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ORIGINAL LABORATORY INVESTIGATION

Quantifying radiation in the axillary bed at the site of lymphedema surgical prevention

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Abstract

Purpose Immediate lymphatic reconstruction (ILR) is a procedure known to reduce the risk of lymphedema in patients undergoing axillary lymph node dissection (ALND). However, patients who receive adjuvant radiotherapy are at increased risk of lymphedema. The aim of this study was to quantify the extent of radiation at the site of surgical prevention.

Methods We recently began deploying clips at the site of ILR to identify the site during radiation planning. A retrospective review was performed to identify breast cancer patients who underwent ILR with clip deployment and adjuvant radiation therapy from October 2020 to April 2022. Patients were excluded if they had not completed radiotherapy. The exposure and dose of radiation received by the site was determined and recorded.

Results In a cohort of 11 patients, the site fell within the radiation field in 7 patients (64%) and received a median dose of 4280 cGy. Among these 7 patients, 3 had sites located within tissue considered at risk of oncologic recurrence and the remaining 4 sites received radiation from a tangential field treating the breast or chest wall. The median dose to the ILR site for the 4 patients whose sites were outside the radiation fields was 233 cGy.

Conclusion Our findings suggest that even when the site of surgical prevention was not within the targeted radiation field during treatment planning, it remains susceptible to radiation. Strategies for limiting radiation at this site are needed.

Keywords Lymphedema prevention · Radiation · Immediate lymphatic reconstruction · Lymphedema

Introduction

Breast cancer related lymphedema (BCRL) is a major cancer survivorship issue that can develop at any point following breast cancer treatment. While the extent of axillary lymph node dissection (ALND) is known to be the single most important risk factor for the development of BCRL, radiation also plays a significant role in BCRL development [1–7]. Regional nodal irradiation (RNI) increases a patient's risk of BCRL due to fibrosis of lymphatic structures [8, 9]. For example, a recent study demonstrated that increasing the extent of axillary irradiation was associated with a significantly greater risk of BCRL [10]. Another study reported that radiation targeting the supraclavicular and axillary lymph nodes conferred a higher risk of BCRL, compared to breast of chest wall radiation alone [3]. Enhanced characterization of radiation delivery to the axillary bed is of growing importance as we consider how radiation may impact newer surgical approaches for the prevention of BCRL including Axillary Reverse Mapping (ARM), Simplified Lymphatic Microsurgical Prevention Healing Approach (S-LYMPHA), and Immediate Lymphatic Reconstruction (ILR).

In response to the growing body of evidence for the efficacy of surgical prevention of BCRL, a recent Consensus Guideline by the American Society of Breast Surgeons reported that, "Newer surgical techniques, such as axillary reverse mapping, lymphatic transfer, and lympho-venous anastomosis are promising both for prevention and for treatment of established lymphedema" and recommended that these procedures be offered for all cases in which ALND is required [11]. Therefore, the number of patients who undergo ALND with a method of lymphedema surgical prevention is

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expected to increase. ILR is a prominent method for surgical prevention of BCRL in which a lymphovenous anastomosis is constructed between disrupted arm lymphatic channels to adjacent axillary venous tributaries at the time ALND, thereby providing a route for the restoration of lymphatic drainage. To our knowledge there has been no prior study on radiation delivery at the site of surgical prevention [3, 8–10]. Therefore, the aim of this proof-of-concept study was to quantify the radiation dose at the site of the ILR anastomosis. Minimizing radiation exposure at the site of surgical prevention may help reduce adverse effects at this critical location.

Methods

We conducted a retrospective review to identify breast cancer patients who underwent ILR with twirl clip deployment and adjuvant radiotherapy from October 2020 through April 2022. Patients were excluded if they had not yet completed radiotherapy. Demographics, oncologic disease characteristics, and treatment data were collected.

Our ILR technique has been previously described [1, 12, 13]. Briefly, ILR was performed in coordination with the breast surgical oncology team immediately following the completion of the ALND. All ILR procedures were performed by a single plastic surgeon (D.S.). During this procedure, a vein graft was harvested from the medial lower leg and anastomosed to an axillary venous tributary using a microvascular anastomotic coupler. This is performed in order to ensure adequate recipient vein length and provide additional venous valves to minimize backbleeding [13]. The divided lymphatic channels draining the upper extremity were identified within the axilla and intussuscepted into the vein graft, following which, a twirl clip was deployed at the site of ILR anastomosis (Fig. 1). The clip was secured to the surrounding soft tissues with three interrupted 9 – 0 nylon sutures. A fat graft was then placed and secured around the anastomotic site and clip. Finally, patency of the lymphovenous anastomosis and restoration of flow of lymph were confirmed.

Following ILR, radiotherapy plans were designed and administered by one of two attending radiation oncologists (D.Y.S. or A.R) per standard of care. All cases were planned using conformal 3D technique with opposed tangents covering the breast or chest wall, which usually but not always include most or all of the lower axillary nodes, and an anterior oblique field including the supraclavicular (SCV) nodes and many or all of the more superior axillary nodes. Patients were routinely treated to the breast or chest wall and the supraclavicular and infraclavicular (Level 3) axillary nodes. Patients with extensive nodal involvement received treatment to the dissected axilla and mammary nodes treated. Axillary boost was not delivered in any cases.

Records were reviewed for radiotherapy variables including dose, targeted regions, and targeted nodal levels. A single radiation oncologist (D.Y.S.) retrospectively utilized radiation planning axial computer tomography images to identify the anatomic location of the clip, and whether the clip was within or outside of the radiation fields. The calculated dose delivered to the clip was determined from the treatment planning software. All data were analyzed descriptively with the clip designating the ILR anastomotic site.

Results

Eleven consecutive patients met the inclusion criteria. All patients were female, had a median age of 60 years, and had confirmed node-positive breast cancer. Patient, oncologic, and intraoperative characteristics are presented in Table 1 and radiotherapy variables are displayed in Table 2. Six patients had a diagnosis of invasive ductal carcinoma (55%), three patients had invasive lobular carcinoma (27%), and two patients had mixed invasive ductal and lobular carcinoma (18%). Six patients received neoadjuvant chemotherapy (55%) of which all chemotherapy regimens were taxane-based. All patients underwent ALND with successful ILR. The median number of lymphatic channels identified during ILR was 2 (range 1–5) and the median number of lymphovenous bypasses performed was 1 (range 1–3).

The anatomic location of the ILR site was in the Level 1 axillary nodal basin in 10 patients (91%) and Level 2 in 1 patient (9%). All 3 axillary levels plus the SCV nodes were deliberately targeted in the radiation fields in 3 patients, and Level 3 and SCV nodes targeted in 8 patients (Fig. 2). Of the 8 patients in whom Levels 1 and 2 axillary nodes were not specifically targeted, the ILR site nonetheless fell within the tangential fields treating the breast or chest wall in 4 patients (Fig. 3A). The ILR site was outside all radiation fields in the remaining 4 patients (Fig. 3B).

The median dose of radiation to the ILR site in the entire cohort (n = 11) was 3939 cGy (range 139–4961 cGy). Doses were substantially higher among patients in whom the ILR site fell within any radiation fields (n = 7), with a median dose of 4280 cGy (range 2191–4961) compared to a median dose of 221 cGy (range 139–280) when the ILR site was outside of all fields (n = 4).

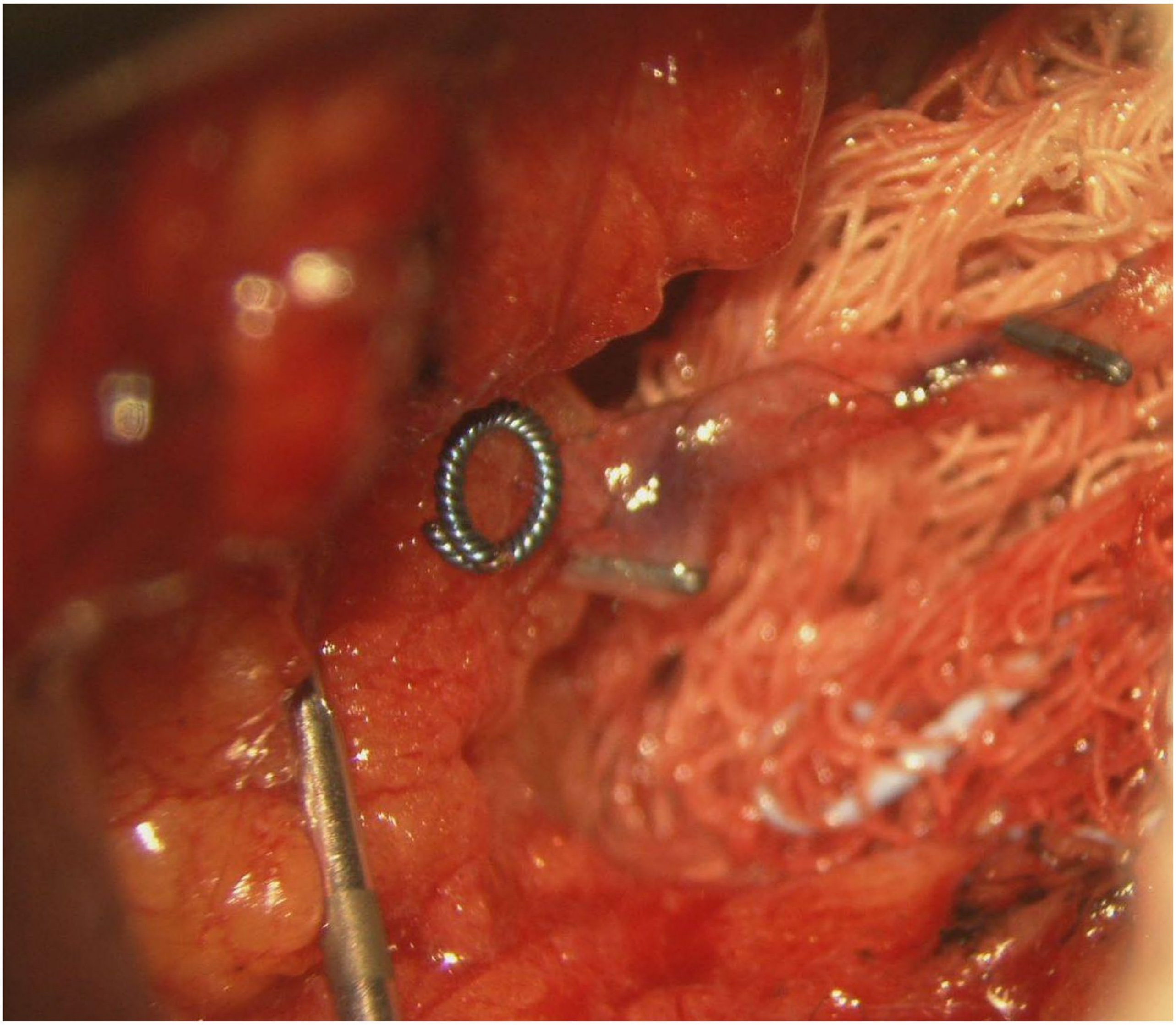

Fig. 1 Twirl clip deployed at the site of the ILR anastomosis

Discussion

In this study, we determined the extent to which radiation was delivered to the site of lymphedema surgical prevention. We demonstrated that the site fell within a radiation field in the majority of patients (n = 7, 63%). The median dose was 4280 cGy in cases in which the site of surgical prevention was directly within the targeted and delivered fields. The dose remained relatively high at 4193 cGy among those whose site was outside of the targeted fields but within the delivered fields. Finally, even among those whose site was outside both the targeted and delivered fields, there was a lower median dose of 233 cGy of radiation delivered.

Because the ILR site was not deliberately targeted in most patients, modifying the radiation may help reduce the dose delivered to the ILR site or perhaps avoid it entirely without increasing the risk of local-regional recurrence of oncologic disease. From a radiotherapy perspective, we can attempt to spare the ILR site by optimizing RNI field design and through modification of radiation delivery techniques, specifically using volumetric modulated arc therapy (VMAT) to improve precision of dose distribution and delivery. Importantly, the same techniques of radiation preservation and delivery can be further applied in patients undergoing other methods of surgical prevention including S-LYMPHA or ARM, as the location of the arm lymphatics would presumably be the same regardless of the preventative technique. Therefore, these findings could be readily extrapolated to better understand radiation delivery and applied in those also undergoing S-LYMPHA or ARM.

Table 1 Patient demographics, oncologic disease characteristics and intraoperative variables

Total *n*	11
Age, years, mean (SD)	59 (11)
Sex*n*(%)	
Male	0 (0)
Female	11 (100)
Race*n*(%)	
Black or African American	3 (27)
Asian	2 (18)
Caucasian	6 (55)
Ethnicity, ***n* (%)**	
Hispanic or Latinx	2 (18)
Non-Hispanic or Latinx	8 (73)
Unknown	1 (9)
Cancer laterality, ***n*(%)**	
Right	5 (45)
Left	6 (55)
Histology of breast cancer, ***n*(%)**	
Invasive ductal carcinoma	6 (55)
Invasive lobular carcinoma	3 (27)
Mixed invasive ductal and lobular carcinoma	2 (18)
Neoadjuvant chemotherapy status*n*(%)	
Neoadjuvant chemotherapy	6 (55)
Taxane-based chemotherapy	6 (55)
Adjuvant systemic therapy status*n*(%)	
Chemotherapy	3 (27)
Hormonal therapy	3 (27)
Both chemotherapy and hormonal therapy	5 (45)
Taxane-based chemotherapy	6 (55)
Axillary Oncologic Intervention	
Sentinel lymph node biopsy, *n* (%)	5 (45)
Lymph nodes removed in SLNB[1], *median* (range)	5 (0–10)
Fine needle aspiration, *n* (%)	1 (9)
Core needle biopsy, *n* (%)	8 (73)
Axillary lymph node dissection, *n* (%)	11 (100)
Immediate lymphatic reconstruction (ILR)	
Number of lymphatics identified, *median* (IQR)	2 (2–3)
Total number of bypasses, *median* (IQR)	1 (1–2)

SD: Standard deviation; R: Range; IQR: Interquartile range; ALND, axillary lymph node dissection; SLNB: sentinel lymph node biopsy. [1] Sentinel node injection only as per the request of breast surgeon in patient with 0 lymph nodes removed

Ultimately, a better understanding of the relationship between arm lymphatic anatomy in the axillary bed, the site of surgical prevention, and the areas at risk of oncologic relapse and hence targeted by radiation, may reduce patient risk of BCRL [14, 15]. As the field of surgical prevention of lymphedema continues to evolve, it is important that breast and lymphatic surgeons directly engage with radiation oncologists to ensure interdisciplinary familiarity with the areas of lymphatic reconstruction for radiation sparing to improve patient outcomes.

This study is not without limitations. This study is not powered for statistical significance and is limited by small sample size. As this is a proof-of-concept study, overall outcomes were not reported and more so, the aim of this study is to bring awareness to the extent of the radiation that reaches the site of surgical prevention, even when it is not within a targeted radiation field during planning. A future area of study includes long term follow-up of this cohort in order to determine the clinically significant dose of radiation received by the site of surgical prevention, in the development of BCRL.

Conclusion

Overall, radiation appears to reach the site of the surgical prevention even when it is not deliberately targeted during treatment planning. Modification of radiation delivery

Table 2 Radiotherapy characteristics at the site of immediate lymphatic reconstruction

Total *n*	11
Radiation dosage, median (range)	
Median dose at clip site	3939 (139–4961)
Maximum dose at clip site	3390 (169–5089)
Radiation target, *n*(%)	
Breast and lymph nodes	4 (36)
Chest wall and lymph nodes[1]	7 (64)
Nodal regional target, *n*(%)	
Level 1	3 (27)
Level 2	3 (27)
Level 3	11 (100)
Supraclavicular (SCV)	11 (100)
Anatomical location of clip, *n*(%)	
Level 1	10 (91)
Level 2	1 (9)
Level 3	0 (0)
Location of clip in radiation field, *n*(%)	
Tangential	4 (36)
Supraclavicular field	2 (18)
Both tangential and supraclavicular field	1 (9)
Outsite of radiation field	4 (36)

[1]Includes reconstructed breast(s)

techniques, further study of arm lymphatic anatomy, and interdisciplinary communication between surgical and radiation oncology teams will be beneficial for minimizing radiation at this site. A future method for investigation could include placement of radio-opaque markers along the length of the vein graft to understand complete dosimetry along the ILR site. Longer term studies characterizing the effects of radiotherapy field design and dose at the site of ILR on the risk of lymphedema development are warranted.

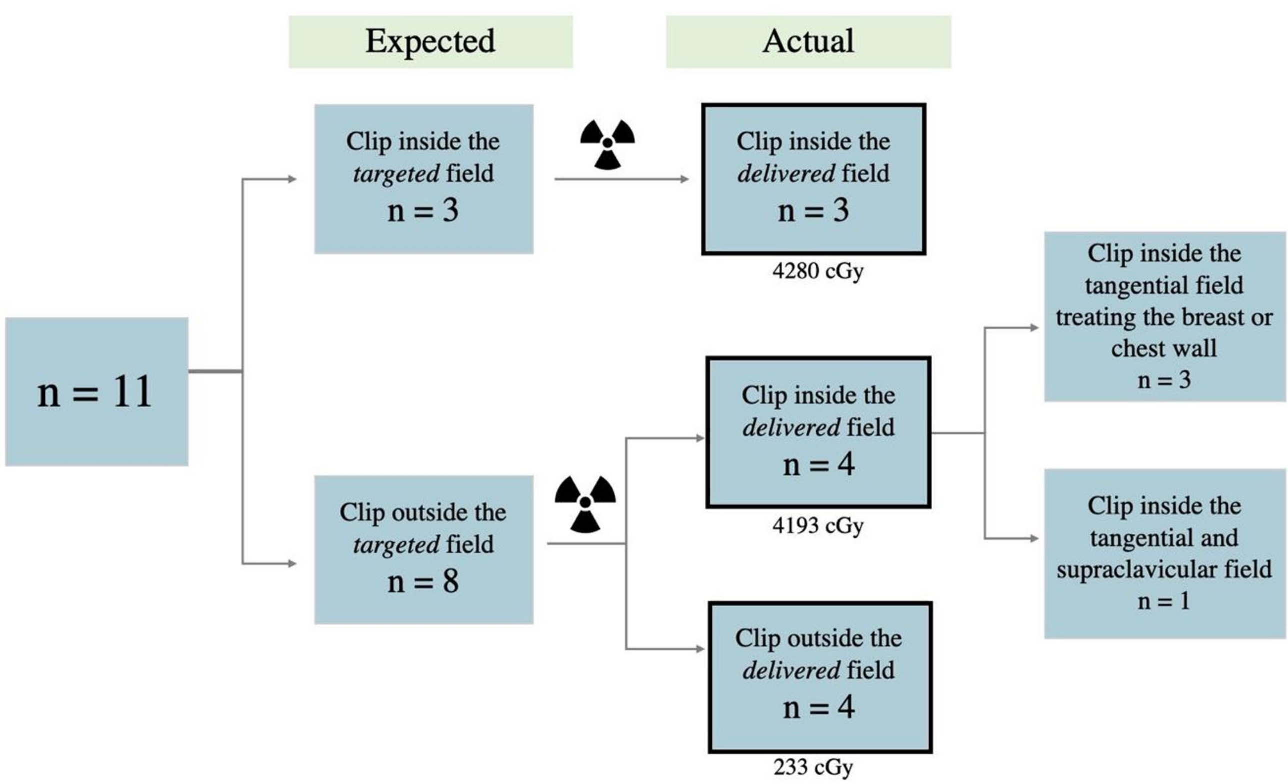

Fig. 2 Breakdown of patient cohort by whether radiation fields reached the site of the ILR anastomosis during radiation planning and delivery. Radiation doses for each group are presented in medians

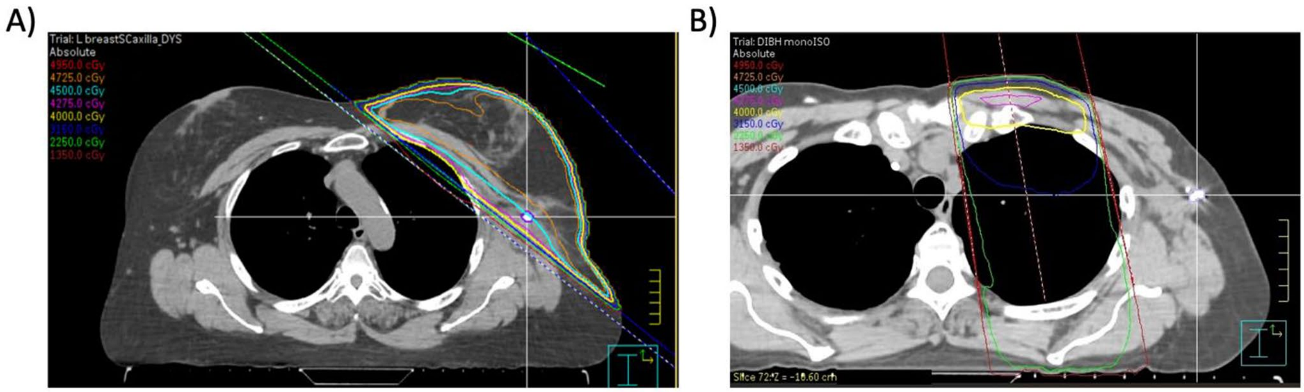

Fig. 3 The clip is visualized in the Level 1 axillary nodal basin within the tangential radiation fields on axial computed tomography image and received a mean dose of 4447 cGy **(A)**. The clip is visualized outside of the radiations fields which were targeted at Level 3 and the supraclavicular nodal basins **(B)**

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Data Availability The datasets generated during and/or analyzed during the current study are not publicly available due containment of protected health information but are available from the corresponding author on reasonable request.

Declarations

Competing Interests The authors have no relevant financial or other non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Beth Israel Deaconess Medical Center Institutional Review Board, Protocol #2022P000234.

Consent to participate Secondary data were utilized for this study and therefore participant consent was not required.

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