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Accessory Lymphatic Drainage Pathways on Indocyanine Green Lymphography in Patients with Breast-Cancer Related Lymphedema

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Abstract

Introduction: Current predictive models of lymphedema risk cannot predict with 100% certainty which patients will go on to develop lymphedema and which will not. Patient-specific anatomical and physiologic differences may be the missing part. We hypothesize that patients with accessory lymphatic pathways may have improved lymphatic drainage, resulting in smaller limb volumes.

Methods: We reviewed indocyanine green (ICG) lymphography images of all patients who presented to our institution for evaluation of breast cancer-related lymphedema. Patients with unilateral upper extremity lymphedema, a full set of bilateral limb measurements, and ICG images of both limbs were included. Other variables of interest included patient demographics and length of follow up. Patients with accessory pathways were determined independently and conflicts were resolved with discussion. Abnormal images were also evaluated for common drainage pathways.

Results: Thirty patients were identified as having accessory lymphatic drainage pathways. These patients had significantly smaller limb volume differences (8.19% (11.22)) compared to patients who did not exhibit these pathways (20.74% (19.76)) ($p < 0.001$). The most common pathway was absence or re-routing of the radial bundle to the ulnar and/or volar bundles ($n = 16$).

Conclusions: The ability to create accessory lymphatic drainage pathways may be associated with improved lymphatic drainage, resulting in smaller limb volumes. Furthermore, certain drainage pathways appear to be more common than others. Description of these pathways should be considered for inclusion in ICG lymphography image grading criteria. Further study is needed clarify the nature of these pathways, and whether these pathways affect subjective symptomology and patient quality of life.

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Introduction:

Although lymphedema is one of the most common and debilitating sequelae of breast cancer treatment, its pathophysiology remains an area of investigation (1–3). Known risk factors include obesity, radiation exposure, taxol exposure, and axillary node surgery, particularly axillary lymph node dissection (ALND) (1, 3–6). However most predictive models cannot calculate with absolute certainty which patients will go on to develop lymphedema and which will not (5, 7, 8).

A potential missing piece of the puzzle may be patient-specific anatomic and physiologic differences, especially post-ALND changes (8–12). Several animal and *in vitro* models of lymphedema have been successfully used to demonstrate lymphangiogenesis or accessory lymphatic drainage (13–19), but human examples remain rarer. Tashiro et al found indocyanine green (ICG) evidence of accessory or collateral lymphatic pathways in the axillary region and lower extremity (20, 21), Mihara et al documented an instance of lymphangiogenesis in the hand after vascularized lymph node transfer (VLNT) (22), and Heydon-White et al have documented collateral lymphatics in the breast after breast conserving therapy (23). However, an examination of de novo accessory lymphatic pathways of the distal arm has not been described.

In this study, we reviewed the various types of lymphatic accessory pathways seen in our institutional database of ICG lymphography images. We hypothesized that patients who develop these accessory pathways are more likely to have improved drainage and less swelling overall compared to patients who do not develop these pathways.

Patients and Methods:

Study Design

This was an Institutional Review Board-approved, retrospective review conducted at Memorial Sloan Kettering Cancer Center. Using a prospectively maintained patient database, we evaluated indocyanine green (ICG) laser lymphography images and videos of all patients presenting to the Division of Plastic Surgery for evaluation and treatment of breast cancer related lymphedema from November 2014 to December 2020. Conservative management is recommended for all patients including compression garments, manual drainage, and lymphedema therapy. Variables of interest included BMI, smoking status, length of follow up since initial nodal surgery, radiation exposure, and chemotherapy. Our standard evaluation includes ICG lymphography imaging and manual bilateral limb volume measurements (24).

ICG lymphography

ICG lymphography was performed bilaterally with subdermal injection of 0.2 mL of 1% plain lidocaine followed by 0.1 mL of indocyanine green dye (2.5 mg/mL aqueous solution) into the first and third webspaces and the volar wrist. Images were acquired at 5-minute, 30-minute, and 1-hour intervals following injection using near-infrared fluorescence lymphography (SPY-PHI, Stryker Corporation, Kalamazoo, MI, USA). Longitudinal linear pathways of the radial, ulnar and volar lymphatic bundles, draining to the axilla were

considered normal (Figure 1a and 1b). Pathological changes on ICG lymphography, including dermal backflow and absence of the radial, ulnar and/or volar lymphatic bundles were considered representations of impaired lymphatic function (25). Transverse linear pathways were considered representations of accessory drainage pathways.

Limb Volume Measurements

Limb volume was measured using the method described by Brorson et al (26) and reported as the difference in volume between the affected arm and contralateral arm. Briefly, this method utilizes circumference measurements taken at 4cm intervals beginning at the wrist and extending to the axillary crease with a no-stretch tape measure. The total arm volume is then calculated using the truncated cone formula (26). The most recent limb volume measurements that coincided with ICG imaging were used.

Patient and Image Evaluations

Two researchers (MC and LK) independently reviewed ICG lymphography images of all patients presenting for lymphedema evaluation at our institution from November 2014 to December 2020. Included patients were those with unilateral upper extremity lymphedema, ICG images of both the affected and unaffected limb, and limb volume measurements. Excluded patients were those with bilateral lymphedema, lower extremity lymphedema, no limb volume measurements, and no images of the contralateral arm. ICG lymphography images used in this review were only those performed prior to any lymphatic surgery (if the patient had subsequent lymphatic surgery). Further, no patient had prior immediate lymphatic reconstruction. Patients with possible accessory lymphatic pathways were identified independently and conflicts were resolved by discussion. Reviewers were blinded to patient arm volume. ICG lymphography images were also staged using the MD Anderson Cancer Center staging criteria (27) (Table 1).

Statistics

Shapiro-Wilk's test was utilized to determine the normality of the data, and Mann-Whitney U test was performed to compare average limb volume difference between patients with and without accessory pathways. Fischer's exact test was performed to compare MD Anderson Cancer Center ICG lymphography staging. A p value of <0.05 was considered significant. Analysis was performed using R 4.0.3.

Results:

Out of 168 total patients who met inclusion criteria, 30 exhibited possible accessory lymphatic pathways (Figure 2, 3). There was no significant difference between patients with and without the pathway in terms of age, BMI, gender, smoking status, nodal surgery, radiation exposure, chemotherapy exposure, or time from initial nodal surgery to ICG evaluation (Table 2). There was a significantly smaller limb volume difference in the group of patients demonstrating accessory pathways (8.19% (11.22)) compared to the group of patients who did not (20.74% (19.757)) ($p < 0.001$). Additionally, a significantly lower ICG stage was observed in the group of patients demonstrating accessory pathways compared to those who did not ($p = 0.0193$).

The most common drainage pathways were absence and re-routing of the radial bundle to the ulnar or volar bundles in the distal arm (n=16) (Figure 2, 3) or rerouting between bundles in the forearm or upper arm (n=16). Two patients exhibited both patterns. These pathways exhibited transverse lymphatics, as opposed to the normal longitudinal pattern. The transverse lymphatic channels appeared to connect a dysfunctional radial, ulnar or volar bundle to another normal, functional bundle. In many cases, a clear area of dermal backflow was seen proximal to the bypass area. These accessory pathways were notably different than hyperplastic lymphatic channel formation that is commonly seen emanating from an area of dermal backflow, and not connecting to a normal functional lymphatic channel (Figure 4).

Discussion:

Although our dataset is small, our results indicate there may be a positive relationship between accessory lymphatic pathways and smaller limb volume differences. This implies some patients may have an improved ability to re-route lymph fluid in response to upstream blockage compared to others, perhaps protecting these patients from significant arm swelling. While predictive models of lymphedema development are fairly accurate, they cannot predict with 100% certainty who will develop lymphedema and who will not. Anatomic changes may be a factor not previously examined.

It is unclear why these accessory drainage pathways are observed and there are multiple possibilities. Possibly, axillary surgery preferentially disrupts the radial bundle upstream, forcing the lymph fluid to drain via the paths of least resistance, along the ulnar or volar bundles. Therefore, lymph fluid that would have drained by the radial bundle is re-routed to the ulnar or volar bundles. It is also unclear whether these pathways are examples of true lymphangiogenesis versus dilatation of pre-existing collaterals (much like the dilatation of varices in the setting of portal hypertension, or choke vessel dilatation in delayed pedicled TRAM flaps) (28).

To our knowledge, there are four studies that have reported on the formation of accessory lymphatic pathways, and none that focus on the distal arm: two by Tashiro et al exploring collateral lymphatic formation in the upper and lower extremity, one case study by Mihara et al exploring lymphangiogenesis in the hand after VLNT, and one study by Heydon-White et al exploring collateral drainage pathways in the breast (20–23). Of the four, Mihara et al were the only ones to perform histochemical analysis, demonstrating the formation of multiple podoplanin-positive vessels in the area of the VLNT, indicating some form of new lymphatic growth (22, 29). Tashiro et al reported on *de novo* accessory pathway formation in both the lower (21) and upper extremity (20), but the bulk of their upper extremity collaterals were limited to the axilla and upper arm. Heydon-White et al limited their examination of collaterals to the breast itself, but found a relationship between lymphedema severity and likelihood of collateral pathway formation (23).

The existence of these accessory pathways also raises the question whether they should be incorporated into current ICG lymphography interpretation scales. The most commonly used ICG lymphatic staging systems are the MD Anderson scale (30) and the Arm Dermal Backflow scale (31). The MD Anderson scale classifies ICG lymphography findings

according to number of patent lymphatic vessels and degree of dermal backflow, with number of vessels decreasing and degree of backflow increasing from Stage 0 to Stage 4, while at Stage 5 is characterized by non-movement of ICG (30). The Arm Dermal Backflow scale is staged from 0 to 5 according to degree of arm involvement and dermal backflow patterning, with stage 0 being normal and stage 5 being diffuse involvement of the entire limb. Neither scale takes into account accessory drainage pathways or other anatomical compensations apart from dermal backflow (32, 33).

Chief among the weaknesses of this paper is the retrospective nature of the study. As such, pre-operative ICG lymphography and baseline measurements were not obtained. However, we used the contralateral arm as a comparison to ensure observed pathways were not normal anatomic variants. Further, follow-up periods and therefore timing of limb volume measurements and ICG lymphography were not standardized. It was difficult to determine taxol exposure or differentiate between neoadjuvant and adjuvant radiation for all patients as some patients did not have their complete oncologic treatment records. Lastly, although the Mascagni-Sappey pathway is known to potentially influence lymphatic drainage of the upper arm, we did not specifically image or target it in our injections, as our focus was the distal arm (10, 33).

Conclusions:

Presence of accessory lymphatic drainage pathways appears to be correlated with a lesser degree of limb swelling. An exploration into the relationship between these accessory drainage pathways and subjective lymphedema symptoms would clarify whether their presence has a clinically meaningful effect on patient quality of life. Further research is needed to clarify the nature of these accessory pathways, which may be part of the missing puzzle in breast cancer-related lymphedema development.

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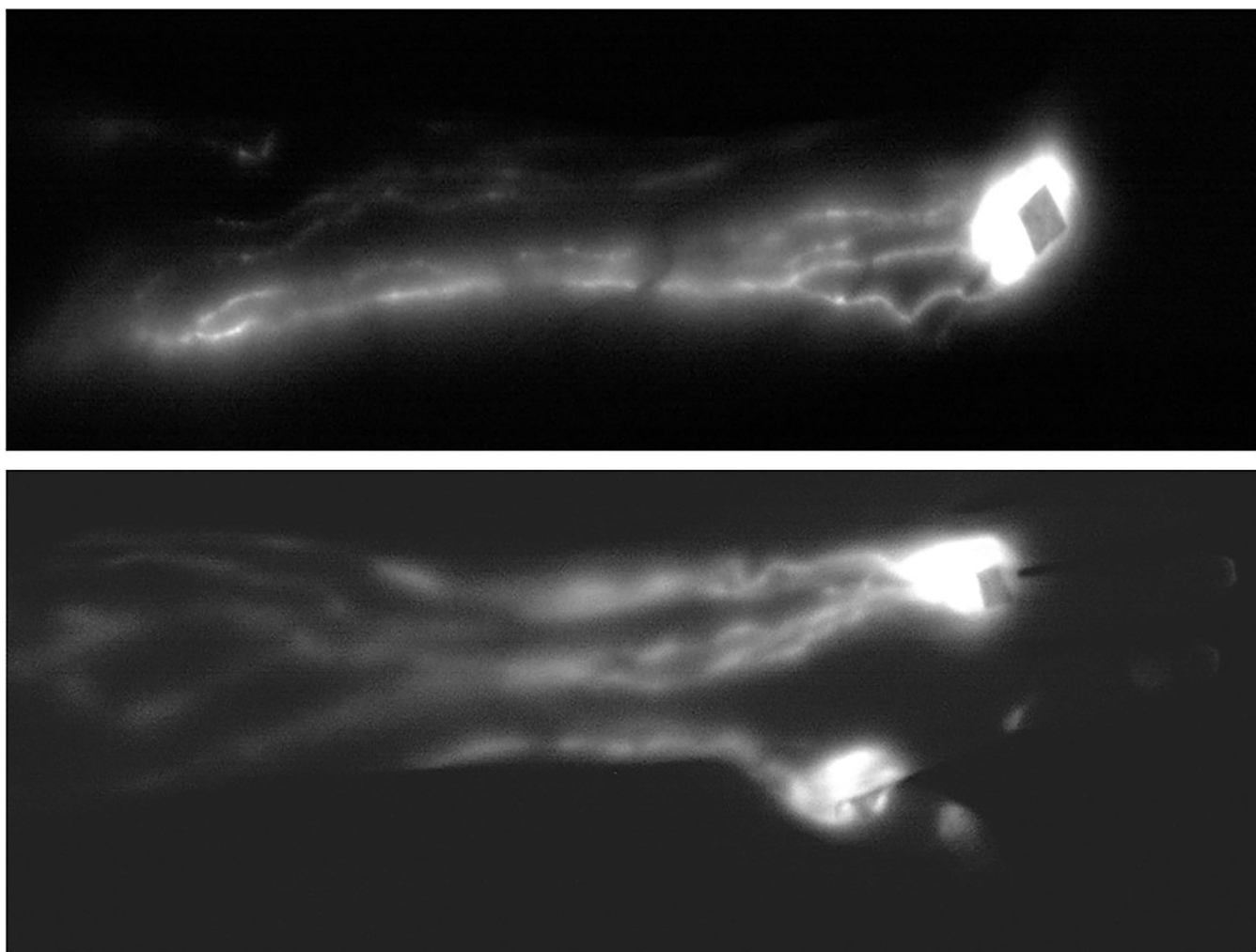


Figure 1:
Normal single-arm indocyanine green (ICG) lymphography images depicting three-bundle drainage
1a: Normal volar bundle with volar injection site.
1b. Normal radial and ulnar bundles with first and third webspace injection sites

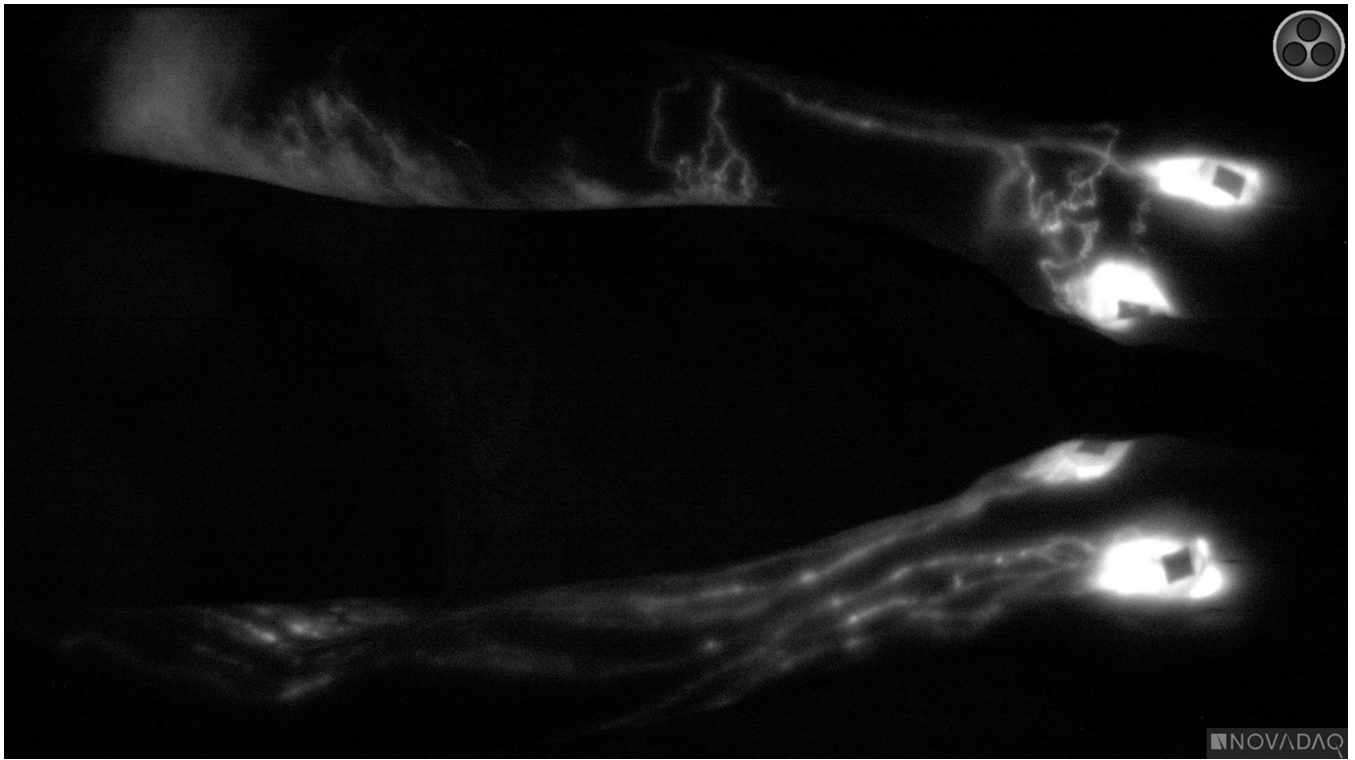


Figure 2:

Two-arm indocyanine green (ICG) lymphography image depicting lymphedema and accessory drainage patterns in the left arm (superior) and normal linear drainage patterns in the right arm (inferior). The radial bundle is absent in the left arm, with two areas of transverse crossover, one from the injection site at the first webspace to the ulnar bundle and one from an area of volar/radial dermal backflow to the ulnar bundle (white triangles).

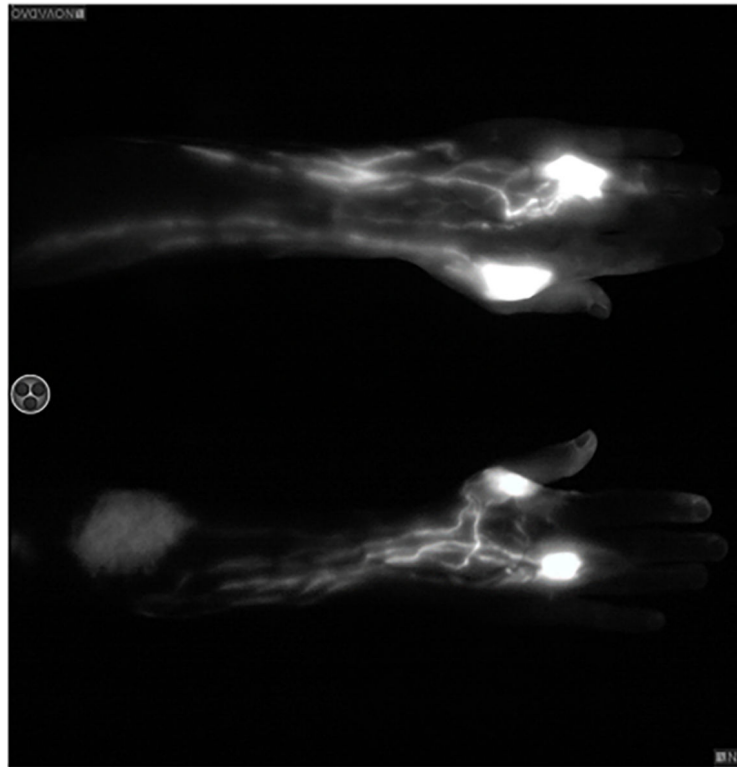


Figure 3:

Two-arm indocyanine green (ICG) lymphography image depicting lymphedema and accessory drainage patterns in the right arm (inferior) and normal linear drainage patterns in the left arm (superior). The radial bundle is absent in the right arm, with one area of transverse crossover to the ulnar bundle (white triangle). Note the area of dermal backflow more proximal on the radial aspect of the arm.

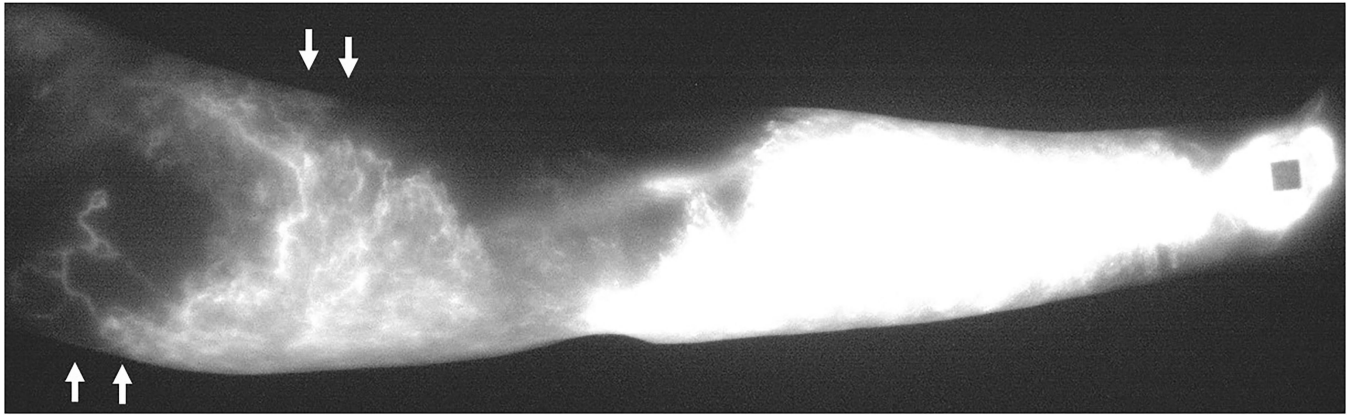


Figure 4:
Indocyanine green (ICG) lymphography image depicting dermal backflow of the volar forearm (area of white out). Hyperplastic, irregularly shaped lymphatic channels which do not connect with a normal lymphatic drainage bundle are seen proximally (white arrows).

Table 1:

MD Anderson Cancer Center ICG lymphography staging system

Stage	Description
0	Normal lymphatics
1	Many patent lymphatic vessels with minimal patchy dermal backflow
2	Moderate number of patent lymphatic vessels with segmental dermal backflow
3	Few patent lymphatic vessels with extensive dermal backflow involving the entire arm
4	No patent lymphatic vessels seen with dermal backflow involving the entire arm with extension to the dorsum of the hand
5	ICG does not move from injection sites

Table 2:

Patient demographics and operative characteristics

	Accessory drainage pathway present n=30	No accessory drainage pathway present n= 138	p-value
Gender			
Female (%)	30 (100%)	135 (98%)	
Male (%)	0 (0%)	3 (2.1%)	
Average age, years (SD)	55.03 (10.94)	55.74 (10.34)	p=0.739
Average BMI, kg/m2 (SD)	25.16 (3.00)	26.11 (4.04)	p=0.230
Smoking status			
Current (%)	0 (0%)	0 (0%)	
Former (%)	14 (46.7%)	50 (36.2%)	
Never (%)	16 (53.3%)	88 (63.8%)	
Nodal surgery			
SLNBx	1 (3.3%)	6 (4.3%)	P=0.801
ALND	29 (6.7%)	132 (95.7%)	
Radiation Exposure			
Yes (%)	26 (86.7%)	122 (88.4%)	p=0.613
No (%)	4 (13.3%)	16 (11.6%)	
Chemotherapy			
Yes (%)	28 (93.3%)	131 (94.9%)	p=0.608
No (%)	2 (6.7%)	7 (5.1%)	
Average time from initial breast surgery, years (SD)	6.08 (4.82)	7.98 (6.11)	p=0.114
Average difference in limb volumes (SD)	8.19% (11.03)	20.74% (19.68)	p=0.001
MD Anderson ICG stage			
1	8 (26.7%)	11 (7.8%)	P=0.02
2	8 (26.7%)	26 (18.8%)	
3	10 (33.3%)	52 (37.7%)	
4	4 (13.3%)	46 (33.3%)	
5	0	3 (2.2%)	

BMI= body mass index; SD= standard deviation; SLNBx=sentinel lymph node biopsy; ALND=axillary lymph node dissection; ICG=indocyanine green