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Analysis of Predictive Factors for Arm Lymphedema Following Salvage Radiotherapy for Patients with Recurrent Breast Cancer

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Objectives: This study aimed to identify clinical and dosimetric risk factors for subsequent arm lymphedema (SAL) in patients with locoregionally recurrent breast cancer who received salvage repeated radiotherapy (RT).
Methods: We retrospectively analyzed 65 patients treated between 2003 and 2017. Regional nodal areas were divided into seven subregions per Gross et al. (2019) and contoured for dosimetric evaluation. Initial and repeated RT plans were deformed and merged to calculate cumulative dose-volume histograms. Equivalent dose in 2 Gy fractions (EQD2)-based parameters (max dose, mean dose, min dose, percentage of volume receving at least n Gy (VnGy)) were assessed. Optimal cut points for dosimetric parameters were determined by maximally selected rank statistics. Multivariable Cox regression and Akaike information criterion (AIC) were applied to identify predictors of SAL.
Results: Salvage surgery was performed in 52% and taxane-based chemotherapy in 45%. Median accumulated prescription dose was 113.0 Gy EQD2. With a median follow-up of 30.4 months, 15 patients (23.1%) developed SAL after a median of 6.4 months. SAL was associated with taxane-based chemotherapy and higher doses to axillary-lateral thoracic junction (ALTJ) and adjacent regions. In multivariable analysis with clinical factors only, taxane-based chemotherapy was significant (HR 4.2, P=0.04). The final model with clinical and dosimetric parameters selected lateral to ALTJ V30 Gy ≥60% (HR 5.35, P=0.001) plus taxane-based chemotherapy (HR 4.73, P=0.02).
Conclusion: SAL occurred in 23% of patients after salvage repeated RT. Taxane-based chemotherapy and lateral to ALTJ V30 Gy ≥60% were risk factors. Applying this dose constraint and early rehabilitation referral may help reduce SAL risk.

Key Words: Lymphedema · Breast Cancer · Locoregional Recurrence · Salvage Repeated Radiotherapy

INTRODUCTION

Radiotherapy (RT) is an important component of breast cancer management and has been proven to reduce locoregional recurrence (LRR) rates and improve overall survival[1-3]. Although recurrence rates following breast conserving therapy (BCT) have improved with therapeutic and technical advances in recent decades, about 10% of patients experienced LRR after initial therapy. Aggressive treatment is important in this group of patients because it can provide long-term disease control and cure chance[4,5]. However, the treatment of locoregionally recurrent breast cancer is challenging considering risk and benefit.

Lymphedema, which significantly impact the patient's quality of life, is one of the most concerning toxicities[6-8]. The incidence of lymphedema after breast cancer treatment is multifactorial and the incidence rate is approximately 3-70%, depending on the extent of axillary surgery, the use of RT, the measurement criteria used and the length of follow-up. RT, especially,

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regional nodal irradiation (RNI) is known to be a risk factor[9-11]. Although modern radiation techniques have reduced the incidence of lymphedema, it remains a significant concern, particularly for patients who need repeated RT[9-11]. However, to date, there is very limited data about lymphedema after salvage RT in patients with locoregionally recurrent breast cancer.

Therefore, we aimed to conduct a comprehensive analysis including clinical factors and dosimetric parameters to predict the risk of subsequent arm lymphedema (SAL) following salvage repeated irradiation in locoregionally recurrent breast cancer.

MATERIAL & METHODS

Patient population

Between January 2003 and December 2017, 245 patients with pathologically confirmed LRR of breast cancer underwent salvage treatment with curative intent at our institution. Among the 245 patients, 82 patients received salvage repeated RT for LRR. After excluding the patients whose RT plans couldn't be restored, a total of 65 patients were included in the final analysis (Fig. 1). The institutional review board of Samsung Medical Center approved this retrospective study (2024-02-066-001).

Treatment

Salvage repeated RT was defined as secondary irradiation to locoregional breast lesion for breast cancer with LRR. Patients underwent computed tomography (CT) simulation. Breast or chest wall and regional nodal target volumes were contoured by the treating physicians according to the ESTRO Breast Cancer Atlas for RT Planning Consensus Definitions. RNI was categorized into 2 types. The extensive RNI group encompassed the entire axilla, including levels 1 to 3, whereas the limited RNI group encompassed the medial paraclavicular region excluding the axillary level 1. RT planning included forward-planned RT with x-rays with or without electrons, or inversed planned intensity modulated RT (IMRT) based on patient anatomy, clinical situation, and physician preference.

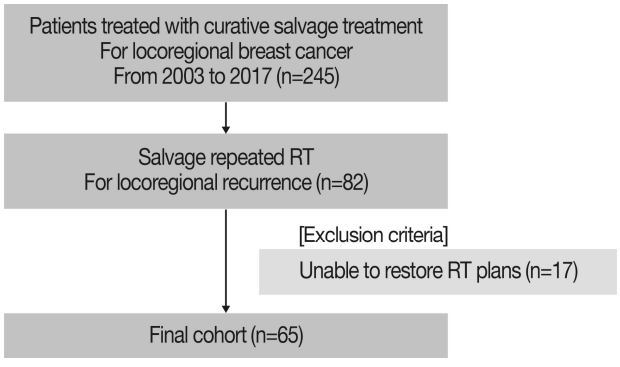


Fig. 1. Inclusion and exclusion criteria

Dosimetric analysis

First, all relevant plans were restored in our treatment planning system (Eclipse, Pinnacle, Raystation). Regional nodal areas were divided into 7 distinct subregions and retrospectively contoured per atlas suggested by Gross et al; 1) medial level I, 2) lateral level I, 3) level II and III, 4) axillary-lateral thoracic vessel junction (ALTJ), 5) lateral to ALTJ, 6) supraclavicular (SCV)/superior-medial region, 7) superior-lateral region[12]. The CT scans, dose distribution and the structure sets of all relevant courses were transferred from Pinnacle/Eclipse/Raystation to MIM software (Version6.4.9, MIM Software Inc, OH, USA). Doses of each course were converted to equivalent dose in 2 Gy per fraction (EQD2) with α/β ratio of 4. Then, initial and repeated RT plans for each patient were deformed and merged to calculate dose-volume histogram at nodal area. Max dose (Dmax), mean dose (Dmean), minimum dose (Dmin), and the percent volume of an organ that receives a radiation dose of n Gray or more (Vn Gy) of each subregion were calculated.

SAL evaluation

SAL was assessed by objective and subjective assessment. Breast surgeons, radiation oncologists, or medical oncologists evaluated the patients for arm lymphedema

at the follow-up visits. Patients who showed symptoms or features related to arm lymphedema were referred to physiatrists specializing in cancer rehabilitation. The attending physiatrist determined whether the patient had SAL based on symptoms and a physical examination with or without arm circumference measurements with a tape. SAL was categorized into four stages: stage 0 (clinically normal with abnormal lymph drainage), stage 1 (edema resolved by limb elevation), stage 2 (edema not resolved by limb elevation), and stage 3 (skin change with fibroadipose deposition).

Follow up and Statistical analysis

Pearson's chi-squared or Fisher's exact tests were performed to compare differences in categorical variables, and Mann-Whitney U test was used to compare differences in continuous variables between groups. SAL development after salvage treatment was the primary outcome. Time was calculated from the start date of salvage RT to the date of SAL diagnosis. Both SAL and censoring were evaluated at the final follow-up.

Maximally selected rank statistics were used to identify optimal cut points of each dosimetric parameter. Multivariable Cox proportional hazards model was performed including only clinical factors with $p<0.05$. A null multivariable Cox proportional hazards model was built including statistically significant clinical factors.

To evaluate whether adding dosimetric parameters to clinical factors improves the predictive power for SAL, each dosimetric parameter was sequentially incorporated into the null multivariable Cox proportional hazards model. Among the dosimetric parameters, those showing significant differences in distribution between the SAL and non-SAL groups were categorized according to their optimal cut points and included in the multivariable models. Separate multivariable models were constructed for each dosimetric parameter in combination with taxane-based chemotherapy. The Akaike information criterion (AIC) was used to identify the best-fitting model among these separate models for predicting SAL. The model with the lowest AIC value was selected as the final model.

Statistical significance was set at $p<0.05$. Analyses were performed using SPSS Statistics version 27.0 (IBM Corp, Armonk, NY, USA) and R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Patient and treatment characteristics are summarized in Table 1. Regarding the initial treatment course, the median age of patients at initial breast cancer diagnosis was 48 years (IQR, 27-67) and the median body mass index (BMI) was 23.5 kg/m^2 (IQR, 17.8-37.1). In total, 25 patients (38.5%) underwent mastectomy and 40 (61.5%) underwent breast conserving surgery; axillary lymph node dissection (ALND) was performed in 42 (64.6%) patients. RNI was administered in 31 (47.7%) patients. Among them, 9 cases included extended RNI. Taxane-based chemotherapy was performed in 42 (64.6%) cases.

About the recurrence, the sites of recurrence were local only in 18 patients (27.7%), regional lymph node only in 39 patients (60.0%), and both local and regional lymph node areas in 8 patients (12.3%). Salvage surgery was performed in 34 cases, including local excision only in 22 patients (33.9%) and mastectomy or axillary lymph node dissection in 12 patients (18.5%).

Fifty-nine patients (90.6%) underwent two courses of RT in total, whereas 6 patients (9.4%) received three courses. The salvage RT field included whole breast (WB) or chest wall (CW) only in 16 patients (24.6%), WB/CW plus axillary lymph nodes (ALN) in 9 patients (13.8%), and supraclavicular or internal mammary nodes in 40 patients (61.6%). True re-irradiation cases accounted for 47 patients (72.3%). The median cumulative irradiation dose was 109.0 Gy (IQR, 100.5–111.5). Salvage taxane-based chemotherapy was administered to 29 patients (44.6%).

Incidence of SAL

The median follow-up time after the completion of

Table 1. Characteristics of Patients (n=65)

Characteristics		N (%)
At initial treatment course		
Age at diagnosis, years	(continuous)	48 [27-67]
Age at relapse, years	(continuous)	65 [31-68]
BMI, Kg/m^2	(continuous)	23.5 [17.8-37.1]
Pathology	Ductal carcinoma in-situ	2 (3.1)
	Invasive cancer	63 (96.9)
Stage	Stage I/II	36 (55.4)
	Stage III	29 (44.6)
Type of breast surgery	Breast conserving surgery	40 (61.5)
	Mastectomy	25 (38.5)
Type of axillary surgery	No	1 (1.5)
	SLNB	22 (33.9)
	ALND	42 (64.6)
Reconstruction	No	59 (90.8)
	Yes	6 (9.2)
RT field	WB or CW	34 (52.3)
	WB or CW + limited RNI	22 (33.8)
	WB or CW + extended RNI	9 (13.9)
Initial RT dose, Gy	(continuous)	59.0 [50.0-60.5]
Taxane based chemotherapy	No	23 (35.4)
	Yes	42 (64.6)
Initial lymphedema	No	60 (92.3)
	Yes	5 (7.7)
At salvage treatment course		
Site of recurrence	Local alone (including skin)	19 (29.2)
	Regional + /-local	46 (70.8)
Salvage treatment	Surgery + RT ± CTx	34 (52.3)
	RT ± CTx	31 (47.7)
Extent of salvage surgery	None	31 (47.69)
	Local excision	20 (30.8)
	Mastectomy or ALND	14 (21.5)
Salvage taxane based chemotherapy	None	36 (55.4)
	Yes	29 (44.6)
Number of RT	2	59 (90.6)
	3	6 (9.4)
Salvage RT modality	3D-CRT	22 (33.8)
	Electron	2 (3.08)
	IMRT	18 (27.7)
	Proton beam therapy	9 (13.8)
	Tomotherapy	8 (12.3)
	3D-CRT -〉 3D-CRT	2 (3.0)
	Electron -〉 3D-CRT	1 (1.5)
	Electron -〉 PBT	1 (1.5)
	PBP -〉 PBT	1 (1.5)
	3D-CRT -〉 IMRT	1 (1.5)
Re-irradiation	No	18 (27.7)
	Yes	47 (72.3)
RT field containing ALN	No	47 (72.3)
	Yes	18 (27.7)
Total RT dose, Gy	(continuous)	109 [100.5-111.5]

*Values are presented as the number of patients (%) or the median [interquartile range].
Abbreviations: BMI,body mass index;SLNB, Sentinel lymph node biopsy;ALND, Axillary lymph node dissection;RT, radiotherapy; CTx, chemotherapy; WB, whole breast;CW, chestwall;RNI, regional nodal irradiation;3D-CRT, Three-Dimensional Conformal RT;IMRT,Intensity-modulated RT.

salvage treatment was 30.4 months (IQR, 19.3-52.5). Fifteen (23.1%) patients developed SAL after salvage

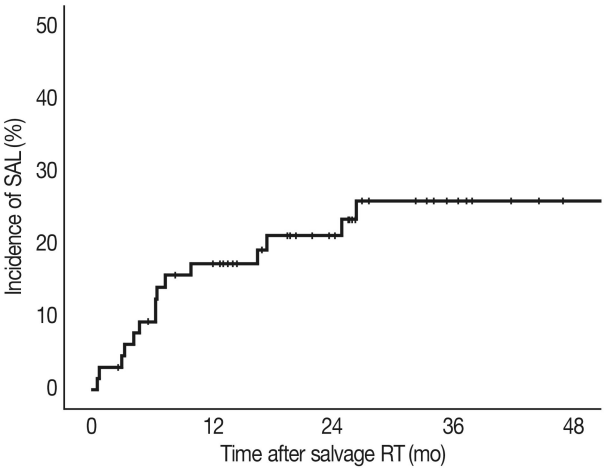


Fig. 2. Cumulative incidence of subsequent arm lymphedema (SAL).

Table 2. Incidence of Subsequent Arm Lymphedema

	Grade 0	Grade 1	Grade 2	Grade 3	Total
Lymphedema	2 (3.1)	1 (1.5)	12 (18.5)	0	15 (23.1)

Values are presented as number (%).
stage 0: clinically normal with abnormal lymph drainage
stage 1: edema resolved by limb elevation
stage 2: edema not resolved by limb elevation
stage 3: skin change with fibroadipose deposition

treatment. The median interval between salvage treatment and SAL occurrence was 6.4 months (IQR, 3.3–16.5). The one-year and two-year cumulative incidence rates SAL were 16.9% and 20.0%, respectively (Fig. 2). Most patients with SAL presented with stage 2 or 3 (N=12, 80%) (Table 2).

Predictive factors for SAL development

When comparing the dose distributions of each regional nodal region between the groups with and without SAL, significant differences were observed in these parameters; Dmean and Dmax of level II & III, Dmean, Dmax, V30 Gy, V40 Gy, V50 Gy of ALTJ, Dmean, Dmax, V30 Gy, V40 Gy, V50 Gy of lateral to ALTJ, Dmean, V30 Gy, V50 Gy of SCV/superiror-medial region, and V30 Gy, V40 Gy, V50 Gy of superior-lateral region (Table 3). For these parameters, the optimal cut-off points were analyzed.

In the univariable Cox regression analysis for identifying clinical predictive factors of SAL, BMI, salvage RT field including ALN region, and salvage taxane-based chemotherapy were found to be significant. In the multivariable analysis, only salvage taxane-based chemotherapy remained as an independent predictor (HR 4.2, 95% CI 1.06-16.54, P=0.04) (Table 4). Additionally, multiple multivariable Cox proportional hazards models were constructed to separately evaluate each significant dosimetric variable in combination with salvage taxane-based chemotherapy. These models were compared using the AIC to select the final model (Table 5). The model incorporating both lateral to ALTJ region D30 Gy ≥60% and taxane-based chemotherapy was identified as the final multivariable model for predicting SAL. Specifically, patients who received taxane-based chemotherapy had a significantly higher risk (HR=4.73, 95% CI=1.26-17.69, P=0.02), while those with V30 Gy ≥60% of the lateral to ALTJ region also demonstrated an elevated risk (HR=5.35, 95% CI=1.85-15.46, P=0.001).

DISCUSSION

In this study, we analyzed the incidence of SAL and identified dosimetric and clinical risk factors for developing SAL in patients undergoing salvage repeated RT for locoregionally recurrent breast cancer. We found that salvage taxane-based chemotherapy and lateral to ALTJ dose were the most significant factors associated with high SAL incidence. Given the limited knowledge about SAL after salvage repeated RT, this study provides important information on the incidence and risk factors for SAL in patients with locoregionally recurrent breast cancer.

The pathogenesis of lymphedema can be explained by mechanical insufficiency due to damage to lymphatic vessels, increased loading of lymphatic ducts, and disruption of normal lymphatic flow patterns. Treatment for breast cancer including surgery, RT, and chemotherapy may induce dysfunction in the lymphatic system, resulting in reduced lymphatic clearance and increased accumulation of protein-rich fluid, thereby

Table 3. Comparison of dosimetric parameters between Subsequent Arm Lymphedema (SAL) and Non-SAL Group

	Non-SAL group (n=50)	SAL group (n=15)	p
1. Medial level I region			
Dmax	51.60 (0.40-113.10)	70.60 (47.90-131.80)	0.08
Dmin	3.65 (0.40-51.70)	17.52 (1.40-77.50)	0.23
V30 Gy	47.38 (0-100)	92.08 (5.52-100)	0.09
V40 Gy	31.20 (0-100)	48.68 (2.92-100)	0.09
V45 Gy	17.76 (0-100)	32.03 (1.72-100)	0.09
V50 Gy	2.14 (0-100)	12.86 (0-100)	0.16
2. Lateral level I region			
Dmax	51.95 (0.400-122.40)	53.60 (41.50-133.40)	0.18
Dmin	11.82 (0.30-74.40)	21.41 (0.33-93.40)	0.26
V30 Gy	72.53 (0-100)	98.23 (21.62-100)	0.06
V40 Gy	60.09 (0-100)	67.97 (0.13-100)	0.18
V45 Gy	49.06 (0-100)	75.32 (0-100)	0.19
V50 Gy	10.51 (0-100)	14.25 (0-100)	0.31
3. Level II & III region			
Dmax	54.00 (0.50-104.60)	86.90 (27.00-136.30)	0.04
Dmean	39.75 (1.07-82.44)	47.30 (6.50-91.97)	0.04
Dmin	3.80 (0.30-51.10)	10.70 (1.30-52.10)	0.07
V30 Gy	79.60 (0-100)	95.22 (0-100)	0.10
V40 Gy	60.32 (0-100)	92.00 (0-100)	0.07
V45 Gy	48.70 (0-100)	82.19 (0-100)	0.12
V50 Gy	28.29 (0-100)	47.17 (0-100)	0.09
4. Axillary-Lateral Thoracic Vessel Junction (ALTJ) Region			
Dmax	46.20 (0.40-97.20)	60.10 (2.80-121.70)	0.02
Dmean	16.15 (0.74-62.88)	39.05 (1.61-66.86)	0.02
Dmin	2.60 (0.20-43.00)	3.50 (0.80-55.30)	0.11
V30 Gy	22.18 (0-100)	62.83 (0-100)	0.03
V40 Gy	7.4 7(0-100)	46.81 (0-100)	0.04
V45 Gy	0.56 (0-99.59)	13.79 (0-100)	0.03
V50 Gy	0 (0-90.15)	7.52 (0-100)	0.07
5. Lateral to ALTJ region			
Dmax	43.50 (0.30-98.30)	50.00 (3.00-114.90)	0.03
Dmean	10.12 (0.38-74.99)	36.55 (1.83-75.64)	0.01
Dmin	1.20 (0.10-36.20)	3.10 (0.20-30.40)	0.05
V30 Gy	8.58 (0-100)	50.43 (0-100)	0.02
V40 Gy	0.42 (0-99.66)	17.02 (0-98.09)	0.04
V45 Gy	0 (0-93.46)	14.34 (0-97.59)	0.03
V50	0 (0-81.43)	0 (0-96.64)	0.10
6. SCV/superior-medial region			
Dmax	51.80 (0.50-105.30)	59.0 (3.50-105.40)	0.05
Dmean	30.70 (0.25-83.47)	42.44 (1.13-79.77)	0.01
Dmin	2.30 (0.10-47.10)	3.580 (0.30-38.50)	0.07
V30 Gy	63.12 (0-100)	83.07 (0-100)	0.02
V40 Gy	55.67 (0-100)	74.09 (0-99.78)	0.03
V45 Gy	35.28 (0-100)	66.56 (0-99.15)	0.02
V50 Gy	5.37 (0-99.55)	18.25 (0-97.73)	0.03
7. Superior-lateral region			
Dmax	5.75 (0.20-54.60)	11.70 (0-106.90)	0.30
Dmean	1.88 (0-48.69)	3.24 (0.68-72.70)	0.05
Dmin	0.55 (0.10-39.20)	0.50 (0.10-28.60)	0.74
V30 Gy	0 (0-100)	0 (0-99.5)	0.04
V40 Gy	0 (0-99.93)	0 (0-98.58)	0.12
V45 Gy	0 (0-81.82)	0 (0-95.21)	0.15
V50 Gy	0 (0-58.95)	0 (0-92.14)	0.03

Abbreviations: Dmax, Max dose; Dmean, mean dose; Dmin, minimum dose, VnGy, the percent volume of an organ that receives a radiation dose of n Gray or more; ALTJ, Axillary-Lateral Thoracic Vessel Junction, SCV, supraclavicular.

Table 4. Risk Factors for Lymphedema (n=65)

		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P
At initial treatment course					
Age at diagnosis, yr	(continuous)	1.1 (0.95-1.06)	0.66		
BMI, Kg/m^2	(continuous)	1.2 (1.05-1.47)	0.01	1.2 (0.97-1.40)	0.09
Type of breast surgery	BCS	-	-		
	Mastectomy	2.7 (0.96-7.61)	0.06		
Type of axillary surgery	No	-			
	SLNB	6.5 (0-22.08)	0.96		
	ALND	9.5 (0-32.48)	0.96		
No of dissected node, initial	〈10	-	-		
	≥10	2.4 (0.60-7.46)	0.18		
RT field	WB or CW	-			
	WB(CW) + limited RNI	0.9 (0.27-3.17)	0.91		
	WB (CW) + extended RNI	2.1 (0.62-7.26)	0.23		
Taxane based CTx	No	-			
	Yes	2.2 (0.62-7.88)	0.22		
Initial lymphedema	No	-			
	Yes	2.2 (0.49-9.82)	0.29		
At salvage treatment course					
Age at relapse, years	(continuous)	1.1 (0.96-1.07)	0.47		
Disease free interval	(continuous)	1.1 (0.98-1.01)	0.71		
Patterns of LRR	Local	-			
	Regional ± Local	1.1 (0.35-3.49)	0.86		
Salvage ALND	No	-			
	Local excision	1.2 (0.42-3.77)	0.67		
	TM or ALND	0.6 (0.14-3.24)	0.62		
No of dissected node, salvage	〈10	-	-		
	≥10	0.51 (0.06-3.87)	0.51		
No of dissected node, total	〈10	-	-		
	≥10	4.3 (0.57-33.11)	0.16		
Re-RT	No	-			
	Yes	1.6 (0.47-5.96)	0.42		
Salvage RT covering ALN	No	-			
	Yes	3.0 (1.15-8.89)	0.03	1.6 (0.54-4.76)	0.38
Salvage taxane CTx	No	-			
	Yes	6.3 (1.76-22.92)	0.01	4.2 (1.06-16.54)	0.04

Abbreviations: BMI,body mass index;BCS, breast conserving surgery;SLNB, Sentinel lymph node biopsy;ALND, Axillary lymph node dissection;RT, radiotherapy;WB, whole breast;CW, chestwall;RNI, regional nodal irradiation;CTx, chemotherapy;LRR, locoregional recurrence;TM, total mastectomy;ALN, axillary lymph node

leading to lymphedema in susceptible patients[8,14-16]. RT, particularly RNI, can lead to fibrosis, anastomosis stenosis, or complete obstruction of lymphatic vessels. In our study, SAL events were developed in a larger proportion and within a shorter interval after salvage treatment compared to what would be expected after initial treatment alone. While lymphatic fibrosis is considered a late-effect toxicity, we interpret these early-onset cases as a consequence of a lymphatic system already substantially compromised by prior initial treatments. In this setting of cumulative lymphatic injury, the addition of salvage RT or taxane based chemotherapy likely acted as the final precipitating factor[17-19].

Meanwhile, the association between taxane-based chemotherapy and lymphedema risk has been consistently reported in previous studies. Our finding that salvage taxane-based systemic therapy was an independent clinical factor associated with high SAL incidence

Table 5. Construction of Final Multivariable Model to Predict Lymphedema Risk

Model variables	AIC
Salvage taxane chemotherapy (Null model)	109.033
Null + level II & III Dmax ≥97 Gy Null + level II & III Dmean ≥66 Gy	105.141
Null + ALTJ Region DMax, ≥72 Gy Null + ALTJ Region DMean, ≥33.6 Gy Null + ALTJ Region V30 Gy ≥49.5% Null + ALTJ Region V40 Gy ≥14% Null + ALTJ Region V45 Gy ≥10%	101.389
Null + Lateral to ALTJ Region DMax, ≥84.9 Gy Null + Lateral to ALTJ Region DMean, ≥32.9 Gy Null + Lateral to ALTJ Region V30 Gy ≥60% Null + Lateral to ALTJ Region V40 Gy ≥44% Null + Lateral to ALTJ Region V45 Gy ≥35%	105.619
Null + SCV/Superior-Medial Region DMean ≥39.81 Gy Null + SCV/Superior-Medial Region V30 Gy ≥75% Null + SCV/Superior-Medial Region V40 Gy ≥70% Null + SCV/Superior-Medial Region V45 Gy ≥10% Null + SCV/Superior-Medial Region V50 Gy ≥28%	104.772
Null + Superior-Lateral Region V30 Gy ≥2% Null + Superior-Lateral Region V50 Gy ≥0.1%	104.835

Abbreviations: Dmax, Max dose; Dmean, mean dose; Dmin, minimum dose, VnGy, the percent volume of an organ that receives a radiation dose of n Gray or more; ALTJ, Axillary-Lateral Thoracic Vessel Junction, SCV, supraclavicular.

(HR 4.2, 95% CI 1.06-16.54, P=0.04) is consistent with existing literature. Taxane-based chemotherapy is considered to result in fluid retention due to increased capillary permeability and anti-endothelial proliferation through antiangiogenic effects. If not prevented or treated early, this increased lymphatic loading can aggravate the mechanical insufficiency of existing lymphatic ducts already compromised by surgery and prior RT. In the salvage setting, where patients have already experienced cumulative lymphatic damage, the addition of taxane therapy may represent a critical threshold that precipitates clinically apparent lymphedema. Therefore, patients who receive taxane-based chemotherapy in the salvage setting may require more frequent monitoring, and early consultation with rehabili- tation specialists may be beneficial for appropriate management[20-22].

Our comprehensive analysis of seven regional nodal subvolumes identified the lateral to ALTJ region as a critical organ at risk for SAL development. Previous research has emphasized the importance of the ALTJ region in lymphedema development. Gross et al. first identified dosimetric predictors of lymphedema risk and demonstrated that multiple regional nodal subvolumes were associated with lymphedema, particularly noting that ALTJ Dmean >36.8 Gy had the most significant effect on lymphedema development[12].

Subsequently, Park et al. validated these findings and developed a multivariable normal tissue complication probability (NTCP) model, identifying ALTJ V35 (>39.9% vs ≤39.9%) as one of the most important factors influencing lymphedema after RT[23]. In breast cancer patients, the radiation dose to the ALTJ is closely associated with the risk of lymphedema because this region anatomically contains the main lymphatic vessels draining the upper extremity. Since the ALTJ is located along the principal outflow pathway, high-dose irradiation to this region can cause lymphatic injury and fibrosis, impairing lymphatic flow and ultimately inducing lymphedema.

The possible reason why lateral to ALTJ region has been shown to correlate most significantly with SAL in the current study, beyond the ALTJ lies in the anatomical and functional diversity of lymphatic pathways. The lateral region also contains lymphatic vessels from the arm and chest wall, and when conventional drainage routes are damaged, alternative lymphatic drainage pathways become more important. High radiation dose to this lateral region may compromise these compensatory pathways, leading to increased lymphedema risk. The lower threshold identified (V30 Gy ≥60%) may reflect the increased sensitivity of already compromised lymphatic systems[12,16,24-27]. Another hypothesis is inaccuracy during the fusion process. There were set-up differences and change of body shape between interval. Although we performed deformable fusion, the dose distribution may not have been calculated with complete accuracy. Therefore, it is possible that the lateral to ALTJ region appeared as the most significant factor, rather than the ALTJ region itself.

Our final multivariable model incorporating both lat-

eral to ALTJ V30 Gy ≥60% and salvage taxane-based chemotherapy provides a practical tool for risk stratification. A lymphedema risk was significantly lower when patients had no risk factors (SAL 0%) and progressively higher with increasing numbers of risk factors (SAL, 40.1% with one risk factor, 66.7% with two risk factors, $p<0.001$). This risk stratification could inform clinical decision-making in several ways. For high-risk patients, more intensive surveillance protocols could be implemented, including baseline and serial limb volume measurements, early referral to lymphedema specialists, and prophylactic interventions. Additionally, when possible, treatment modifications such as limiting the lateral extension of radiation fields or considering alternative chemotherapy regimens might be appropriate for very high-risk patients.

Based on our findings, incorporating dose constraints for the lateral to ALTJ region (specifically, limiting V30 Gy to <60%) should be considered when planning salvage repeated RT for locoregionally recurrent breast cancer. Modern radiation techniques such as IMRT or volumetric modulated arc therapy may be particularly valuable in achieving these dose constraints while maintaining adequate target coverage. The identification of specific dosimetric thresholds provides radiation oncologists with quantitative guidance for treatment planning optimization. However, the balance between lymphedema risk reduction and adequate disease control must be carefully considered, as compromising target coverage to reduce lymphedema risk could potentially impact locoregional control outcomes.

To our knowledge, this analysis represents the first study to examine dosimetric parameters by generating accumulated EQD2 of all relevant RT courses in the salvage repeated RT setting for locoregionally recurrent breast cancer. However, several limitations must be acknowledged. First, the relatively small sample size may have reduced statistical power for detecting associations with some variables. Larger multi-institutional studies would provide more robust validation of our findings. Second, the retrospective nature and lymphedema assessment methods may have led to underestimation of asymptomatic lymphedema cases. Although we incorporated both subjective and objective assessment methods, prospective studies with standardized measurement protocols would provide more accurate incidence data. Third, as the maximally selected rank statistics method used to determine the optimal cut-point for a continuous variable entail multiple testing, the associated effect size may be overestimated and the statistical significance inflated. Therefore, external validation using an independent dataset is warranted to enhance generalizability. Fourth, this study has the inherent risk of multiple testing due to the comprehensive evaluation of numerous dosimetric parameters and anatomical subregions. This extensive exploration may have increased the likelihood of reporting false-positive findings by chance. Consequently, the interpretation of the identified dosimetric predictors requires careful consideration and independent validation in future studies. Fifth, some error in dose calculation may have occurred due to differences in patient positioning and anatomy between initial and salvage RT. Finally, our dose-volume histogram analysis, while comprehensive, does not identify specific anatomical structures or lymphatic pathways that are most critical for lymphedema development. Future studies incorporating lymphatic imaging or more detailed anatomical modeling may provide additional insights.

In conclusion, salvage repeated RT was associated with a SAL incidence of 23.1% in this cohort. Salvage taxane-based chemotherapy and lateral to ALTJ V30 Gy ≥60% were associated with an increased SAL risk. The observed association suggests that incorporating dose constraints (V30 Gy <60%) for the lateral to ALTJ region may warrant careful consideration in future treatment planning. Early rehabilitation consultation is recommended for high-risk patients identified through this preliminary risk stratification. These findings offer initial guidance for optimizing care in the challenging salvage treatment setting.

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