Variable Anatomy of the Lateral Upper Arm Lymphatic Channel: An Anatomical Risk Factor for Breast Cancer–Related Lymphedema

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Background: The lateral upper arm channel is an accessory lymphatic pathway that drains the upper extremity by means of the deltopectoral groove and supraclavicular nodes, thereby bypassing the axilla. Its variable connectivity to the forearm has not been studied in vivo.
Methods: Indocyanine green (ICG) lymphography was performed preoperatively to map the superficial and functional arm lymphatics in breast cancer patients without clinical or objective evidence of lymphedema. A retrospective review was performed to extract demographic, ICG imaging, and surgical data.
Results: Sixty patients underwent ICG lymphography before axillary lymph node dissection between June of 2019 and October of 2020. In 59%, the lateral upper arm lymphatic channel was contiguous with the forearm (long bundle). In 38%, the lateral upper arm lymphatic channel was present but not contiguous with the forearm (short bundle). In 3%, the lateral upper arm pathway was entirely absent. Seven patients developed at least one sign of lymphedema during postoperative surveillance, of which 71% demonstrated the short bundle variant.
Conclusion: Although the lateral upper arm pathway is most often present, its connections to the forearm are frequently absent (short bundle), which, in this pilot report, appears to represent a potential risk factor for the development of lymphedema. *(Plast. Reconstr. Surg.* 152: 422, 2023.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, V.

The incidence of breast cancer–related lymphedema (BCRL) is heavily influenced by specific risk factors. A recent meta-analysis reports the incidence of lymphedema (LE) after axillary lymph node dissection (ALND) at 14%, and those who underwent ALND with regional lymph node dissection at 33%.[1] Although other risk factors have been described, the exact pathophysiology of the development of this disease remains elusive. One theory is that there is a genetic predisposition to the development of LE. However, studies have reported that a mere 1% to 3% of BCRL is attributable to an underlying genetic source.[2] Another prevailing theory is that anatomical variation underpins susceptibility to BCRL. Specifically, the lateral upper arm channel, also known as the Mascagni-Sappey pathway, or lateral bundle, has been posited to be a backup pathway of the arm.[3,4] Based on cadaveric dissections, we know that the pathway courses along the cephalic vein in the upper arm and drains the upper extremity by means of the deltopectoral groove and supraclavicular nodes, thereby bypassing the axillary basin.[5,6] However, our understanding of the connections of the lateral upper arm channel to the distal forearm lymphatic channels has only been

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described in cadavers.[7] Anatomical variations in the connections of the lateral upper arm channels to the forearm channels may be an important factor in a patient's relative ability to reroute lymphatic fluid out of the arm after an axillary lymph node dissection and prevent the development of LE. However, this anatomical variability has never been studied when evaluating superficial and functional lymphatics in vivo. If specific anatomical variations were found to predispose a patient to BCRL, this would have profound implications for how we evaluate and manage breast cancer patients.

Early anatomical descriptions of upper extremity lymphatics began with Mascagni in the eighteenth century and Sappey in the nineteenth century.[5,6] In the 1990s, Leduc et al. hypothesized that backup pathways, such as the lateral upper arm or tricipital channels, were important for lymphatic drainage after mastectomy.[4] Kubik zeroed in on these alternate pathways of the upper arm in his study of cadavers who had undergone ALND. He found that the upper extremity drained by means of the lateral upper arm channel if it connected to the supraclavicular nodes. He also identified two main variants of the lateral upper arm pathway—short and long—and found that only the long variant connects to the lymphatics of the forearm. Kubik hypothesized that LE occurs when the forearm and medial upper arm are not connected to the lateral upper arm, causing lymph to be forced through the cutaneous plexus over the lymphatic watersheds to reach the lateral upper arm channel for drainage out of the arm.[3] In the twenty-first century, Suami clarified that the development of BCRL is more complex than the mere presence or absence of these alternate pathways.[8] In a review of historical lymphangiography data, lymphatic pathway variations that included drainage to the supraclavicular, internal mammary, and contralateral axillary nodes were observed in patients after ALND, but none of these were seen in healthy patients.[9] This finding suggests that alternate pathways have the potential to develop after an injury, but it is unclear whether all people have the potential to generate these alternate pathways, or whether these pathways need to be present in some form before injury. Given the prior observations by Leduc et al. and Kubik in the twentieth century, the presence or absence of lateral upper arm channel connections to the forearm may affect an individual's ability to adequately bypass lymphatic flow out of the arm following an ALND. In our prior study of in vivo upper extremity superficial and functional lymphatic anatomy, three forearm channels were consistently identified with variable connections to the medial and/or lateral upper arm channels.[10] Moreover, forearm channels that coursed in the dorsum of the forearm were more likely to connect to the lateral upper arm channel than if they coursed in the volar forearm.[10]

In this study, we performed indocyanine green (ICG) lymphography specifically for the purpose of further defining the lateral upper channel and its variable connections to the forearm. We use a targeted ultrasound-guided injection specific to the lateral upper arm channel and staggered this injection after our initial three distal hand and forearm injections to allow for detailed description of the functional connection, if present, of the lateral upper arm channel to the forearm.[7] This technique and study cohort allows us to uniquely describe the lateral upper arm channel and its variable anatomical connections to the forearm.

PATIENTS AND METHODS

Retrospective Review

A retrospective review of our lymphatic surgery Research Electronic Data Capture database was performed. Institutional review board approval was obtained (protocol no. 2020P000274). Consecutive patients with a diagnosis of node-positive breast cancer undergoing ipsilateral preoperative ICG lymphography were identified. Patient demographics, cancer characteristics, and surveillance data were extracted for analysis. Exclusion criteria included (1) any subjective or objective evidence of LE before ICG imaging, (2) any surgical history involving the extremity, and (3) no postoperative surveillance visits completed at the time of analysis.

Surveillance

All patients at our institution who undergo ALND with or without immediate lymphatic reconstruction undergo postoperative surveillance with certified lymphedema therapists, as has been described previously.[11] Briefly, this includes volume measurements, bioimpedance spectroscopy (ImpediMed, Inc., Carlsbad, CA), and completion of the Lymphoedema Quality of Life tool and the 36-Item Short-Form Health Survey. A diagnosis of LE is defined when a

patient (1) reports symptoms of LE as corroborated by a certified LE therapist and (2) demonstrates at least one objective metric of LE (10% increase in relative volume change and/or L-Dex scores greater than 10 from preoperative measures). The diagnosis is termed "transient" LE if these criteria are met within 6 months of the patient's last cancer treatment (excluding hormonal therapy). Further specifics on our diagnostic criteria have been previously published.[12]

ICG Lymphography

Under sterile conditions, 0.1 cc of stock (2.5 mg/cc) ICG solution (Akorn, Inc., Lake Forest, IL) mixed with 25 mg of albumin per cubic centimeter was injected intradermally at three anatomical locations: 1 cm proximal to the first and fourth web spaces on the dorsum of the hand and 1 cm proximal to the wrist crease in the volar forearm. After mapping of the superficial and functional lymphatics of the hand and forearm, a fourth injection was performed overlying the cephalic vein 4 cm proximal to the antecubital crease using ultrasound guidance. The locations of these injections were based on the lymphosome concept and represent all the previously identified zones of the hand, forearm, and lateral upper arm pathway.[7,13] A near-infrared imaging device, the Hamamatsu PDE-Neo II (Mitaka USA, Inc., Denver, CO) was used to visualize the superficial lymphatic channels of the extremity. Specifically, visualization, and mapping of the lymphatic channels was performed using the "mapping" mode, which displays green over black and white digital subtraction. All ICG lymphographies were performed by one of two members of the lymphatic surgery team, and final interpretation was performed by a single lymphatic surgeon (D.S.) for all studies.

The median channel was defined as the channel arising from the volar forearm injection. The radial channel was identified as that arising from the first webspace injection. The ulnar channel was defined as the pathway arising from the fourth webspace injection. Continuation of these pathways into the upper arm were labeled as medial and/or lateral upper arm channels. The lateral upper arm channels were defined as those coursing along the cephalic vein (identified using ultrasonography before injection) in the lateral upper arm. Medial upper arm channels were those that coursed medial to the cephalic vein toward the basilic vein in the medial upper arm.

RESULTS

Demographics

Sixty breast cancer patients underwent preoperative ICG lymphography between June of 2019 and October of 2020 who did not meet any exclusion criteria (Table 1). Average age at the time of axillary surgery was 56 ± 12 years. Average body mass index was 26.6 ± 8.0 kg/m^2. Most patients were female [n = 59 (98%)].

Cancer and Operative Characteristics

All patients had node-positive disease, established by means of prior sentinel lymph node biopsy (42%), core needle biopsy (47%), or fine needle aspiration (11%) (Table 2). The median number of nodes removed during sentinel lymph node biopsy in those patients was 2.5 [interquartile range (IQR), 2 to 4). The median number of nodes removed during ALND was 15 (IQR, 11 to 20), and the median number of positive nodes was 1 (IQR, 0 to 3). Most patients underwent neoadjuvant chemotherapy [n = 42 (70%)].

Anatomical Analysis

Two patients were found to have nonlinear channels, and were thus excluded from anatomical analysis.

Lateral Upper Arm Channel Present and Connected to Forearm Lymphatics

Long Bundle Scenario

The lateral upper arm pathway was visualized after the initial three hand and distal forearm

Table 1. Demographics

Characteristic	All Patients in Cohort (%)	Patients with Evidence of LE on Follow-Up (%)
No.	60	7
Mean age at surgery ± SD, yr	55.7 ± 11.9	58.6 ± 18.7
Mean BMI at surgery ± SD, kg/m^2	26.6 ± 8.0	29.6 ± 6.5
Female sex	59 (98)	7 (100)
Race		
White	41 (68)	4 (57)
Black	10 (17)	3 (43)
Asian	5 (8)	0 (0)
Other/unknown	4 (7)	0 (0)
Ethnicity, non-Hispanic	3 (5)	0 (0)

BMI, body mass index.

Table 2. Cancer and Operative Characteristics

	All Patients in Cohort (%)	Patients with Evidence of LE on Follow-Up (%)
No.	60	7
Node-positive disease	60 (100)	7 (100)
Sentinel lymph node biopsy	25 (42)	3 (43)
Nodes removed		
Median	2.5	1
IQR	2–4	—[a]
Core needle biopsy	28 (47)	2 (28.5)
Fine needle aspiration	7 (11)	2 (28.5)
Nodes removed during ALND		
Median	15	15
IQR	11–20	11.5–16
Nodes positive from ALND		
Median	1	3
IQR	0–3	0–6.5
Neoadjuvant chemotherapy	42 (70)	5 (71)
Taxane-based	39	4
Adjuvant chemotherapy	18 (30)[b]	6 (86)
Taxane-based	13[c]	4
Adjuvant radiotherapy	54 (90)	7 (100)
RLND	48[d]	7

RLNR, regional lymph node radiation.
[a]Unable to calculate given $n = 3$.
[b]One patient's adjuvant chemotherapy status unknown.
[c]One patient's taxane-based adjuvant chemotherapy status unknown.
[d]Four patients' RLNR status unknown.

injections, and before the targeted cephalic injection, in 34 patients (59%) (Fig. 1, *above*). In all these patients, at least one of the forearm pathways connected to the lateral upper arm pathway. [**See Video (online)**, which shows ICG images demonstrating the long bundle, short bundle, and no lateral upper arm channel phenotypes.]

Short Bundle Scenario

The lateral upper arm pathway was not visualized after the initial three distal hand and forearm injections, but was visible after the targeted cephalic injection, in 22 patients (38%) (Fig. 1, *center*). In these patients, there was no connection between the forearm channels and the lateral upper arm channel [**see Video (online)**].

Lateral Upper Arm Channel Not Identified

After both distal hand and forearm injections and the targeted injection over the cephalic vein, the lateral channel was not visualized in two patients (3%) (Fig. 1, *below*). In both cases, the radial and ulnar forearm channels connected to the medial upper arm pathway only. In one patient, targeted injection over the cephalic yielded a single channel that coursed directly to the medial upper arm pathway.

Long Bundle Scenario: Variable Forearm Contributions

In these 34 patients, connections to the lateral upper arm pathway varied with regard to (1) number of connections to the lateral upper arm and (2) which channels contributed to the lateral upper arm pathway (Fig. 2). One connection to the lateral upper arm pathway was established by the radial channel alone in 16 patients (47%) and the ulnar channel alone in 10 patients (29%). Two connections to the lateral upper arm pathway were established by one connection to the radial and one connection to the ulnar forearm channel in eight patients (24%).

Lymphedema

Of the 58 patients included in the analysis, two patients met criteria for LE during postoperative surveillance and three additional patients met criteria for transient LE. Two additional patients, who did not meet the criteria for LE, were placed in compression garments based on symptoms or objective criteria alone. Of these seven patients of interest, five (71%) demonstrated a lateral upper arm channel not connected to the forearm (short bundle). The average follow-up at the time of analysis was 7 ± 5 months.

DISCUSSION

In this study, variants of the lateral upper arm channel, previously identified in cadaveric studies as the Mascagni-Sappey pathway or lateral bundle, were identified in patients without lymphatic disease in vivo. The lateral upper arm channel was identified in the vast majority of patients (97%), and was connected to the forearm (long bundle) in the majority of patients (59%). The lateral upper arm channel was present, but not connected to the forearm (short bundle) in 38% of patients. Moreover, patients in our cohort who developed signs and symptoms concerning for LE predominantly (71%) exhibited the short bundle variant of the lateral upper arm channel.

We identified the lateral upper arm channel in most patients (97%). Leduc et al. identified

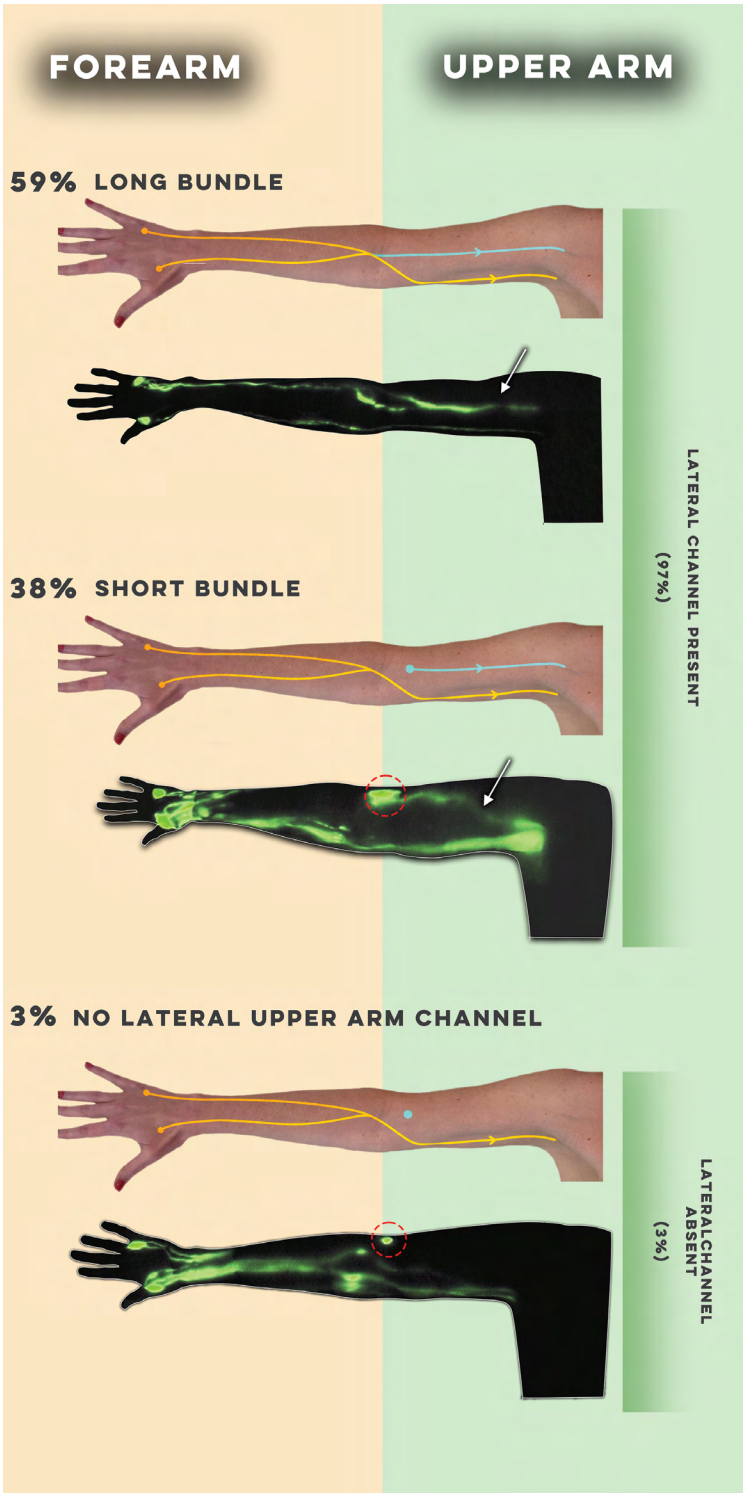

Fig. 1. Schematic of the anatomical variants of the lateral upper arm channel. Representative ICG lymphographs of right upper extremities with the palm pronated demonstrating the respective anatomical variants of the lateral upper arm channel. These images were created from stills taken from a video captured with the PDE-Neo II. Stills were extracted from the video and stitched together, and no other alterations were made. The *white arrow* indicates the lateral upper arm channel. The *dashed red circle* demonstrates the site of the dye injection immediately overlying the cephalic vein.

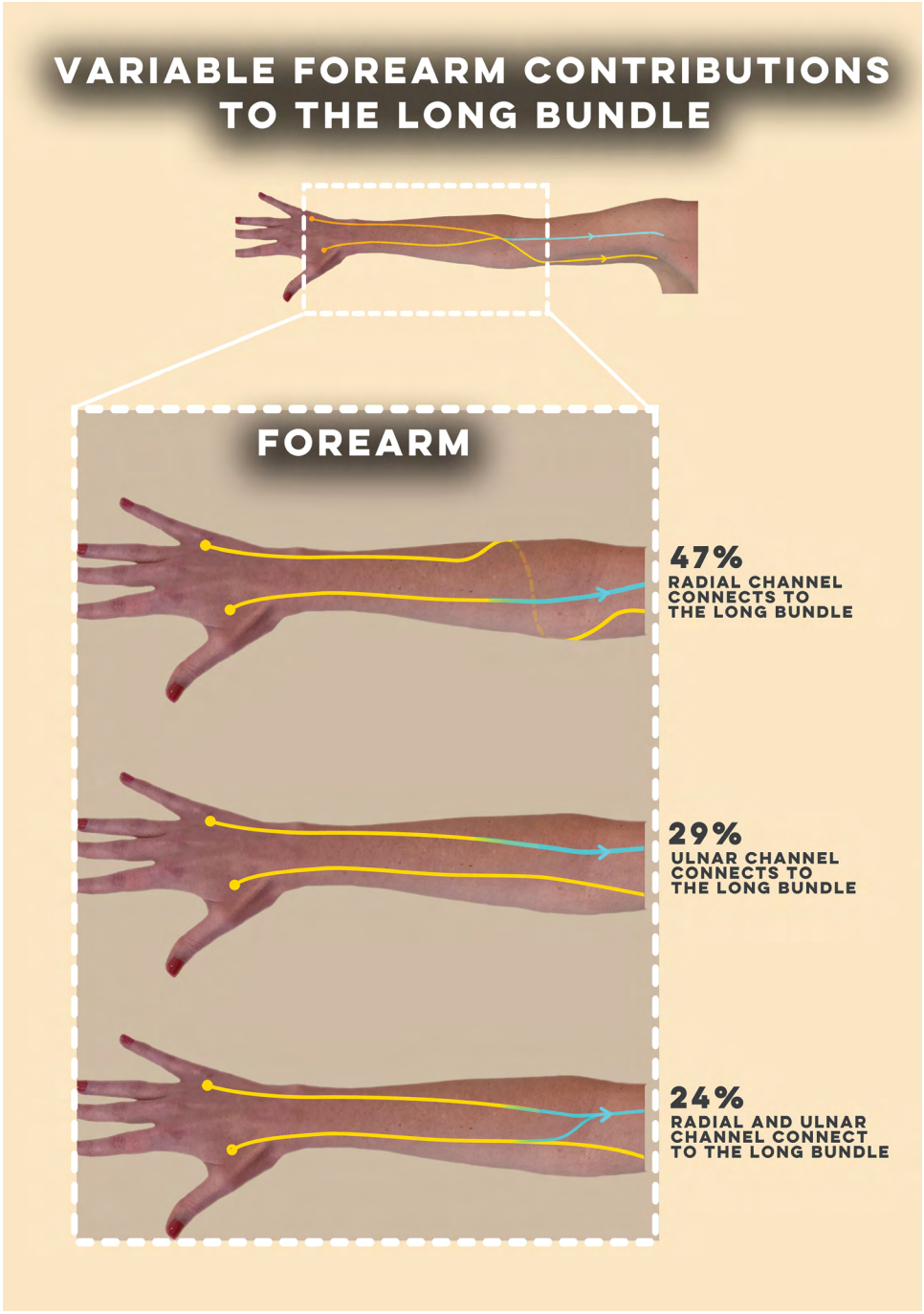

Fig. 2. Schematic demonstrating the variable forearm channel connections to the long bundle lateral upper arm channel.

this pathway in 76% of cadavers without LE.[4] The discrepancy between their findings and ours may be related to the difference between cadaveric versus in vivo functional imaging. In addition, the majority of their cadavers were fetal, and we do not know enough about the comparative lymphatic anatomy between fetuses and adults to know whether this could affect the lymphatic anatomy. Interestingly, our group has previously published that the lateral upper arm channel was present in 78% of patients with functional in vivo imaging.[7] However, since that publication, our imaging technique has been significantly refined, which has led to higher sensitivity in visualizing and mapping lymphatic channels. Specifically, we previously used the standard ICG white-on-black

imaging mode, which overall has a lower sensitivity than the green mode with digital subtraction. After reviewing our early work on mapping the lymphatic anatomy of the arm, anatomist Hiroo Suami recommended we switch to using green mode with digital subtraction.[14] The inclusion dates for this study were determined based on when our group began consistently using the green mode with digital subtraction for imaging, and this likely explains the discrepancy in our own reporting on the presence of the lateral upper arm channel.

The lateral upper arm channel connected to at least one channel of the forearm in 59% of our cohort. Kubik named this phenotype the long bundle, and only identified it in 17% of cadaveric dissections. Of significant note, all of his cadavers had a history of LE. Moreover, he described this bundle as only being connected to the radial forearm bundle.[3] Our study found a much higher proportion of long bundles (59%) and found that connections existed to both the radial and ulnar forearm channels. Leduc, in another cadaveric study, described variants of the lateral upper arm channel and also noted that the lateral upper arm channel connected to the anterior or posterior radial channels in concordance with Kubik's conclusions.[4] Based on these anatomical studies, it appears that connection between the lateral upper arm pathway and the ulnar channel of the forearm has not been identified in cadaveric dissection. In our study, we confirm the presence of functional connections between the ulnar forearm channel and lateral upper arm channel. Specifically, of the 34 long bundles we identified, 29% were connected to the ulnar channel of the forearm.

The lateral upper arm channel was not connected to the forearm in 38% of patients. Kubik named this variant a short bundle, and hypothesized that this would predispose patients to BCRL after ALND. By identifying the cephalic vein with ultrasound, and performing a targeted, staggered injection, it became obvious that many patients did have a lateral upper arm channel that did not functionally connect to the forearm. Although only 38% of our cohort had a short bundle, 71% of our patients who developed at least one sign of LE demonstrated this anatomy. This is commensurate with Kubik's finding that 83% of the cadavers with LE had a short bundle phenotype.[3] Our findings support Kubik's claim that these patients may be at greater risk of developing BCRL. Specifically, after an ALND, as the arm lymph drains from distal to proximal, it must traverse the cutaneous plexus in the watershed areas between the forearm and lateral upper arm to reach alternate outflow tracts out of the extremity. In the future, anatomical variations may guide which patients would benefit the most from nonsurgical and surgical preventative approaches.

This study is limited by the fact that it is descriptive and retrospective. Although we have made observations based on the outcomes we have tracked, a larger prospective study would be needed for statistical power and to make claims of causation. In addition, although the study of functional anatomy has some benefit over cadaveric study, it also has drawbacks. The anatomy we are able to visualize is dependent on our imaging modality, which is limited to a shallow depth of penetration, and by our injection sites. However, exciting imaging modalities are currently being refined, including magnetic resonance lymphography, that might allow us to overcome the shallow depth of penetration.

CONCLUSIONS

In this study, we have described the in vivo incidence of the short and long bundle variants of the lateral upper arm channel. We were able to identify the lateral upper arm channel in the vast majority of patients (97%), although 38% demonstrated no functional connection to the forearm. We also found that when connected to the forearm (long bundle), the lateral upper arm channel connected to the radial and ulnar forearm channels, in contrast to prior anatomical description that only found radial connections. Although our study is underpowered to draw a statistical claim, we believe that the short bundle's outsized prevalence in our cohort of patients who developed any signs or symptoms consistent with LE indicates that this anatomical variant may represent an independent risk factor for the development of BCRL, supporting a pure anatomical hypothesis made over 40 years ago.

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DISCLOSURE

The authors have no financial interests or conflicts of interest to declare in relation to the content of this article.

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REFERENCES

1. Johnson AR, Kimball S, Epstein S, et al. Lymphedema incidence after axillary lymph node dissection: quantifying the impact of radiation and the lymphatic microsurgical preventive healing approach. *Ann Plast Surg.* 2019;82:S234–S241.
2. Miaskowski C, Dodd M, Paul SM, et al. Lymphatic and angiogenic candidate genes predict the development of secondary lymphedema following breast cancer surgery. *PLoS One* 2013;8:e60164.
3. Kubik S. The role of the lateral upper arm bundle and the lymphatic watersheds in the formation of collateral pathways in lymphedema. *Acta Biol Acad Sci Hung.* 1980;31:191–200.
4. Leduc A, Caplan I, Leduc O. Lymphatic drainage of the upper limb. Substitution lymphatic pathways. *Eur J Lymphol Related Problems* 1993;4:11–18.
5. Mascagni P. Vasorum lymphaticorum corporis humani. In: *Historia & Iconographia.* Senis, Switzerland: P. Carli Edit; 1787.
6. Sappey P. Anatomie, physiologie, pathologie des vesseaux lymphatiques consideres chez l'homme et les vertebres. Available at: http://ci.nii.ac.jp/naid/10012361149/. Accessed July 10, 2020.
7. Johnson AR, Granoff MD, Suami H, Lee BT, Singhal D. Real-time visualization of the Mascagni-Sappey pathway utilizing ICG lymphography. *Cancers (Basel)* 2020;12:1195.
8. Suami H. Anatomical theories of the pathophysiology of cancer-related lymphoedema. *Cancers (Basel)* 2020;12:1338.
9. Suami H, Koelmeyer L, Mackie H, Boyages J. Patterns of lymphatic drainage after axillary node dissection impact arm lymphoedema severity: a review of animal and clinical imaging studies. *Surg Oncol.* 2018;27:743–750.
10. Granoff MD, Pardo JA, Johnson AR, et al. The superficial and functional lymphatic anatomy of the upper extremity. *Plast Reconstr Surg.* 2022;150:900–907.
11. Johnson A, Fleishman A, Tran BN, et al. Developing a lymphatic surgery program: a first-year review. *Plast Reconstr Surg.* 2019;144:975e–985e.
12. Johnson AR, Fleishman A, Granoff MD, et al Evaluating the impact of immediate lymphatic reconstruction for the surgical prevention of lymphedema. *Plast Reconstr Surg.* 2021;147:373e–381e.
13. Suami H, Taylor G, Pan W-R. The lymphatic territories of the upper limb: anatomical study and clinical implications. *Plast Reconstr Surg.* 2007;119:1813–1822.
14. Suami H. Verbal communication regarding ICG imaging technique. Available at: https://lymphaticnetwork.org/treating-lymphedema/the-lymphedema-symposium-2018/anatomy-of-the-lymphatic-system. Accessed January 22, 2021.