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THE UPPER ARM LYMPHOSOME: WATERSHED OF UPPER ARM LYMPHATIC PATHWAYS EVALUATED WITH INDOCYANINE GREEN LYMPHOGRAPHY

H. Sakai, T. Miyazaki, R. Tsukuura, T. Yamamoto

Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, Tokyo, Japan

ABSTRACT

Understanding lymphatic anatomy of the upper extremity is necessary for treatment of upper extremity lymphedema (UEL). This study aimed to clarify the watershed of upper arm lymphosomes using fluorescent lymphography with multi-site injection of indocyanine green (ICG). Limbs contralateral to breast cancer treatment side of breast cancer survivors were included to evaluate upper arm lymphosomes. 0.1ml of ICG was injected intra-dermally at these 3 points in the mid-lateral upper arm: at the level of one (U_1), two (U_2), and three quarters (U_3) from the lateral edge of the acromion to the lateral epicondyle of the humerus. Fluorescent images were obtained to determine the upper arm lymphatic pathway patterns. An injection site with multiple lymphatic pathways was evaluated as a watershed point. A total of twenty-one limbs were included. The lymphatic pathways from the U_1/ U_2/ U_3 were anteromedial patterns in 20/13/6 (95.2%/90.5%/28.6%), and posterolateral patterns in 3/13/19 (14.3%/61.9%/90.5%), respectively. Both patterns were identified in 2/12/5 (9.5%/57.1%/23.8%), and no pattern in 0/1/1 (0%/4.8%/4.8%). Based on study results, the true watershed was determined as an approximate line from the posterolateral side of the lateral edge of the acromion to the anteromedial side of the lateral epicondyle of the humerus rather than a mid-arm line.

Keywords: Lymphedema; Supermicrosurgery; Indocyanine green lymphography; Lymphatic anatomy; Manual lymph drainage.

INTRODUCTION

Upper extremity lymphedema (UEL) is a chronic edematous disease caused by disruption of the lymphatic transport function in the upper extremity. Nonoperative treatments such as compression therapy and manual lymph drainage (MLD) are generally applied first to manage UEL (1-3), and surgical treatment is considered for progressive cases refractory to conservative treatments. Among various lymphedema surgeries, lymphaticovenular anastomosis (LVA) is effective and the least invasive surgical treatment (4-9), and becoming popular as a surgical option for relatively early-stage UEL (10). In LVA surgery, a collecting lymph vessel is anastomosed to a recipient venule or a small vein in an intima-to-intima coaptation manner with supermicrosurgical techniques which allows anastomosis of vessels with diameter of 0.5 mm or smaller. Via a created anastomosis, congested lymph can be drained into venous circulation, improving lymph circulation and lymphedematous conditions (4-10).

For effective MLD and successful LVA, it is necessary to understand the lymphatic pathways in the extremities since the therapeutic

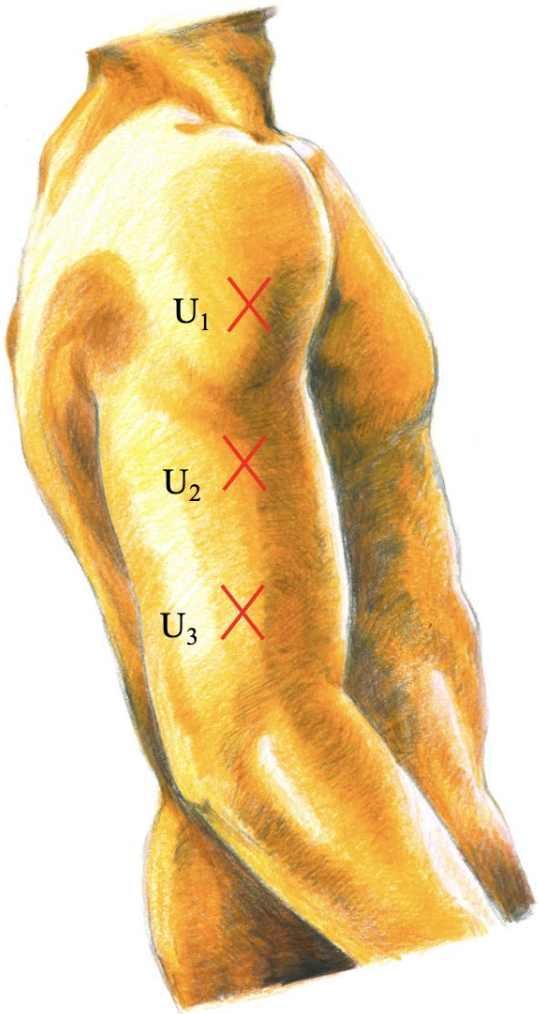

Fig. 1. *Indocyanine green injection sites included one (U1), two (U2), and three quarters (U3) from the lateral edge of the acromion to the lateral epicondyle of the humerus.*

efficacy of MLD or LVA is based on lymphosome drainage of congested lymph within the lymphosome. Although several previous biomedical experimental studies investigated and clarified anatomy of the collecting lymph vessels in the upper extremity, most visualized lymphat-ic pathways of upper extremity by injecting dyes at the fingertips, interdigital web, or palmar side of wrist and followed vessels toward axillary lymph nodes. Although it is important to understand these main lymphatic pathways which flow into the axillary lymph nodes via anteromedial forearm-to-upper arm pathways dominantly or via anterolateral or median forearm-to-upper arm pathways, it is also of importance to understand the posterior and anterolateral sides of lymphatic pathway of the upper arm. Previous studies in cadavers have clarified the anatomy of collecting lymph vessels in the upper extremity revealing the lymphatic vessels and lymph nodes territories, but what is lacking is studies in living humans. Lymphedema of the upper arm, especially around the elbow affects range of motion (ROM) and quality of life (QOL) in patients with UEL. Taken together, the posterior and anterolateral sides of lymphatic pathway of upper arm have not been well-visualized and need clarification.

Although there are few previous studies addressing the lymphatic anatomy of the upper arm (11-13), It is important to clarify more clearly the upper arm lymphatic anatomy for optimizing management of UEL. The aim of this study was to investigate the watershed of the upper arm lymphosomes in patients with UEL using indocyanine green (ICG) lymphography (14-23).

METHODS

Medical records of breast cancer survivors who underwent ICG lymphography for secondary lymphedema evaluation from February 2021 to December 2021 were reviewed. ICG lymphography was performed in bilateral upper extremities to compare the lymphographic findings of the affected limb to those of the contralateral limb as a control. Contralateral limbs of breast cancer treatment side were included to evaluate the normal upper arm lymphatic watershed.

Upper arm ICG lymphography was performed with intradermal ICG injections as previously reported (17). Briefly, 0.1ml of ICG (0.25% Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan) was injected intra-dermally at 3 points in the mid-lateral upper arm; at the levels of one (U_1), two (U_2), and three (U_3) quarters from the lateral edge of the acromion to the

TABLE 1
ICG stage based on ICG lymphography findings

	ICG lymphography findings
Stage 0	Linear pattern only (no DB pattern)
Stage I	Linear pattern + Splash pattern*
Stage II	Linear pattern + Stardust/Diffuse pattern (1 region)**
Stage III	Linear pattern + Stardust/Diffuse pattern (2 regions)**
Stage IV	Linear pattern + Stardust/Diffuse pattern (3 regions)**
Stage V	Stardust/Diffuse pattern only (no Linear pattern)

** Splash pattern is usually seen around the axilla; ** Upper extremity is divided into 3 regions; the upper arm, the forearm, and the hand; DB= dermal backflow; ICG= indocyanine green.*

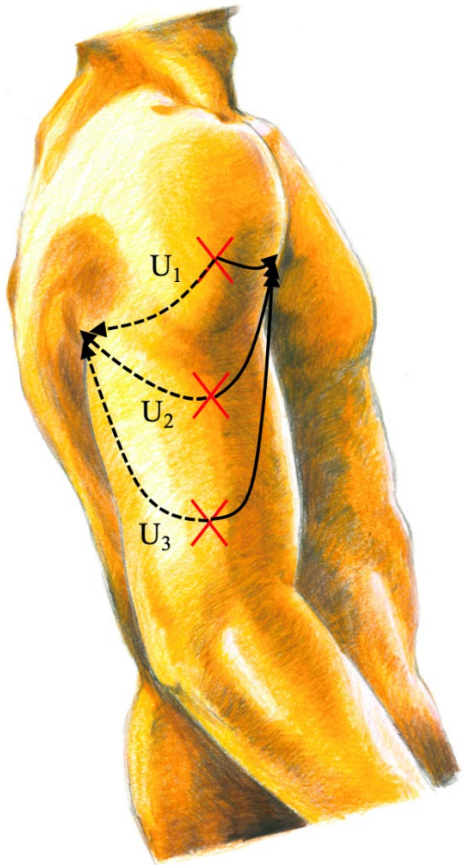

Fig. 2. *The upper arm lymphatic pathway patterns; anteromedial patterns (solid arrow lines) and posterolateral patterns (dotted arrow lines) were evaluated to observe lymph flows from injection points U1-3.*

lateral epicondyle of the humerus (*Fig. 1*). Immediately after ICG injection, Linear pattern was marked using a near-infrared camera (Photodynamic Eye-neo; Hamamatsu Photonics, Hamamatsu, Japan). At a plateau phase, ICG lymphography findings of breast cancer treatment side limbs were evaluated and ICG stage was determined (*Table 1*).

Clinical data collected included sex, age, body mass index (BMI), breast cancer treatments, ICG stage of the affected limbs, and the upper arm lymphatic pathway patterns of the contralateral limbs. The upper arm lymphatic pathway patterns; anteromedial patterns and posterolateral patterns were evaluated to observe lymph flows from U_{1-3} (*Fig. 2*). An injection point showing multiple lymphatic pathways was evaluated as a watershed point. This retrospective observational study was approved by the institution's ethical review board (approval number NCGM-G-004179-00), and all patients gave written consent before conducting the study.

RESULTS

Twenty contralateral limbs of 21 breast cancer survivors (20 female and 1 male) were included. Age ranged from 40 to 85 years (average, 61.6 years), and BMI ranged from 16.6 to 27.5 kg/m^2 average, 22.18 kg/m^2). Cancer treatments included axillary lymph node dissection

TABLE 2
Characteristics of 21 breast cancer survivors in the study

Sex (%)	
Male	1(4.8%)
Female	20 (95.2%)
Age, years (mean and range)	61.6 (40-85)
BMI, kg/m^2 (mean and range)	22.18 (16.6-27.5)
Cancer treatments (number and %)	
axillary lymph node dissection	21 (100%)
axillary irradiation	18 (85.7%)
chemotherapy	15 (71.4%)
ICG stage of breast cancer treatment sides (number and %)	
Stage 0	1 (4.8%)
Stage I	0
Stage II	2 (9.5%)
Stage III	11 (52.4%)
Stage IV	6 (28.6%)
Stage V	1 (4.8%)

BMI= body mass index; ICG= indocyanine green.

TABLE 3
ICG Lymphography Lymphatic pathway patterns

	Laterality	U_1	U_2	U_3
1	Right	M	M	L
2	Right	M	M + L	L
3	Right	M	-*	-*
4	Right	M	M + L	L
5	Right	M	M	L
6	Right	M	M + L	L
7	Right	M	M + L	L
8	Right	M + L	M + L	L
9	Right	M	M	M + L
10	Right	M	M + L	M + L
11	Right	M	M + L	L
12	Right	L	L	L
13	Left	M	M	L
14	Left	M + L	M + L	L
15	Left	M	M	L
16	Left	M	M	M + L
17	Left	M	M	L
18	Left	M	M + L	L
19	Left	M	M + L	M
20	Left	M	M + L	M + L
21	Left	M	M + L	M + L

M= anteromedial pattern; L= posterolateral pattern.

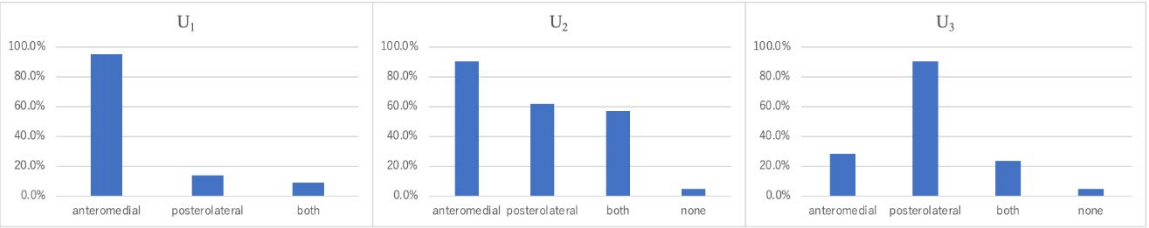

Fig. 3. *(Left) The lymphatic pathways from the U_1 were anteromedial patterns in 20 (95%) cases, and posterolateral patterns in 3 (14%) cases with both patterns identified in 2 (10%) cases. (Center) The lymphatic pathways from the U_2 were anteromedial patterns in 13 (91%) cases, and posterolateral patterns in 13 (62%) cases with both patterns identified in 12 (57%) cases and no pattern in 1 (5%) case. (Right) The lymphatic pathways from the U_3 were anteromedial patterns in 6 (29%) cases, and posterolateral patterns in 19 (91%) cases with both patterns identified in 5 (24%) cases, and no pattern in 1 (5%) case.*

in all cases, axillary irradiation in 18 (85.7%) cases, and chemotherapy in 15 (71.4%) cases. ICG stage of breast cancer treatment sides included stage 0 in 1 case (4.8%), stage II in 2 case (9.5%), stage III in 11 case (52.4%), stage IV in 6 case (28.6%), and stage V in 1 case (4.8%) (*Table 2*). ICG stage of the contralateral limb was stage 0 in all cases and no patients had abnormal finding on the non-affected limb.

The lymphatic pathways from the U_1 were anteromedial patterns in 20 (95.2%) cases, and posterolateral patterns in 3 (14.3%) cases; both patterns were identified in 2 (9.5%) cases. The lymphatic pathways from the U_2 were anteromedial patterns in 13 (90.5%) cases, and posterolateral patterns in 13 (61.9%) cases; both patterns were identified in 12 (57.1%) cases, and no pattern in 1 (4.8%) case. The lymphatic pathways from the U_3 were anteromedial patterns in 6 (28.6%) cases, and posterolateral patterns in 19 (90.5%) cases; both patterns were identified in 5 (23.8%) cases, and no pattern in 1 (4.8%) case (*Table 3*) (*Fig. 3*).

DISCUSSION

This study clarified the watershed of upper arm lymphosomes which was found to be located along the line from the lateral edge of the acromion to the lateral epicondyle of the humerus. There are few investigations describing how to determine watersheds of lymphatic pathways and we previously reported the watershed of the thigh lymphosomes by elucidating the points which showed multiple lymphatic pathways on ICG lymphography. If an ICG injected point is not at a watershed point, ICG lymphography would constantly show one direction lymph flow and only at a watershed point can multi-directional lymph flows be observed. In this study, several cases showed both anteromedial and posterolateral lymphatic pathways from U_1, U_2, or U_3. Therefore, it could be considered that the watershed of upper arm lymphosome is nearby the line which the lateral point of acromion to the lateral epicondyle of humerus. Nevertheless, expecting the precise location of the watershed of upper arm lymphosome, anteromedial patterns of lymphatic pathway at U_1 were superior to posterolateral patterns and typically the watershed of that site would be more posterolateral indicating variability. On the other hand, posterolateral patterns of lymphatic pathway at U_3 were superior to anteromedial patterns. The watershed of that distal site of the upper arm would be more anteromedial (*Fig. 4*).

The result of this study can be applied for UEL evaluation and treatment. First, lymphedema of the upper arm, especially around the elbow affects ROM of the elbow joint, which can be improved by addressing the upper arm lymphatic pathways revealed by this study. The upper arm lymphatic pathways can be addressed with MLD or LVA to improve the elbow joint's ROM limited due to upper arm lymphedema. This is particularly important for MLD (1-3), because the watershed and the direction of upper arm lymphatic pathways are not precisely

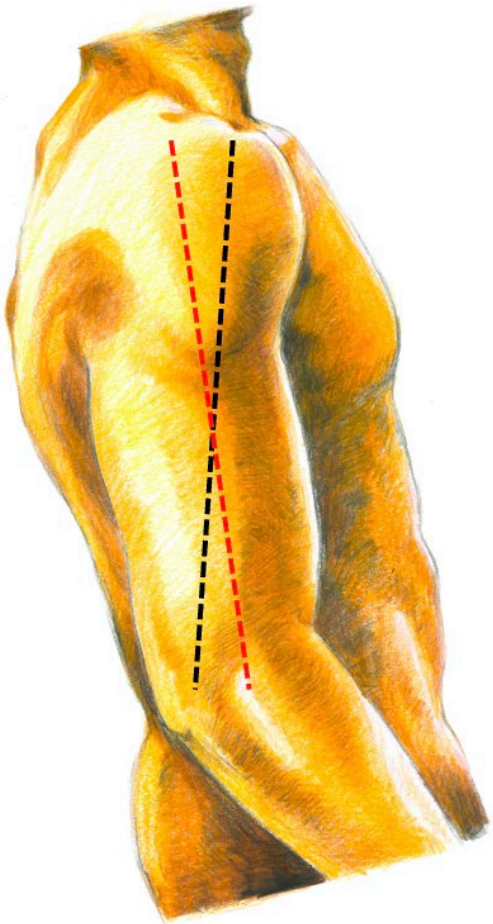

Fig. 4. *Study results in identification of upper arm watershed. The red dashed line indicates the precise line used for the three injections in the upper arm. The black dashed line depicts the lateral edge of the acromion to the lateral epicondyle of the humerus connected line which more closely represents the identified watershed (watershed of the proximal point of the upper arm would be more posterolateral from U1, and distal point of the upper arm would be more anteromedial from U3).*

described in most previous studies and textbooks (14-16). Based on these study results, MLD should be done to facilitate lymph flow from the watershed line toward the axillary lymph nodes posterolaterally and anteromedially through the upper arm. Future studies should investigate and document the possibility of a shift in watersheds depending on the ICG stage and the presence of dermal backflow in individuals with lymphedema.

Second, conventional ICG injection sites at the wrist and/or interdigital spaces are not enough to visualize whole upper extremity lymphatic pathways (17-23). Additional injections at several points of upper arms are required to precisely localize upper arm superficial lymphatic pathways. Although previous studies reported usefulness of multisite injection of ICG for comprehensive lymphosomes evaluation (24), this study is the first to clarify watershed of the upper arm. Conventional ICG injection sites at wrist and interdigital spaces cannot visualize all of the upper arm and forearm lymphatic pathways, as their flows start from the lateral or posterior aspect of the upper arm and the forearm. ICG should be injected at the initial points of the lymphatic pathways where are also the watersheds of lymphosomes (25,26).

Third, previously ignored or underestimated upper arm lymphedema can be appropriately addressed with multisite injection upper arm ICG lymphography. Trauma or tumor resection in the upper arm not affecting the major medial lymphatic pathways but affecting the lateral upper arm lymphatic pathways may cause upper arm lymphedema, which could not be appropriately diagnosed with conventional ICG lymphography or lymphoscintigraphy. These cases would be diagnosed as intact with conventional lymphography (17).

Limitations of this study include the small number of cases of only Japanese cancer survivors with relatively low BMI. The results may not be applied in other ethnic groups, and anatomical location of the upper arm lymphatic pathways may be differently visualized in obese cases. As cancer survivors, some may have different lymphatic pathways due to breast cancer treatments even though ICG lymphography stage was stage 0 in all cases on the normal contralateral arms. Study results could also be influenced by cancer treatments and particularly in limbs ipsilateral to the breast cancer which our study did not examine. To minimize painful ICG injection sites, this study employed the 3 injection sites along the line from the lateral edge of the acromion to the lateral epicondyle of the humerus, but more precise watershed of

lymphatic pathways could potentially be visualized with more injection sites (27). True identification of the watershed should produce images with approximately equal distribution to anterior and posterior locations and exact injections along the watershed pathway would allow these findings.

Further studies with volunteers are required to elucidate comprehensive lymphatic anatomy of the upper extremity, to optimize protocol of ICG lymphography, and to confirm clinical usefulness of the elucidated anatomy for UEL treatments with MLD or LVA. Multisite ICG injections at the true upper arm watershed line could play an important role in comprehensive evaluation of UEL.

CONCLUSION

Study results indicate that watershed of the upper arm lymphosomes is found on an approximate line from the posterolateral side of the lateral edge of the acromion to the anteromedial side of the lateral epicondyle of the humerus. In addition, multisite upper arm ICG injections allow visualization of lateral upper arm lymphatic pathways which would not be visualized with conventional ICG injections at the wrist and the interdigital spaces.

CONFLICT OF INTEREST

All authors declare that no financial conflict of interest exist.

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Takumi Yamamoto, MD, PhD
Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine
1-21-1 Toyama, Shinjuku-ku, Tokyo, 162-8655 Japan.
Phone: +81 3 3202 7181, Fax: +81 3 3207 1038
E-mail: tyamamoto-tky@umin.ac.jp