The Impact of Taxane-based Chemotherapy on the Lymphatic System

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Background: Breast cancer–related lymphedema affects 700,000 breast cancer survivors in the United States. Although taxane-based chemotherapy regimens are commonly used in the treatment of breast cancer, the impact of taxanes on the lymphatic system remains poorly understood. This study aims to examine the influence of taxane-based chemotherapy on lymphatic function in breast cancer patients.

Methods: A retrospective review of a prospectively-maintained database was performed. Consecutive patients with node positive breast cancer who underwent preoperative indocyanine green (ICG) lymphangiograms were identified. Information including patient demographics, baseline measurements, cancer characteristics, and treatment information were retrieved. Preoperative ICG lymphangiography videos were analyzed and lymphatic contractility was quantified for each subject. Multiple regions of interest were selected on each lymphatic channel and signal intensity was recorded for 3 minutes to generate contractility curves. Each lymphatic contraction was identified using a novel, systematic, and algorithmic approach.

Results: Twenty-nine consecutive patients with unilateral node-positive breast cancer were included for analysis. Average patient age was 54.5 (13) years and mean BMI was 26.8 kg/m^2 (4). The mean lymphatic contractility of patients who received taxane-based neoadjuvant chemotherapy was 0.7 contractions/minute (c/m) (n = 19) compared to 1.1 c/m in those who received no neoadjuvant therapy (n = 10), ($P = 0.11$). In subgroup analysis, patients who reported taxane induced neuropathy demonstrated significantly lower lymphatic contractility values than those who were asymptomatic or did not receive any chemotherapy ($P = 0.018$).

Conclusions: In this study, we used a novel method for quantifying and evaluating lymphatic contractility rates in routine ICG lymphangiograms. Diminished lymphatic contractility was noted in patients who received taxane-based neoadjuvant chemotherapy compared with those who did not. Taxane-based neoadjuvant chemotherapy may adversely affect the lymphatic system in the breast cancer population. A larger patient cohort with longer follow-up time is needed to validate this finding and evaluate any potential association with breast cancer–related lymphedema development.

Key Words: breast cancer–related lymphedema, taxane-based chemotherapy, lymphatic contractility

(*Ann Plast Surg* 2019;82: S173–S178)

Breast cancer–related lymphedema (BCRL), or swelling of the affected extremity, affects up to 20% of the estimated 3.5 million breast cancer survivors living in the United States (U.S.).[1] This complication is more likely to occur in patients with established risk factors including axillary lymph node dissection, adjuvant radiation, and elevated MI.[2–4] The potential interplay between chemotherapy, specifically taxanes, and the development of lymphedema (LE) is a controversial topic. The use of antineoplastic agents, including taxanes, has increased as breast surgeons have shifted toward more conservative interventions.[5–8] Given the increasing prevalence of taxane-based chemotherapy in the treatment of breast cancer patients and the significant adverse impact of breast cancer-related LE on survivorship, it is important to further study this potential relationship.[2,9]

Taxanes are regularly used for those with node-positive breast cancer because of increased survival rates.[10,11] Unlike anthracycline-based chemotherapy, taxane agents have been associated with fluid accumulation in women treated for early and metastatic breast cancer.[12,13] One proposed mechanism is that systemic taxane exposure leads to increased capillary permeability and subsequent fluid accumulation in the interstitial space.[14,15] Another proposed mechanism is that taxane-based therapy may lead to systemic lymphatic dysfunction as evidenced by abnormal lymphoscintigraphy findings (ie, decreased lymphatic drainage) of the lower (unaffected) extremities in breast cancer patients who received taxane chemotherapy.[16] Existing studies have reported varying findings on the relationship between taxane-based treatment and development of BCRL.[5,17–19] Cariati et al[5] report that adjuvant taxane-based chemotherapy administration was one of the strongest risk factors for BCRL development.[5] In fact, in this study, patients undergoing axillary lymph node dissection (ALND) who received taxanes were 3 times more likely to develop BCRL compared with those who received no adjuvant treatment. This finding has been replicated in other studies.[18,20,21] However, other studies report that taxanes have minimal effect on BCRL development.[19,22] One prospective cohort trial of over 1000 patients found that administration of taxane chemotherapy had no association with LE development compared to no chemotherapy and nontaxane chemotherapy[19] The relationship of taxane administration, in the neoadjuvant setting, and BCRL development has received comparatively less attention. A study by Jung et al. found that patients who received neoadjuvant chemotherapy (NAC) with taxanes had a higher risk of LE compared to those receiving neoadjuvant chemotherapy without taxanes.[3] However, overall, it is unclear from currently published studies the true effect of neoadjuvant taxane-based chemotherapy on lymphatic function.

Using a novel, systematic, and algorithmic approach that our group had previously developed to measure lymphatic contractility, we attempt to assess the effect of taxane based NAC on lymphatic contractility. Specifically, using standard of care preoperative lymphangiograms of node positive breast cancer patients, we evaluated whether those who received neoadjuvant taxane chemotherapy demonstrated any change in contractility rates compared to those patients who received no neoadjuvant therapies. We hypothesize that lymphatic contractility in patients who receive taxane-based NAC would be reduced compared to those who did not receive chemotherapy.

In this pilot study, we performed a retrospective review of our ICG lymphangiography video repository of node positive breast cancer patients.

Received January 8, 2019, and accepted for publication, after revision January 14, 2019.
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Conflicts of interest and sources of funding: The authors did not receive any funding for this study. They have no financial disclosures and report no conflicts of interest.
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ISSN: 0148-7043/19/8203–S173
DOI: 10.1097/SAP.0000000000001884

METHODS

Study Design

A retrospective review of a prospectively maintained REDCap[23] lymphatic surgery video repository was performed. Institutional review board approval was obtained for this project. Our study design is illustrated in Figure 1. Consecutive patients with unilateral node positive breast cancer undergoing preoperative ICG lymphangiography of the ipsilateral extremity from January 2018 to September 2018 were identified. Patient demographics, cancer characteristics and treatment, baseline LE measurements, and operative specifics were retrieved. Additionally, information regarding taxane-specific treatment effects (ie, neuropathy) were reviewed. Patients who had undergone prior ALND or radiation of the operative extremity were excluded from analysis. ICG Lymphangiography videos for each patient were identified and used for contractility analyses. Independent t-tests were used to compare continuous variables between groups. Differences in contractility values between 3 groups were assessed with one-way analysis of variance. χ^2 tests were used for categorical variables. All tests were 2-tailed, and significance was set at an alpha value of P less than 0.05. All analyses were performed using IBM SPSS Version 22.01 (IBM Corp., Armonk, NY).

ICG Lymphangiography Technique

Under sterile conditions, 0.1 mL of a 0.625-mg/mL solution of ICG with albumin was injected intradermally proximal to the first and fourth web spaces of the hand. The near-infrared camera was fixated on a Mitaka PDE Flex Arm (Mitaka Kohki Co. Ltd., USA) 10 cm above the dorsum of the patient's hand such that both injection sites were visible (Fig. 2). Three-minute ICG lymphangiograms of the dorsum of the hand were recorded immediately after injection. All injections and recordings were performed by the senior author (D.S.).

Video Analysis

Lymphangiography videos were imported into VLC (VideoLAN, Paris, France) and JPEG images of each frame were extracted using the scene filter. Extracted images were imported into ImageJ and stabilized using the StackReg plug-In (National Institutes of Health, Bethesda, MD). At least 2 regions of interest (ROI) were manually selected on the brightest visible lymphatic channel in closest proximity to the injection site. Average pixel signal intensity within the ROI was recorded and plotted in Microsoft Excel (Microsoft Corporation, Redmond, WA). Average signal intensity data per second of video for each ROI was uploaded into Matlab (MathWorks, Natick, MA), and the Peakfinder

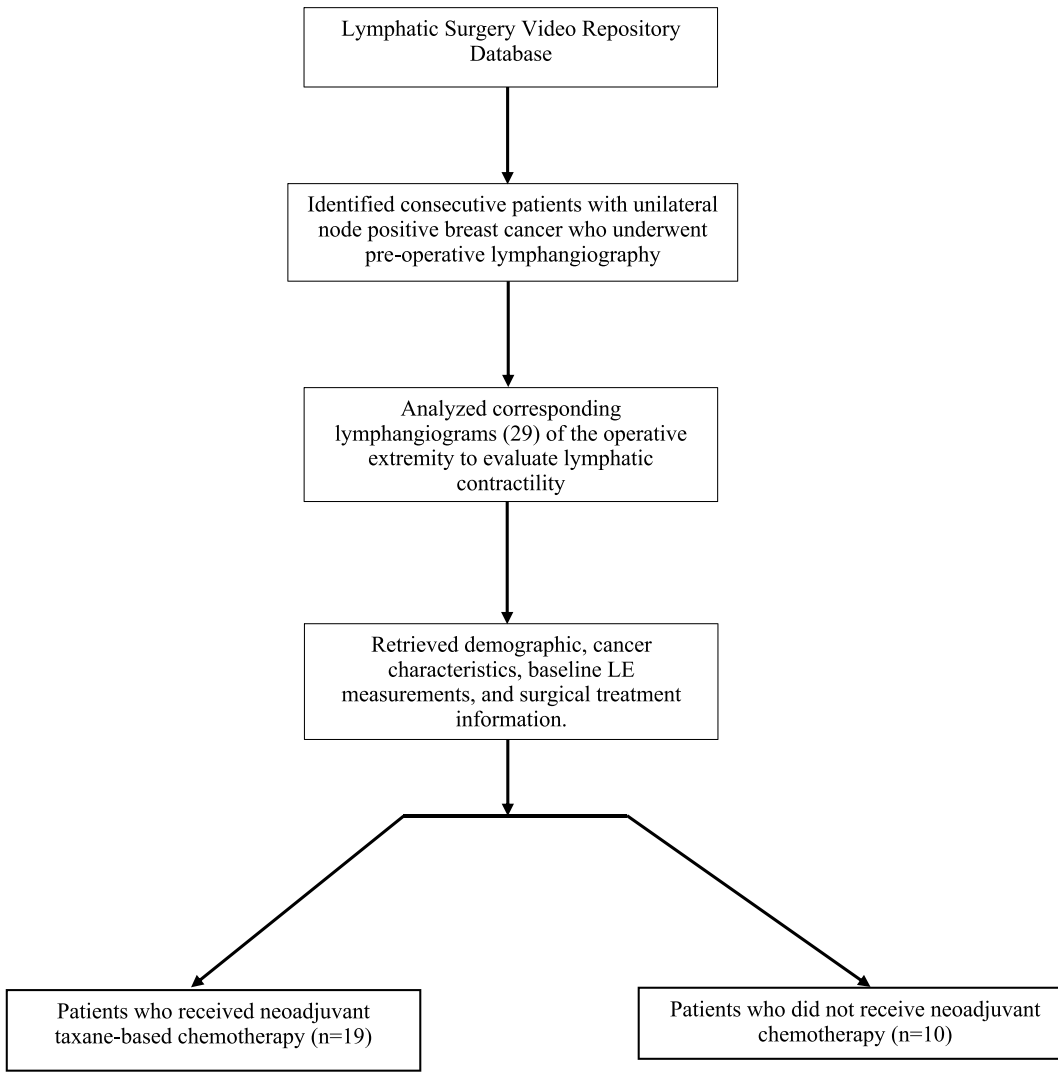

FIGURE 1. Study design.

FIGURE 2. ICG lymphangiography setup.

script (Copyright 2016, Nathanael C. Yoder) was used to identify signal intensity peaks. Peakfinder source code is publicly available at https://www.mathworks.com/matlabcentral/fileexchange/25500-peakfinder-x0-sel-thresh-extrema-includeendpoints-interpolate. The number of identified peaks was divided by the length of the video (in minutes) to yield contractility rate in contractions per minute (c/m). A second ROI on the same channel was then selected to assess reproducibility of results and eliminate noise introduced from exposure and video variation. The results from the 2 ROIs were averaged to account for discrepancies. All analyses were performed by a single researcher (M.D.G.) who was blinded to patient treatment group.

RESULTS

Twenty-nine patients with unilateral breast cancer who underwent preoperative ICG lymphangiography were initially identified. Of these, 19 patients received taxane-based NAC and 10 patients did not receive any NAC. Patients in each group were well matched with respect to age, BMI, ethnicity, race, and baseline objective measurements demonstrating no evidence of LE at time of lymphangiography (Table 1). There were no differences in cancer stage ($P = 0.23$). However, there were more patients in the taxane-based NAC group diagnosed with invasive ductal carcinoma (100%) compared to those patients not receiving NAC (60%). The median (range) time period from end of neoadjuvant treatment to operative intervention was 29 days (22–110 days) (Table 2).

The average contractility rate of patients undergoing taxane-based neoadjuvant chemotherapy (n = 19) was 0.74 c/m (0–2.08). The mean contractility rate for patients who did not undergo taxane-based NAC (n = 10) was 1.10 c/m (0.42–1.83). A 32.3% comparative reduction in contractility rate was observed in the taxane-based NAC group ($P = 0.12$).

Patient NAC regimens, presence of taxane-based symptoms, and respective contractility rates can be found in Table 3. Of those who reported symptomatic taxane-related neuropathy, the average contractility rate was 0.49 c/m (n = 11) compared to 1.07 c/m in those without symptoms (n = 8) ($P = 0.03$). Further, there were significant differences in contractility values among 3 different cohorts: (1) patients who received taxane-based NAC and reported neuropathy symptoms, (2) patients who received taxane-based NAC and reported no symptoms, and (3) patients who did not receive NAC ($P = 0.018$) (Fig. 3).

There was appreciable variability observed in the contractility rates between the 4 different taxane-based NAC regimens. The mean contractility rate for the most common chemotherapy regimen, adriamycin cyclophosphamide-paclitaxel, was 0.76 c/m (n = 14). The patient in our cohort who underwent adriamycin and cyclophosphamide-paclitaxel, herceptin, and pertuzumab had the highest contractility rate (2.08 c/m) (n = 1). The mean contractility for patients undergoing adriamycin, cyclophosphamide, paclitaxel, and herceptin was 0.33 c/m (n = 3). Individual lymphatic contractility curves for a taxane-based NAC patient and non-NAC patient are illustrated in Figure 4.

DISCUSSION

In this pilot study, we did not identify a statistically significant difference in the lymphatic contractility rates between patients who

TABLE 1. Demographics and Baseline Measurements

	Taxane-based Neoadjuvant Chemotherapy (n = 19)	No Neoadjuvant Chemotherapy (n = 10)	*P*
Age, mean (SD)	50.4 (12)	62.5 (13)	0.06
Gender, female, n (%)	14 (100)	9 (100)	
BMI, mean (SD)	27.6 (4)	25.3 (4)	0.15
Ethnicity, Hispanic, n (%)	1 (5)	1 (10)	0.68
Race, white, n (%)	17 (89)	8 (80)	0.48
Volumetry* differential % mean (min-max)	−0.2 (−6 to 4)	−0.36 (−10 to 7)	0.94
L-Dex, mean (min-max)	−1.4 (−8 to 8.4)	2.5 (−5.2 to 10.5)	0.11

*Volumetry, calculated based on the truncated cone formula using circumferential measurements taking at predefined anatomic locations on both extremities.
SD, standard deviation; BMI, body mass index; kg/m^2.

TABLE 2. Cancer Characteristics

	Taxane-based Neoadjuvant Chemotherapy (n = 19)	No Neoadjuvant Chemotherapy (n = 10)	*P*
Cancer type, IDC, n (%)	19 (100)	6 (60)	0.001
Cancer stage, mean (SD)	2.6 (0.5)	2.3 (0.5)	0.23
Time from completion of treatment to surgery: median (min-max), d	29 (22–110)		

IDC, invasive ductal carcinoma.

received taxane-based NAC and those who did not. Upon subgroup analysis, those patients who reported symptoms of taxane-based neuropathy demonstrated a statistically significant lower contractility rate compared to asymptomatic patients and patients who did not receive any NAC. Moreover, there was significant heterogeneity within the contractility values of patients receiving different taxane-based NAC regimens.

This study was primarily intended to explore any potential differences between patients receiving who did and did not receive taxane-based NAC. Although we did find a decreased contractility rate in the taxane-based NAC group, this finding was not statistically significant. A larger sample size is needed in order to better evaluate the effect of taxanes, and different taxane combination regimens, on lymphatic contractility. Additionally, follow-up data are needed to determine if there is any correlation between contractility values and LE development.

Our subgroup analysis demonstrated a statistically significant reduction in lymphatic contractility in those patients reporting taxane-based neuropathy. This finding warrants further discussion on how taxanes may influence lymphatic contractility. Although the mechanism of taxane-mediated neuropathy has been well studied, the effect of taxanes on lymphatic contractility has not.[24,25] Interestingly, from an embryologic standpoint, research has highlighted significant existing similarities in signaling pathways used in both the nervous and vascular systems.[26] If taxanes do indeed contribute to systemic lymphatic dysfunction, then it could be contended that they predispose cancer patients to postoperative LE if administered in the neoadjuvant or adjuvant setting. Evidence for global lymphatic dysfunction secondary to taxane use has been suggested. In 1 study, patients who received taxane-based treatment for breast cancer had abnormal lower-limb lymphoscintigraphy findings, irrespective of whether or not they eventually developed BCRL.[16] This supports the hypothesis that taxanes may have a global impact on lymphatic function and can even predispose patients, particularly those in the neoadjuvant setting, to LE.

Although our study does present a novel technique to quantify contractility values in diverse patient populations, it is not without limitations. The lymphangiogram videos analyzed are taken as part of standard of care and are limited to recordings of the dorsum of the hand of the operative extremity. Unintentional bias could have been introduced by the subjective selection of the regions of interest on the lymphatic channel analyzed. This potential bias was mitigated by the selection of at least 2 regions of interest on each channel and by averaging the findings of both. Furthermore, all contractility analyses, including region of interest selection, were performed by a researcher blinded to patient treatment group. Additionally, contractility of lymphatics of other areas of the arm could not be quantified. Finally, our study was only able to quantify contractility at the time of ICG lymphangiogram recording in a unique patient population without a clinical diagnosis of

TABLE 3. Patient Taxane-based NAC Regimens and Characteristics

Taxane-NAC Group Subject ID	Taxane-NAC Regimen	Patient Reported Neuropathy	Contractility (c/m)
1	AC-T	N	1.42
2	AC-T	N	0.75
3	AC-T	N	0.75
4	AC-T	N	1.5
5	AC-T	N	0.58
6	ACTH	N	1
7	Experimental regimen	Y	0.25
8	AC-THP	Y	2.08
9	AC-T	Y	0.83
10	AC-T	N	1.4
11	AC-T	N	1.2
12	AC-T	Y	0.67
13	AC-T	Y	0.92
14	ACTH	Y	0
15	ACTH	Y	0
16	AC-T	Y	0
17	AC-T	Y	0
18	AC-T	Y	0
19	AC-T	Y	0.667

AC-T, adriamycin and cyclophosphamide-paclitaxel; ACTH, adriamycin, cyclophosphamide, paclitaxel, and herceptin; AC-THP, adriamycin and cyclophosphamide-paclitaxel, herceptin, and pertuzumab; experimental regimen, paclitaxel, carboplatin, and adriamycin.

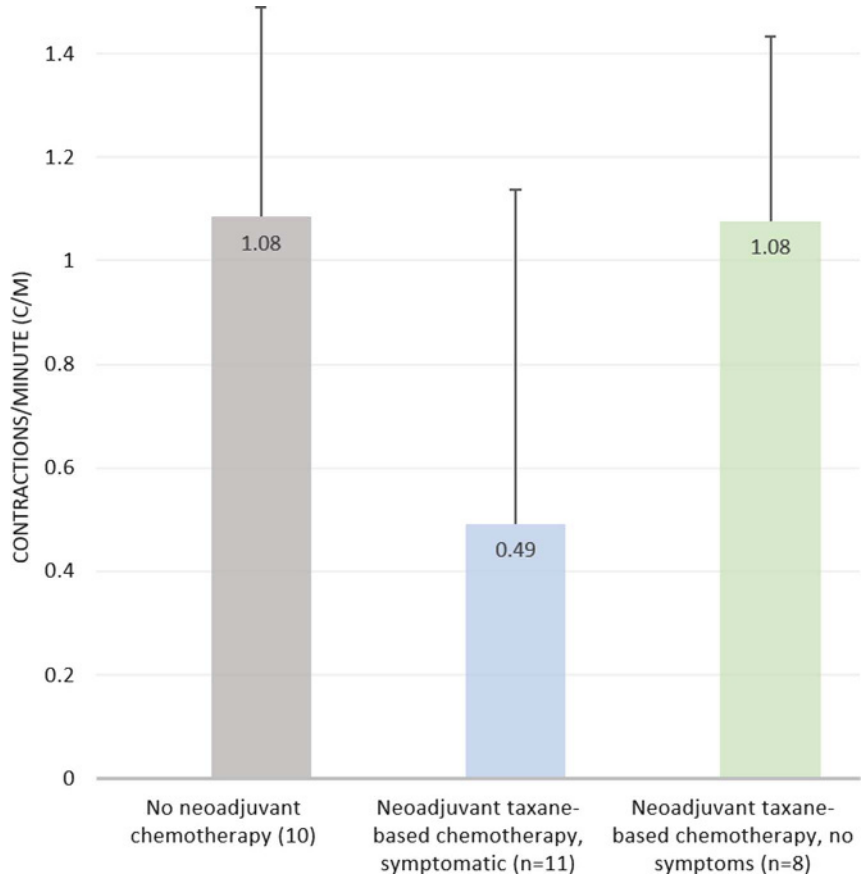

FIGURE 3. Contractility results across 3 subgroups.

LE. At this time, imaging of the contralateral extremity is not part of standard of care, hindering our ability to compare lymphatic contractility values of both patient extremities. Follow-up data and repeat lymphangiograms of these patients would be necessary to correlate contractility rates to lymphatic disease development in this patient cohort. However, this falls outside the aim and scope of the present study. We do believe that the determination of and any changes in contractility for both preventative and chronic LE patients is a fruitful area for future research.

The relationship between taxane administration and development of one of the most significant cancer survivorship burdens, LE, warrants further investigation. Additional study into the mechanism of action of taxanes and its interplay with the lymphatics is clearly needed and will enrich our understanding of a fundamental treatment component of breast cancer therapy.

CONCLUSIONS

Our pilot study systematically quantified and compared lymphatic contractility in patients who did and did not receive taxane-based NAC. We found that mean lymphatic contractility values did significantly differ between patients who reported taxane-based neuropathy and those who did not report symptoms or did not receive NAC. Further study with larger patient populations is needed to validate these findings.

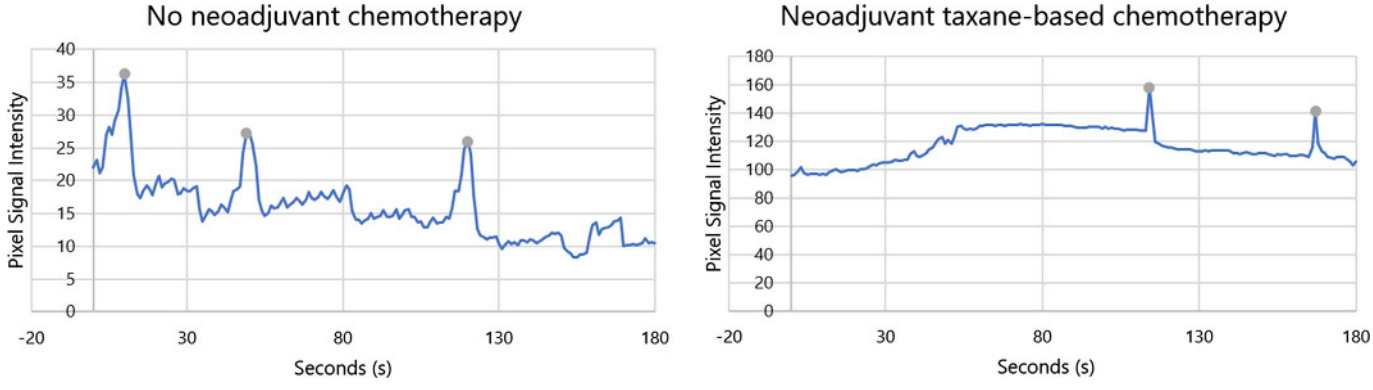

FIGURE 4. Individual lymphatic contractility curves.

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