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BRIEF REPORT

A Prospective Study of Radiation Therapy After Immediate Lymphatic Reconstruction: Analysis of the Dosimetric Implications

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Purpose: Axillary lymph node dissection (ALND) and regional nodal irradiation (RNI) are the primary causes of breast cancer-related lymphedema (BCRL). Immediate lymphatic reconstruction (ILR) is a novel surgical procedure that reduces the incidence of BCRL after ALND. The ILR anastomosis is placed in a location thought to be outside the standard radiation therapy fields to prevent radiation-induced fibrosis of the reconstructed vessels; however, there is excess risk of BCRL from RNI even after ILR. The purpose of this study was to understand the radiation dose distribution in relation to the ILR anastomosis.
Methods and Materials: This prospective study included 13 patients treated with ALND/ILR from October 2020 to June 2022. A twirl clip deployed during surgery was used to identify the ILR anastomosis site during radiation treatment planning. All cases were planned using a 3D-conformal technique with opposed tangents and an obliqued supraclavicular (SCV) field.
Results: RNI deliberately targeted axillary Levels 1 to 3 and the SCV nodal region in 4 patients and was limited to Level 3 and SCV nodes in 9 patients. The ILR clip was located in Level 1 in 12 patients and Level 2 in 1 patient. In patients with radiation directed at only Level 3 and SCV, the ILR clip was still within the radiation field in 5 of these patients and received a median dose of 3939 cGy (range, 2025-4961 cGy). The median dose to the ILR clip was 3939 cGy (range, 139-4961 cGy) for the entire cohort. The median dose was 4275 cGy (range, 2025-4961 cGy) when the ILR clip was within any radiation field and 233 cGy (range, 139-280 cGy) when the clip was outside all fields.
Conclusion: The ILR anastomosis was often directly irradiated with 3D-conformal techniques and received substantial radiation dose, even when the site was not deliberately targeted. Long-term analysis will help determine whether minimizing radiation dose to the anastomosis will decrease BCRL rates.

Introduction

Breast cancer-related lymphedema (BCRL) is a chronic and potentially debilitating consequence of breast cancer treatment. The disease is caused by impairment of the lymphatic drainage in the extremity leading to chronic inflammation. It is estimated that BCRL affects 20% to 49% of breast cancer patients.[1-3] The primary risk factors for BCRL are axillary lymph node dissection (ALND) and regional nodal irradiation (RNI). Prior studies have found that the risk of lymphedema after ALND alone is 14.1% and 33.4% with ALND and RNI.[4]

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Disclosures: none.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Once BCRL develops, it is largely irreversible.[5,6] Historically, the management of BCRL has been reactionary, only starting after a patient has already developed the disease. Despite interventions designed to minimize complications, BCRL is a progressive disease that causes physical, psychological, and financial distress to patients.[7]

Recent studies have found that a novel microsurgical procedure, immediate lymphatic reconstruction (ILR), can help prevent BCRL. Feldman et al reported a 12.5% rate of BCRL after ALND and ILR compared with 30.6% in historical control patients.[8] Recent studies have shown BCRL rates of 4.6% after ALND and ILR and 10.6% after ALND and ILR plus RNI.[5]

Radiation therapy contributes to the development of BCRL by causing chronic fibrosis of the lymphatics, leading to obstruction and insufficient drainage of the extremity.[9] The ILR anastomosis is most often placed in axillary Level 1 because this region is typically not included in the radiation therapy target for patients undergoing ALND. As RNI increases the risk of BCRL even with ILR, the purpose of this study was to evaluate the radiation dose distribution in relation to the location of the ILR anastomosis.

Methods

Study population

This prospective cohort study included 13 patients who underwent ALND with ILR followed by breast or chest wall radiation plus RNI at a tertiary care center between October 2020 and June 2022. The study was approved by the institutional review board.

Surgical technique

Patients were injected with fluorescent dye before the ALND. Venous branches of the axillary vein were identified and evaluated. Transected lymphatic channels were visualized, isolated, and measured (Fig. 1A). A stitch was then passed through a tributary vein and lymphatic channels to facilitate parachuting the lymphatic channels into the vein.[2] The lymphatic reconstruction was then secured. Lymphatic flow and anastomotic patency were confirmed.[10] A fat graft was then wrapped around the anastomotic site to secure it. A twirl clip was placed at the site of anastomosis (Fig. 1B).

Radiation technique

All patients were treated with 3D-conformal external beam radiation therapy to the breast or chest wall and regional lymphatics. Opposed tangents were used to cover the breast or chest wall. A single obliqued field or opposed obliques were used to cover the regional lymphatics. The undissected axilla, specifically axillary Level 3, and the supraclavicular (SCV) nodal basin were always targeted. Depending on the extent of nodal involvement, axillary Levels 1 and 2 were deliberately included in the radiation fields on an individualized basis. The internal mammary nodes were included in the tangent fields when targeted.

A

B

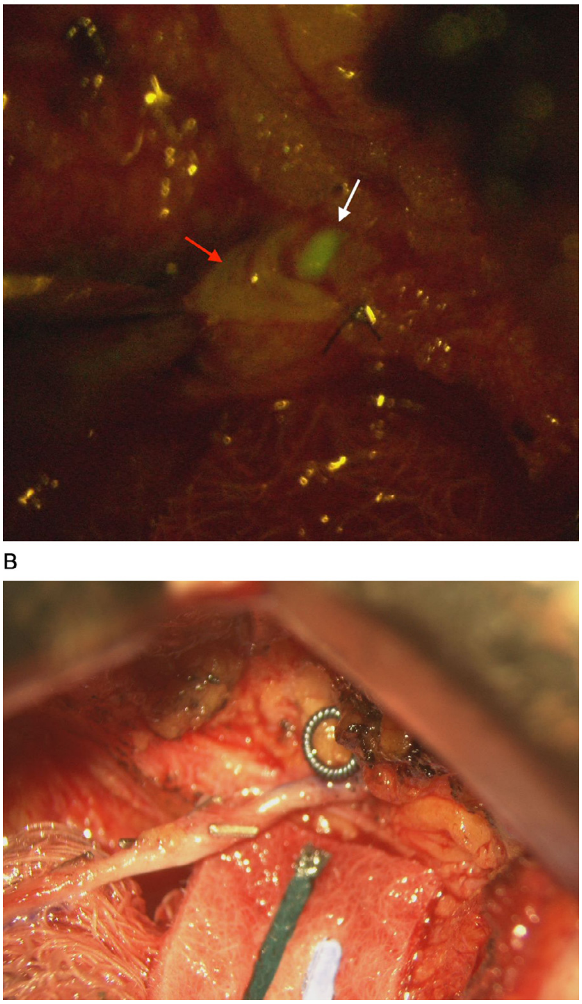

Fig. 1. Intraoperative images during immediate lymphatic reconstruction. (A) Intraoperative photo demonstrating an arm lymphatic channel (white arrow) fluorescing. The arm lymphatic has been placed into the recipient vein (red arrow). Sutures seal the lymphatic channel into the vein. (B) After completion of the anastomosis, a twirl clip is placed at the site of anastomosis and secured before fat graft placement.

Statistical analysis

Descriptive statistical analyses were performed. Stata/BE version 17.0 (StataCorp LLP) was used for analysis.

Results

Full demographic, disease, and treatment characteristics of our population are described in Table 1.

Table 1 Demographic, disease, and treatment characteristics of the study population

Characteristic	Patients n (%)	
Age (y), median (range)	60 (36-73)	
Ethnicity		
Hispanic or Latino	2 (15)	
Not Hispanic or Latino	10 (77)	
Not reported	1 (8)	
Race		
White	7 (54)	
Black or African American	3 (23)	
Asian	2 (15)	
Other	1 (8)	
Anatomic stage at diagnosis, AJCC 8th Edition		
I	2 (15)	
II	5 (38)	
III	6 (46)	
IV	0 (0)	
TNM staging (clinical)		
Primary tumor		
T0	3 (23)	
T1	3 (23)	
T2	2 (15)	
T3	2 (15)	
T4	3 (23)	
Regional lymph nodes		
N0	3 (23)	
N1	6 (46)	
N2	2 (15)	
N3	2 (15)	
Distant metastasis		
M0	13 (100)	
TNM staging (pathologic)	ypTNM	pTNM
Primary tumor		
Tx	0 (0)	1 (8)
T0	5 (38)	0 (0)
T1	2 (15)	1 (8)
T2	0 (0)	3 (23)
T3	1 (8)	0 (0)
Regional lymph nodes		
N0	4 (31)	0 (0)
N1	2 (15)	2 (15)
N2	0 (0)	2 (15)
N3	2 (15)	1 (8)

(*Continued*)

Table 1 (*Continued*)

Characteristic	Patients n (%)
Cancer laterality	
Left	6 (46)
Right	7 (54)
Bilateral	0 (0)
Tumor grade	
grade 1	0 (0)
grade 2	4 (31)
grade 3	6 (46)
Unable to grade	3 (23)
Histology	
IDC	8 (62)
ILC	3 (23)
Mixed IDC/ILC	2 (15)
Estrogen receptor status	
ER +	9 (69)
ER −	4 (31)
HER2 status	
HER2 +	3 (23)
HER2 −	10 (77)
Chemotherapy	
Neoadjuvant only	4 (31)
Adjuvant only	4 (31)
Both adjuvant and neoadjuvant	4 (31)
No chemotherapy	1 (8)
Type of nodal intervention before ALND*	
SLNB	6 (46)
FNA	1 (8)
Core needle biopsy	9 (69)
Type of breast surgery	
Breast conservation	3 (23)
Mastectomy without reconstruction	6 (46)
Mastectomy with reconstruction	2 (15)
ALND only	2 (15)

Some percentages may not add up to 100% because of rounding.

Abbreviations: AJCC = American Joint Committee on Cancer, ALND = axillary lymph node dissection, FNA = fine needle aspiration, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, SLNB = sentinel lymph node biopsy.

* Patients may have had more than one procedure before ALND

The median prescribed dose to the breast or chest wall/reconstructed breast was 4500 cGy (range, 4000-5000 cGy) in a median of 18 fractions (range, 15-25 fractions). The SCV field median dose was 4000 cGy (range, 4000-5000

Table 2 Radiation treatment details

Radiation target	n (%)
Primary target	
Breast	5 (38)
Chest wall/reconstructed breast	8 (62)
Nodal target	
Levels 1-3 and SCV	4 (31)
Level 3 and SCV	9 (69)
IMNs included	
Yes	3 (23)
No	10 (77)
Dose and fractionation	Median (Range), cGy
Breast/chest wall/reconstructed breast dose	4500 (4000-5000)
Breast/chest wall/reconstructed breast fractions	18 (15-25)
Nodal dose	4000 (4000-5000)
Nodal fractions	16 (15-25)
Boost	n (%)
Yes	4 (31)
No	9 (69)

Some percentages may not add up to 100% because of rounding.
Abbreviations: IMN = internal mammary node, SCV = supraclavicular.

cGy) in a median of 16 fractions (range, 15-25 fractions). Four patients received a boost to the tumor bed or mastectomy scar, with a median dose of 1125 cGy (range, 1000-1250 cGy) in a median of 5 fractions (range, 4-5 fractions) (Table 2).

Table 3 Radiation targets relative to ILR location

Radiation targets and ILR location	Patients n (%)	Median dose, cGy
Radiation targeted level 1-3 + SCV		
ILR clip within radiation fields	4 (31)	4278
ILR clip outside of radiation fields	0 (0)	—
Radiation targeted level 3 + SCV		
ILR clip within radiation fields	5 (38)	3939
ILR clip outside of radiation fields	4 (31)	233

Some percentages may not add up to 100% because of rounding.
Abbreviations: ILR = immediate lymphatic reconstruction, SCV = supraclavicular.

The nodal target volume deliberately included axillary Levels 1 to 3 and the SCV nodes in 4 patients (31%) and was limited to axillary Level 3 and SCV nodes in the remaining 9 patients (69%). Internal mammary nodes were included in 3 patients (23%). The ILR clip was located within axillary Level 1 in 12 patients (92%) and in Level 2 in 1 patient (8%). The ILR clip was located within the tangent fields in 6 patients (46%), within the SCV field in 2 patients (15%), spanned both the tangent and SCV fields in 1 patient (8%), and was completely out of any radiation field in 4 patients (31%).

In the 9 patients for whom the radiation target was limited to Level 3 and the SCV region, the ILR clip was located in Level 1 of the axilla for all of the patients. Despite not specifically targeting axillary Level 1 in these 9 patients, the ILR clip was still included in the radiation field in 5 of these patients:

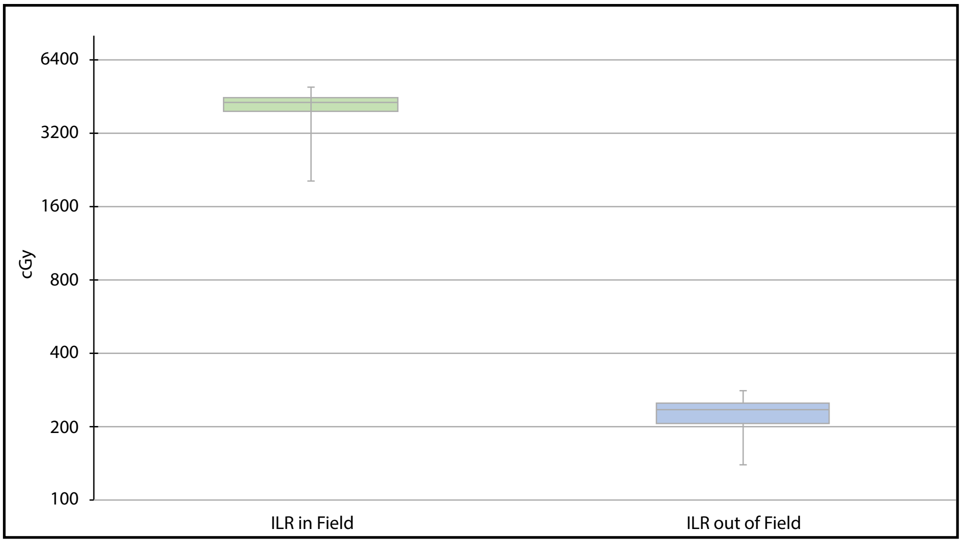

Fig. 2. Radiation dose at the site of the immediate lymphatic reconstruction anastomosis.

the clip was included in the tangential fields in 4 patients and spanned both the tangent field and the obliqued SCV field in 1 patient. The clip was outside of all the radiation fields in the remaining 4 patients. The ILR clip was within the radiation fields for the 4 patients with all axillary levels and the SCV nodes deliberately targeted (Table 3).

The median dose to the ILR clip for the entire population was 3939 cGy (range, 139-4961 cGy). For the 9 patients in whom the ILR clip was within any radiation field, the median dose was 4275 cGy (range, 2025-4961 cGy). In the 5 patients in whom the ILR clip was located within the radiation field even though the intended target was only the undissected axilla (Level 3) and SCV nodes, the median radiation dose was 3939 cGy (range, 2025-4961 cGy). For the 4 patients in whom the ILR clip was outside all radiation fields, the median dose was 233 cGy (range, 139-280 cGy) (Figs. 2 and 3).

Discussion

The addition of RNI to ALND has been shown to increase the risk of BCRL because of the development of chronic

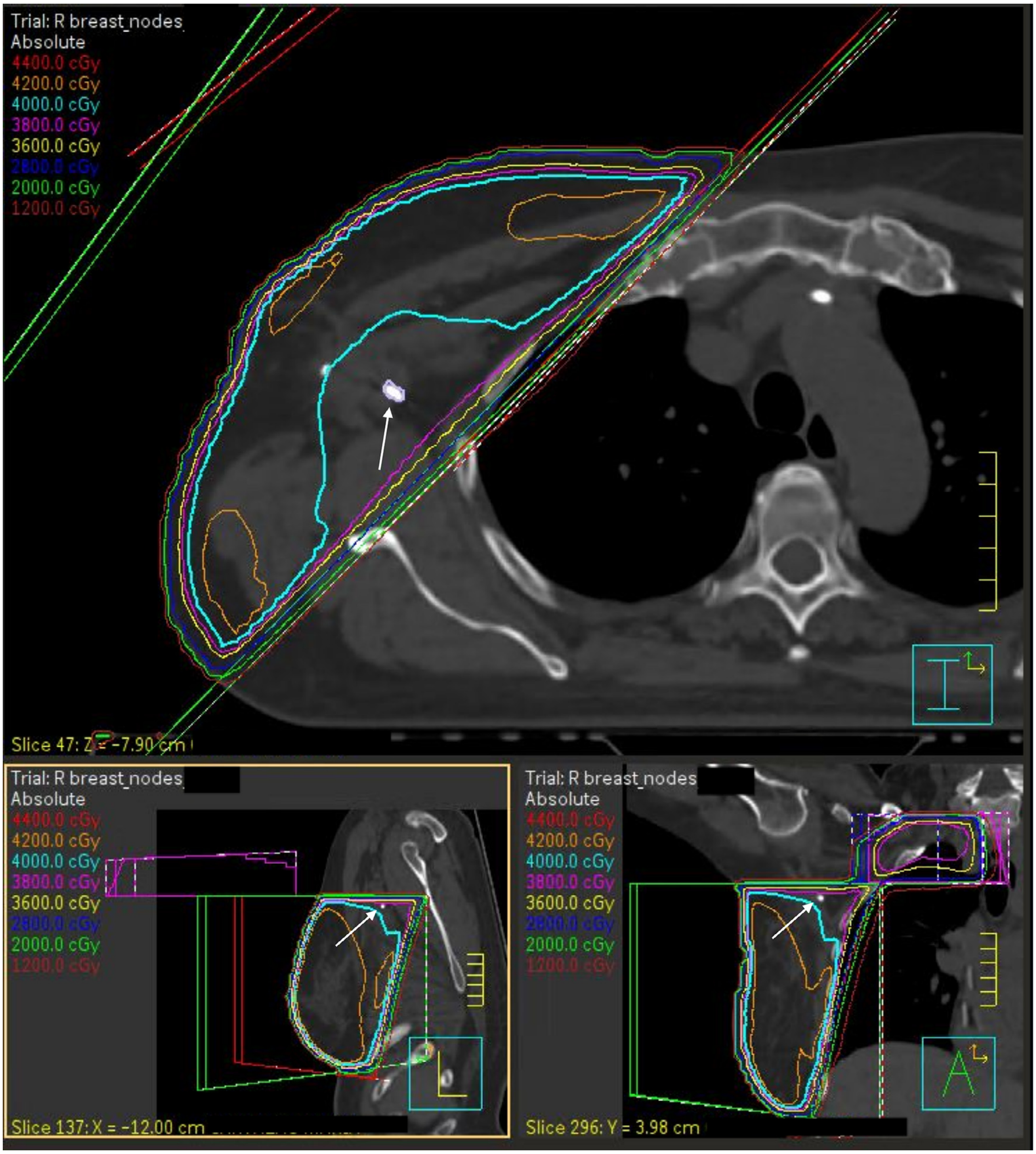

Fig. 3. Beam arrangement and dose distribution relative to the immediate lymphatic reconstruction site. Axial, sagittal, and coronal computed tomography images of radiation beam arrangements relative to the ILR site in a representative patient. This patient had the right breast, axillary Level 3, and the supraclavicular region targeted. The immediate lymphatic reconstruction clip at the site of the anastomosis is contoured in lavender and highlighted by the white arrow.

fibrosis, which can result in lymphatic obstruction.[11,12] Although it is known that ILR can reduce the rate of lymphedema after ALND and RNI,[4,13] there is still excess risk of BCRL with the addition of RNI. Understanding the radiation dose delivered to the site of the ILR anastomosis can help elucidate the reason for this excess risk of BCRL. This is the first report to evaluate the dose delivered to the ILR site with traditional treatment planning approaches.

The acceptance of sentinel node biopsy as the primary modality of axillary staging means that patients who undergo ALND have substantial nodal involvement and almost always receive adjuvant RNI. For patients who require RNI after ALND, the primary nodal target is most often the undissected axilla and SCV region. Though some patients with extensive nodal involvement have the full axilla treated after ALND, this is less common. As such, the ILR anastomosis is placed in Level 1 of the axilla, outside of the typically targeted fields.

In our study, we found that the ILR was located in Level 1 of the axilla in 12 of 13 patients. Though the intended radiation therapy target was the undissected axilla in the majority of patients, the ILR anastomosis within Level 1 of the axilla was still included in the radiation field for 5 of these patients. In these patients, the ILR site received a substantial dose of radiation, with a median of 3939 cGy.

To ensure appropriate coverage of the breast or chest wall, traditional 3D-conformal approaches to radiation planning involve using tangential fields that often include portions of Levels 1 and 2 of the axilla. This is the case even though radiation oncologists may not be specifically targeting these regions for patients who have undergone ALND. Given the proximity of the ILR to the primary target of the breast or chest wall, irradiation of the ILR site at doses expected to cause fibrosis of small veins and lymphatics occurred more frequently in this study than we anticipated. The exposure of the ILR site may potentially reduce the effectiveness of ILR. Long-term follow-up is required to determine the effect of such doses on the development of BCRL.

Other treatment planning techniques, including volumetric arc radiation therapy or intensity modulated radiation therapy, may allow for more targeted radiation treatment plans compared with a 3D-conformal approach and limit incidental axillary radiation.[14,15] Minimizing radiation dose to axillary Levels 1 and 2 has been shown to decrease the risk of BCRL, even in the absence of preventative strategies, like ILR.[16] Prior studies have shown that, in certain situations, using volumetric arc radiation therapy or intensity modulated radiation therapy techniques can reduce the dose delivered to the ILR site[17]; however, the clinical implications of this are still unknown.

Radiation techniques that limit the dose to the anastomotic site without compromising target dose are the subject of ongoing research. Additionally, collaboration with our plastic surgery colleagues and exploring surgical techniques that place the ILR site more distal to the axilla may further reduce the risk of BCRL.

Conclusions

The ILR anastomotic site often received a substantial radiation dose in this study using 3D-conformal techniques, even when the ILR site was not deliberately targeted. Long-term analysis of these data will help determine whether minimizing the radiation dose to the anastomosis will decrease rates of BCRL.

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