6.8% (38/558). Patients with higher BMI, increased axillary disease burden, and axillary radiation had higher risks of developing arm lymphedema. The results of this study indicate that the procedure reduced the arm lymphedema

**TABLE 1** Baseline characteristics of participants

| | ALND + DEPART $N = 543$ | ALND $N = 648$ | $p$ value |
|---|---|---|---|
| Patients, no. (%) | | | 0.088[a] |
| SLNB+ | 224 (41.3) | 236 (36.4) | |
| CN+ | 319 (58.7) | 412 (63.6) | |
| Age, mean (min, max), years | 51.3 (29, 79) | 52.6 (31, 76) | 0.993[b] |
| BMI, mean (min, max), kg/m$^2$ | 23.4 (18.4, 29.8) | 23.6 (18.4, 29.7) | 0.214[a] |
| Histology, no. (%) | | | 0.237[a] |
| Ductal | 337 (62.1) | 429 (66.2) | |
| Lobular | 39 (7.2) | 52 (8.0) | |
| Mixed | 41 (7.5) | 47 (7.3) | |
| Other | 126 (23.2) | 120 (18.5) | |
| No. of nodes removed, mean (min, max) | 14.3 (9, 25) | 18.9 (10, 33) | $< 0.001$[b] |
| Pathological nodal status, no. (%) | | | 0.131[a] |
| $N_0$ | 184 (33.9) | 225 (34.7) | |
| $N_1$ | 203 (37.4) | 204 (31.5) | |
| $N_2$ | 114 (21.0) | 164 (25.3) | |
| $N_3$ | 42 (7.7) | 55 (8.5) | |
| Pathological stage, no. (%) | | | 0.183[a] |
| I | 133 (24.5) | 152 (23.5) | |
| II a | 182 (33.5) | 185 (28.5) | |
| II b | 65 (12.0) | 88 (13.6) | |
| III | 163 (30.0) | 223 (34.4) | |
| Tumor subtype, no. (%) | | | 0.189[a] |
| ER/PR+, HER2– | 348 (64.1) | 392 (60.5) | |
| ER/PR+, HER2+ | 24 (4.4) | 27 (4.2) | |
| ER–, PR–, HER2+ | 78 (14.4) | 124 (19.1) | |
| ER–, PR–, HER2– | 93 (17.1) | 105 (16.2) | |
| Regional nodal radiation, no. (%) | 307 (56.5) | 393 (60.6) | 0.151[a] |
| Breast surgery, no. (%) | | | 0.262[a] |
| Mastectomy | 396 (73.0) | 491 (75.7) | |
| Breast-conserving surgery | 147 (27.0) | 157 (24.2) | |
| Resection of level III, mo. (%) | 15 (2.8) | 21 (3.2) | 0.631[a] |

*ALND* axillary lymph node dissection, *DEPART* iDEntification and Preservation of ARm lymphaTic system, *BMI* body mass index, *HER2* human epidermal growth factor receptor 2

[a]Chi square test

[b]Nonparametric test

**TABLE 2** Characteristics of the DEPART + ALND surgery

| | |
|---|---|
| Identification rate of arm sentinel nodes | 83.2% (573/689) |
| No. of arm sentinel nodes[1] | 2.0 (1–3) |
| Identification rate of subsequent-echelon arm lymph nodes | 97.4% (558/573) |
| No. of subsequent-echelon arm lymph nodes[a] | 5.8 (3–8) |
| Identification rate of complete ALS | 81.0% (558/689) |
| No. of total arm lymph nodes[1] | 7.6 (5–11) |
| Metastasis rate of arm lymph nodes | 6.8% (38/558) |

*ALND* axillary lymph node dissection, *DEPART* iDEntification and Preservation of ARm lymphaTic system, *ALS* arm lymphatic system

[a]Mean (min–max)

**TABLE 3** First reported site of treatment failure for patients

| | ALND + DEPART $N = 543$ | ALND $N = 648$ | $p$ Value[a] |
|---|---|---|---|
| Arm lymphedema (by volumetric method) | 18 (3.3%) | 99 (15.3%) | < 0.001 |
| Arm lymphedema (reported subjectively) | 33 (6.1%) | 104 (16.0%) | < 0.001 |
| Local recurrence | 8 (1.5%) | 9 (1.4%) | 0.903 |
| Regional recurrence | 10 (1.4%) | 8 (1.2%) | 0.392 |
| Distant metastasis | 27 (5.0%) | 30 (4.6%) | 0.783 |

*ALND* axillary lymph node dissection, *DEPART* iDEntification and Preservation of ARm lymphaTic system

[a]Chi square test

rate from 15.3 to 3.3% after 37-month median follow-up, while the regional recurrence rate showed no difference between the two groups (1.4% and 1.2%, respectively).

ARM has been studied for a decade with the aim of reducing the lymphedema rate since its introduction by Thompson from the USA and Nos from France.[2,3] Several issues remain to be solved, including the unsatisfactory identification rate, oncological safety, and the effectiveness of reducing arm lymphedema. Three mapping materials have been employed in the ARM technique, viz. blue dye, ICG, and isotype. The identification rates using these tracers have been reported to be 46.6–90.3%, 66.7–88%, and 75–100%, respectively.[13,19–21] In the present study, we employed ICG and MB to identify the arm sentinel nodes in the axilla basin. Subsequently, 0.1–0.2 ml MB was injected into the arm sentinel nodes to visualize the subsequent-echelon nodes and efferent lymphatics (Fig. 1c). The detection rate for ALS obtained in the present study (81.0%) indicates that the DEPART technique was effective in the majority of patients. The unsatisfactory identification rate [83.2% (573/689)] of arm sentinel nodes in the present study might have resulted from the absence of arm sentinel nodes in the axilla basin or our imperfect dissection. The anatomic variations of arm lymphatic drainage in terms of to its location in the axilla in relation to the subclavian vein include medial or lateral apron, above or just below and juxtaposed to the vein, and a sling well below the vein in the axilla,[22,23] which could provide guidance for detecting the arm sentinel nodes and improve the identification rate.

Another question that needs to be answered is how many arm lymph nodes and lymphatics can be identified. In the observational study of Tausch et al., saving at least one (ranging from one to four) ARM node in 71 patients failed to decrease the occurrence of lymphedema with 19-month median follow-up.[24] This finding may be partly explained by the nonrandomized design or the insufficient number of preserved arm lymph nodes. Injecting tracing material into the internal bicipital sulcus of the ipsilateral arm usually only reveals the arm sentinel nodes. However, the preservation of arm sentinel nodes was insufficient for patients who underwent the ARM technique in previous studies. ARM nodes were indeed the arm sentinel nodes, and the second- or third-echelon arm lymph nodes were not identified using the ARM technique. Preserving limited arm lymph nodes and lymphatics might contribute to the lack of significant difference between the ALND alone and ALND plus ARM techniques in terms of lymphedema.[7] Undeniably, the advent of the ARM technique has scientific impact on obviating postoperative arm lymphedema. Based on ARM, the DEPART technique is not a novel technique. This technique emphasizes the key procedure of "staged tracing" (Supplementary Fig. 4), which allows identification of both efferent lymphatics and subsequent-echelon blue nodes located deeper in the axillary basin at Berg's levels II and III. This key procedure of "staged tracing" is replicable, and has been previously applied in some cases by Nos et al.[25] and Ponzone et al.[26] Nos et al.[25] identified the ARM nodes using isotope in 15 patients, in whom 0.1–0.2 cc blue dye was injected into the ARM nodes to help visualize the efferent lymphatics. Similarly, Ponzone et al.[26] reinjected the first blue node before its excision with 0.1 ml patent blue dye to identify the efferent lymphatics in five patients. In the present study, the second efferent channels were visualized by injecting 0.1 ml MB to the arm sentinel nodes (Fig. 1d). Meticulously dissecting the lymphatics, more arm lymph nodes could be revealed. Consequently, "staged tracing" is a beneficial method for recognizing the arm lymphatic system in the axilla to perform DEPART.

The controversy regarding the oncologic safety of arm lymph node preservation has not been settled. There are two possible reasons for metastasis involving the arm lymph nodes. Breast and arm lymph nodes typically converge to infraclavicular nodes in Berg's level III. In addition, anatomical variations of crossover between breast and arm lymph nodes may exist in Berg's level I or II.[4] Few studies have detailed the methods of pathological examination for ARM nodes that were performed during surgery. Ikeda et al.[27] retrospectively evaluated the

accuracy of FNAC in removed arm nodes, in which 35 of 45 (77.8%) arm nodes were able to achieve a definite outcome. And evaluation of the status of arm nodes by TIC is simpler and faster than FNA in the assessment of intraoperative metastasis in Thompson and Ochoa's previous cumulative experience.[2,12] Prior to the trial, we analyzed the accuracy of FNAC, TIC, and pFS, and the outcomes confirmed that pFS could accurately evaluate the status of nodes without compromising their function. In the present study, the gross arm nodes were examined with intraoperative pFS and removed if positive. The metastasis rate of arm lymph nodes was 6.8% (38/558), suggesting direct invasion or lymphatic interconnections from metastatic breast nodes.

Findings from this randomized trial confirm the hypothesis that using ALND plus DEPART results in fewer arm lymphedema events overall compared with ALND alone. Approximately 3.3% of the patients in the study group had an arm lymphedema complication compared with 15.3% in the control group. The only randomized study comparing ALND + ARM versus ALND was reported by Yue et al., which showed the effectiveness and oncological safety of ARM. The study had median follow-up of 20 months, and at the last evaluation, there were 42 patients who developed arm lymphedema, measured by circumferential differences, in the control group (33.07%) and 7 (5.93%) in the experimental group ($p < 0.001$).[16] Tummel et al.[5] prospectively studied 654 patients who underwent 685 ARM procedures with SLNB and/or ALND, revealing a 0.8% objective lymphedema rate for SLNB and 6.5% for ALND with 26-month median follow-up. That study confirmed the efficacy of ARM in reducing postoperative lymphedema compared with historical controls. In addition, a total of 81 blue ARM lymphatic transections occurred in their study, and 33 of those patients had an ARM lymphatic reanastomosis. Notably, there was no arm lymphedema (0/33) when reanastomosed with median follow-up of 14 months. Compared with the large cohort study by Tummel et al., our prospective randomized study developed a modified ARM technique (DEPART technique) to increase the recognition of arm lymph nodes and evaluate the effect of intraoperative pFS. However, we have no experience performing lymphatic reanastomosis, which is an effective method to remedy arm lymphatics that have been carelessly transected.

There are several limitations to this study. The study was a single-surgeon design and was performed in two institutions, which is a major limitation. Second, to ensure accurate evaluation of the surgical procedure, patients who underwent NAC were excluded from this study; they will be analyzed in a future study. Third, there are logistical problems with the use of radioisotopes in China, thus MB was used both in SLNB and in "staged tracing," and SLNs were removed after the identification of the arm sentinel nodes and the "staged tracing" procedure. Lymph from breasts and arms is drained by different afferents, which enter breast and arm sentinel nodes, respectively. The source of the afferents, derived from the breast or arm, could help to distinguish SLNs from arm sentinel nodes.[9,28] Notably, the proportion of BCS (25.5%) in this study was unsatisfactory, mainly resulting from its low prevalence and acceptance to patients in China. Usually, the proportion of BCS is 20–30% in the majority of tertiary referral institutions in China.[29] Subjective discrepant judgment of sonologists in our institutions and surgical statistical bias from the same surgeon might have led to the high rate of metastasis for SLNs. Data from a single center in China described a false-negative ultrasound rate of 52.2% (47/90) in patients with stage T1 disease and one or two metastatic lymph nodes.[30]

## CONCLUSIONS

Application of DEPART in ALND led to a lower frequency of arm lymphedema than ALND alone during median 37-month follow-up. Locoregional recurrence showed no significant difference between the two groups. The DEPART technique is of great significance in reducing arm lymphedema in breast cancer patients who undergo ALND.

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## REFERENCES

1. Togawa K, Ma H, Sullivan-Halley J, et al. Risk factors for self-reported arm lymphedema among female breast cancer survivors: a prospective cohort study. *Breast Cancer Res*. 2014;4:414.
2. Thompson M, Korourian S, Henry-Tillman R, et al. Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. *Ann Surg Oncol*. 2007;6:1890–95.
3. Nos C, Lesieur B, Clough KB, Lecuru F. Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection. *Ann Surg Oncol*. 2007;9:2490–96.
4. Hama Y, Koyama Y, Urano Y, Choyke PL, Kobayashi H. Simultaneous two-color spectral fluorescence lymphangiography with near infrared quantum dots to map two lymphatic flows from the breast and the upper extremity. *Breast Cancer Res Treat*. 2007;1:23–28.
5. Tummel E, Ochoa D, Korourian S, et al. Does axillary reverse mapping prevent lymphedema after lymphadenectomy? *Ann Surg*. 2017;5:987–92.
6. Schunemann E, Dória MT, Silvestre JBCH, Gasperin P, Cavalcanti TCS, Budel VM. Prospective study evaluating oncological safety of axillary reverse mapping. *Ann Surg Oncol*. 2014;7:2197–202.

7. Bains SK, Stanton AWB, Cintolesi V, et al. A constitutional predisposition to breast cancer-related lymphoedema and effect of axillary lymph node surgery on forearm muscle lymph flow. *The Breast*. 2015;1:68–74.
8. Beek MA, Gobardhan PD, Schoenmaeckers EJP, et al. Axillary reverse mapping in axillary surgery for breast cancer: an update of the current status. *Breast Cancer Res Treat*. 2016;3:421–32.
9. Suami H, Taylor GI, Pan W. The lymphatic territories of the upper limb: anatomical study and clinical implications. *Plast Reconstr Surg*. 2007;6:1813–22.
10. Pavlista D, Eliska O. Analysis of direct oil contrast lymphography of upper limb lymphatics traversing the axilla—a lesson from the past: contribution to the concept of axillary reverse mapping. *Eur J Surg Oncol*. 2012;5:390–4.
11. Ahmed M, Rubio IT, Kovacs T, Klimberg VS, Douek M. Systematic review of axillary reverse mapping in breast cancer. *Br J Surg*. 2016;3:170–8.
12. Ochoa D, Korourian S, Boneti C, Adkins L, Badgwell B, Klimberg VS. Axillary reverse mapping: five-year experience. *Surgery*. 2014;5:1261–8.
13. Ngui NK, French J, Kilby CJ, Pathmanathan N, Elder EE. Axillary reverse mapping in patients with breast cancer: is it oncologically safe? *J Surg Oncol*. 2016;7:726–31.
14. Noguchi M, Noguchi M, Ohno Y, et al. Feasibility study of axillary reverse mapping for patients with clinically node-negative breast cancer. *Eur J Surg Oncol*. 2016;5:650–6.
15. Foster D, Choy N, Porter C, Ahmed S, Wapnir I. Axillary reverse mapping with indocyanine green or isosulfan blue demonstrate similar crossover rates to radiotracer identified sentinel nodes. *J Surg Oncol*. 2018;3:336–40.
16. Yue T, Zhuang D, Zhou P, et al. A prospective study to assess the feasibility of axillary reverse mapping and evaluate its effect on preventing lymphedema in breast cancer patients. *Clin Breast Cancer*. 2015;4:301–6.
17. Han JW, Seo YJ, Choi JE, Kang SH, Bae YK, Lee SJ. The efficacy of arm node preserving surgery using axillary reverse mapping for preventing lymphedema in patients with breast cancer. *J Breast Cancer*. 2012;1:91.
18. Beaton DE, Wright JG, Katz JN. Development of the QuickDASH: comparison of three item-reduction approaches. *J Bone Jt Surg Am*. 2005;5:1038–46.
19. Noguchi M, Noguchi M, Nakano Y, Ohno Y, Kosaka T. Axillary reverse mapping using a fluorescence imaging system in breast cancer. *J Surg Oncol*. 2012;3:229–34.
20. Noguchi M, Yokoi M, Nakano Y. Axillary reverse mapping with indocyanine fluorescence imaging in patients with breast cancer. *J Surg Oncol*. 2010;n/a–n/a.
21. Nos C, Clough KB, Bonnier P, et al. Upper outer boundaries of the axillary dissection. Result of the SENTIBRAS protocol: multicentric protocol using axillary reverse mapping in breast cancer patients requiring axillary dissection. *Eur J Surg Oncol*. 2016;12:1827–33.
22. Boneti C, Korourian S, Bland K, et al. Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy. *J Am Coll Surg*. 2008;5:1038–42.
23. Boneti C, Korourian S, Diaz Z, et al. Scientific impact award: axillary reverse mapping (ARM) to identify and protect lymphatics draining the arm during axillary lymphadenectomy. *Am J Surg*. 2009;4:482–7.
24. Tausch C, Baege A, Dietrich D, et al. Can axillary reverse mapping avoid lymphedema in node positive breast cancer patients? *Eur J Surg Oncol*. 2013;8:880–6.
25. Nos C, Kaufmann G, Clough KB, et al. Combined axillary reverse mapping (ARM) technique for breast cancer patients requiring axillary dissection. *Ann Surg Oncol*. 2008;9:2550–5.
26. Ponzone R, Cont NT, Maggiorotto F, et al. Extensive nodal disease may impair axillary reverse mapping in patients with breast cancer. *J Clin Oncol*. 2009;33:5547–51.
27. Ikeda K, Ogawa Y, Komatsu H, et al. Evaluation of the metastatic status of lymph nodes identified using axillary reverse mapping in breast cancer patients. *World J Surg Oncol*. 2012;10:233.
28. Suami H, Pan W, Mann GB, Taylor GI. The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: a human cadaver study. *Ann Surg Oncol*. 2008;3:863–71.
29. Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. *Lancet Oncol*. 2014;7:e279–89.
30. Zhang Y, Wang C, Xu Y, et al. Sensitivity, specificity and accuracy of ultrasound in diagnosis of breast cancer metastasis to the axillary lymph nodes in Chinese patients. *Ultrasound Med Biol*. 2015;7:1835–41.