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The influence of axillary surgery and radiotherapeutic strategy on the risk of lymphedema and upper extremity dysfunction in early breast cancer patients

Si-Yue Zheng [a,1], Chu-Ying Chen [a,b,1], Wei-Xiang Qi [a], Gang Cai [a], Cheng Xu [a], Rong Cai [a], Xiao-Fang Qian [a], Kun-Wei Shen [c], Lu Cao [a,**], Jia-Yi Chen [a,*]

[a] Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[b] Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, China
[c] Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

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ABSTRACT

Purpose: To explore the risk factors for breast cancer-related lymphedema (BCRL) and upper extremity dysfunction (UED) in patients with early breast cancer after modern comprehensive treatment and to compare the toxicity of different treatment strategies.

Methods: From 2017 to 2020, a total of 1369 female patients with pT1-3N0-1M0 breast cancer who underwent adjuvant radiotherapy in our centre were retrospectively reviewed. BCRL and UED were identified by the Norman and QuickDASH questionnaires. The incidence, severity and risk factors for BCRL and UED were evaluated.

Results: After a median follow-up of 25 months, a total of 249 patients developed BCRL; axillary lymph node dissection (ALND), increased number of dissected nodes, right-sided and hypofractionated radiotherapy containing RNI were found to be significant risk factors (all p values < 0.05). The sentinel lymph node biopsy (SLNB)+ regional nodal irradiation (RNI) group had a significantly lower BCRL risk than the ALND + RNI group (10.8% vs. 32.5%, HR = 0.426, p = 0.020), while there was no significant difference between ALND vs. ALND + RNI or SLNB vs. SLNB + RNI. A total of 193 patients developed UED, and ALND (p = 0.02) was the only significant risk factor. The SLNB + RNI group had a significantly decreased risk of UED compared with the ALND + RNI group (7.5% vs. 23.9%, HR = 0.260, p = 0.001), and there was no significant difference between SLNB vs. SLNB + RNI or ALND vs. ALND + RNI.

Conclusion: Aggressive ALND remains the primary risk factor for BCRL and UED while RNI does not. Thus, replacing ALND with tailored radiotherapy would be an effective preventive strategy in early breast cancer patients.

1. Introduction

Breast cancer–related lymphedema (BCRL) and shoulder mobility disorder represent the most frequent upper-extremity toxicities of operable breast cancer. Aggressive local regional therapy, including axillary lymph node dissection (ALND) and regional nodal irradiation (RNI), has been well recognized as risk factors, and systemic therapy, such as taxane-based chemotherapy, has also been documented as a risk factor [1,2].

The new paradigm of surgery and radiotherapy has resulted in a lower complication rate. The AMAROS trial, which compared ALND with sentinel lymph node biopsy (SLNB) plus axillary radiotherapy (ART) in cN0/SLN + patients, revealed that the increase >10% in the arm circumference in the SLNB + ART group was significantly lower than that in the ALND group at 5 years (24.5% vs. 11.9%, p < 0.001), with a low number of axillary recurrences in both groups (10-year cumulative incidence in ALND vs. ART: 0.93% vs. 1.82%, HR = 1.71) [3]. The prospective study of Naoum et al. enrolled 1815 patients from 2005

* Corresponding author.
** Corresponding author.
E-mail addresses: cl11879@rjh.com.cn (L. Cao), cjy11756@rjh.com.cn (J.-Y. Chen).
[1] These authors contributed equally to this work and should be considered co-first authors.

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to 2018, and the 5-year BCRL rates in the ALND group were significantly higher than those in the SLNB + RNI group (24.9% vs. 10.7%, p = 0.02) with comparable local control rates [4].

However, most of the previous studies defined the application of RNI as a binary variable, which made it difficult to determine the relationship among radiotherapy to the supraclavicular, internal mammary, and axillary lymph node fields and BCRL risk. A study by Gross et al. including 526 patients from 1999 to 2013 found that radiotherapy in the upper level I and II axilla after ALND conferred a higher risk of BCRL [5]. Gross et al. also analysed the data from the MA20 trial and found that extensive RNI to the full axilla was one of the risk factors for BCRL [6]. Nevertheless, the majority of SLN-positive patients routinely underwent ALND during the period of the above two studies, while ART was only applied when too few lymph nodes were removed or more than 3 lymph nodes were positive [7]. Since omitting ALND for breast cancer patients with a limited nodal burden has been acknowledged following the results of the Z0011 and AMAROS trials, the effect of RNI on BCRL with evolving surgical practice remains unclear [3,8].

To date, there is no sufficient data supporting the potential of decreasing upper extremity toxicities with de-escalation of axillary surgery followed by RNI in the Chinese population. Therefore, our study sought to quantify the incidence and severity of BCRL and upper extremity dysfunction (UED) among Chinese patients receiving different local-regional treatment modalities and to explore the associated risk factors.

2. Methods and materials

2.1. Patients

Data from female breast cancer patients who underwent definitive surgery followed by adjuvant radiotherapy from June 2017 to June 2020 at Ruijin Hospital were retrospectively collected. Eligible patients were women with invasive breast cancer who were aged ≥18 years, underwent mastectomy or breast-conserving surgery (BCS), underwent SLNB or ALND, were in stage pT1-3N0-1M0 according to the American Joint Committee on Cancer (8th edition), and received adjuvant radiotherapy to the breast or chest wall with or without RNI. We excluded male patients, patients who received neoadjuvant therapy, had bilateral breast cancer, had T4 tumours, had more than 3 positive nodes, had distant metastasis and patients unable to complete the questionnaires.

2.2. Radiotherapy

The dose to the breast or chest wall with or without RNI was 50 Gy in 25 fractions over 5 weeks for conventional fractionated radiotherapy (CFRT) with a boost radiation of 10 Gy in 5 fractions to the tumor bed for most patients after BCS and 40 Gy in 15 fractions over 3 weeks for hypofractionated radiotherapy (HFRT) with a boost of 10 Gy in 4 fractions. RNI included supraclavicular (SCV) ± internal mammary node (IMN)± ART (only for SLN-positive patients who did not undergo ALND). The addition of RNI and the type of fractionation were determined by the physicians and the randomization of the HARVEST trial (NCT03829553) for the participating patients. The volume delineation and definition of the breast or chest wall were based on the Radiation Therapy Oncology Group (RTOG) contouring guidelines [9]. The contouring of RNI was in accordance with our previous report [10]. The dose volume constraints of normal tissue and the target volume were in accordance with the protocol of the HARVEST trial (NCT03829553) [11].

2.3. BCRL and UED definitions

The Norman questionnaire was distributed to the enrolled patients, which has been validated as a detection tool for BCRL using self-reported symptoms [12]. In the questionnaire, the patients reported whether there were size differences in their hands, lower arms, and upper arms and, if so, they reported the date when the swelling was noticed. The degree of swelling was divided as follows: slight, which was defined as only the patient would notice it, with 1 point; noticeable, which was defined as being able to be noticed by close people but not strangers, with 2 points; and very noticeable, which was defined as being able to be noticed by strangers, with 3 points. The total score ranges from 0 to 9 points, and the diagnosis is 1–3 points for mild BCRL, 4–6 points for moderate BCRL, and 7–9 points for severe BCRL [13].

The short-form of the Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire was also distributed to the enrolled patients. It included 6 items about the difficulty in performing different physical activities, 2 items about the severity of pain, and 3 items about the effect on daily life of upper extremity problems. The patients rated the difficulty or severity of the 11 questions as none, mild, moderate, severe or extreme based on their current state. The score ranges from 0 to 100. A higher score reflects more severe UED, and the cut-off scores are 0–15 for normal, 16–40 for having problems but working, and more than 40 for being unable to work [14]. The DASH/QuickDASH questionnaire is a well-characterized instrument for upper extremity assessment. It has been validated in the general population, especially for breast cancer survivors [15].

2.4. Statistical analysis

Baseline characteristics of each group and the whole cohort were described. Using the Kaplan−Meier method, the cumulative incidence of BCRL in the 4 treatment groups was calculated from the day of surgery to the day when patients recognized BCRL. Cox regression and logistic regression were used to investigate the factors associated with BCRL and UED, in which factors with $p < 0.1$ in univariate analysis were included in multivariate analysis, and two-sided $P < 0.05$ was considered statistically significant. Controlling for the discovered risk factors, Cox regression and logistic regression were performed for the comparison of the BCRL and UED outcomes of the 2 subgroups among the 4 treatment groups, and $p < 0.025$ was considered statistically significant after Bonferroni correction. Descriptive analysis reflected the proportions of BCRL and UED cases of different severities among the 4 treatment strategies. All statistical analyses were performed by SPSS version 23.0 and R version 4.0.3.

3. Results

From June 2017 to June 2020, a total of 1369 female patients with pT1-3N0-1M0 breast cancer treated with adjuvant radiotherapy were enrolled in our study. The median follow-up duration was 25 months (interquartile range [IQR] 15–35 months). The median age was 53 years (range 22–88 years), and the median body mass index (BMI) was 23.11 kg/m2 (IQR 21.16–25.31 kg/m2). Among these patients, 751 (54.9%) underwent SLNB + WBI, 93 (6.8%) underwent SLNB + RNI, 39 (2.8%) underwent ALND + WBI, and 486 (35.5%) underwent ALND + RNI. The baseline characteristics of each group and the whole cohort are listed in Table 1.

With a median follow-up of 25 months, 249 people (18.2%) developed BCRL among the entire cohort, which comprised 74 (9.85%) of 751 patients in the SLNB group, 10 (10.75%) of 93 patients in the SLNB + RNI group, 7 of 39 (17.95%) patients in the ALND group, and 158 of 486 (32.51%) patients in the ALND + RNI group. The cumulative incidence of BCRL stratified by treatment groups is presented in Fig. 1.

In univariate analysis, mastectomy, right-sided breast cancer, tumor in the lateral quadrant, larger tumor, ALND, greater number of positive or dissected nodes, use of chemotherapy or anti-HER2 targeted therapy, SCV or IMN irradiation, and HFRT containing RNI were associated with BCRL with P values of <0.1. Multivariable logistic regression identified right-sided breast cancer, ALND, greater number of dissected nodes, and HFRT containing RNI as significant predictors of BCRL (all $p < 0.05$)

Table 1
Baseline characteristics of all patients.

	SLNB + WBI	n = 751 (54.9%)	SLNB + RNI	n = 93 (6.8%)	ALND + WBI	n = 39 (2.8%)	ALND + RNI	n = 486 (35.5%)	Overall	n = 1369
	N or median	% or IQR	N or median	% or IQR	N or median	% or IQR	N or median	% or IQR	N or median	% or IQR
Age (y)	54	45–63	50	40–60	49	40–60	53	45–63	53	45–63
BMI (kg/m2)	23.1	21.1–25.5	23.2	20.9–24.4	23.9	21.7–25.4	22.9	21.1–25.1	23.1	21.2–25.3
Menopausal status										
Premenopausal	327	43.5%	49	52.7%	18	46.2%	199	40.9%	593	43.3%
Postmenopausal	424	56.5%	44	47.3%	21	53.8%	287	59.1%	776	56.7%
Surgery type										
Mastectomy	0	0.0%	18	19.4%	0	0.0%	399	82.1%	417	30.5%
Lumpectomy	751	100.0%	75	80.6%	39	100.0%	87	17.9%	952	69.5%
Tumor laterality										
Left	384	51.1%	47	50.5%	20	51.3%	256	52.7%	707	51.6%
Right	367	48.9%	46	49.5%	19	48.7%	230	47.3%	662	48.4%
Tumor location										
Lateral	425	56.6%	62	66.7%	24	61.5%	305	62.8%	816	59.6%
Median or central	326	43.4%	31	33.3%	15	38.5%	181	37.2%	553	40.4%
Tumor size (cm)	1.2	1.2–2.0	1.8	1.5–2.5	1.5	1.1–1.8	2.5	1.7–3.0	1.9	1.4–2.5
No. of positive nodes										
0	740	99.5%	7	7.5%	38	97.4%	9	1.9%	794	58.0%
1	11	0.5%	63	67.7%	1	2.6%	241	49.6%	316	23.1%
2	0	0.0%	21	22.6%	0	0.0%	148	30.5%	169	12.3%
3	0	0.0%	2	2.2%	0	0.0%	88	18.1%	90	6.6%
No. of dissected nodes	4	3–5	5	3–6	13	10–17	18	14–22	6	3–16
Histologic type and grade										
IDC Grade 1	82	10.9%	4	4.3%	5	12.8%	15	3.1%	106	7.7%
IDC Grade 2	382	50.9%	56	60.2%	17	43.6%	257	52.9%	712	52.0%
IDC Grade 3	209	27.8%	29	31.2%	13	33.3%	171	35.2%	422	30.8%
Others	78	10.4%	4	4.3%	4	10.3%	43	8.8%	129	9.4%
Histologic type and grade										
Luminal A	188	25.0%	16	17.2%	11	28.2%	63	13.0%	278	20.3%
Luminal B (HER2-)	340	45.3%	51	54.8%	14	35.9%	231	47.5%	636	46.5%
Luminal B (HER2+)	62	8.3%	9	9.7%	4	10.3%	64	13.2%	139	10.2%
HER2 positive	42	5.6%	7	7.5%	4	10.3%	70	14.4%	123	9.0%
Triple negative	119	15.8%	10	10.8%	6	15.4%	58	11.9%	193	14.1%
Chemotherapy										
No	294	39.1%	7	7.5%	12	30.8%	13	2.7%	326	23.8%
Yes	457	60.9%	86	92.5%	27	69.2%	473	97.3%	1043	76.2%
Hormonal therapy										
No	160	21.3%	19	20.4%	9	23.1%	130	26.7%	318	23.2%
Yes	591	78.7%	74	79.6%	30	76.9%	356	73.3%	1051	76.8%
Herceptin										
No	652	86.8%	78	83.9%	31	79.5%	355	73.0%	1116	81.5%
Yes	99	13.2%	15	16.1%	8	20.5%	131	27.0%	253	18.5%
SCV radiation										
No	751	100.0%	4	4.3%	39	100.0%	0	0.0%	794	58.0%
Yes	0	0.0%	89	95.7%	0	0.0%	486	100.0%	575	42.0%
IMNI										
No	751	100.0%	33	35.5%	39	100.0%	128	26.3%	951	69.5%
Yes	0	0.0%	60	64.5%	0	0.0%	358	73.7%	418	30.5%
ART										
No	751	100.0%	23	24.7%	39	100.0%	484	99.6%	1297	94.7%
Yes	0	0.0%	70	75.3%	0	0.0%	2	0.4%	72	5.3%
Fractionation										
CFRT	85	11.3%	84	90.3%	7	17.9%	395	81.3%	571	41.7%
HFRT-WBI	666	88.7%	0	0.0%	32	82.1%	0	0.0%	698	51.0%
HFRT-RNI	0	0.0%	9	9.7%	0	0.0%	91	18.7%	100	7.3%

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RNI, regional nodal irradiation; WBI, whole breast irradiation; IQR, interquartile range; BMI, body mass index; IDC, invasive ductal carcinoma; SCV, supraclavicular; IMNI, internal mammary node irradiation; ART, axillary radiotherapy; CFRT, conventional fractionated radiotherapy; HFRT, hypofractionated radiotherapy; WBI, whole breast irradiation.

(Table 2).

Taking into account the risk of BCRL with different treatment strategies, a multivariate Cox regression model was performed to control the above risk factors, including tumor laterality, number of dissected lymph nodes, and fractionation of radiotherapy. There was no significant difference between the SLNB group and the SLNB + RNI group (HR = 1.781, p = 0.233) or between the ALND + RNI group and the ALND group (HR = 0.381, p = 0.066). The SLNB + RNI group had a significantly lower BCRL risk than the ALND + RNI group (HR = 0.426, p = 0.020) (Table 3).

A total of 193 (14.1%) of 1369 patients developed UED at the last follow-up. Univariate analysis showed that the factors associated with UED included mastectomy, tumor in the lateral quadrant, larger tumor, ALND, greater number of positive or dissected nodes, use of chemotherapy, SCV or IMN irradiation, and HFRT containing RNI (all $p < 0.1$). ALND was the only independent predictor of UED in multivariate analysis (p = 0.013) (Table 4).

Since ALND was the only factor contributing to UED, a univariate logistic regression model was used to compare treatment strategies in pairs. The addition of RNI had no significant effect on the occurrence of

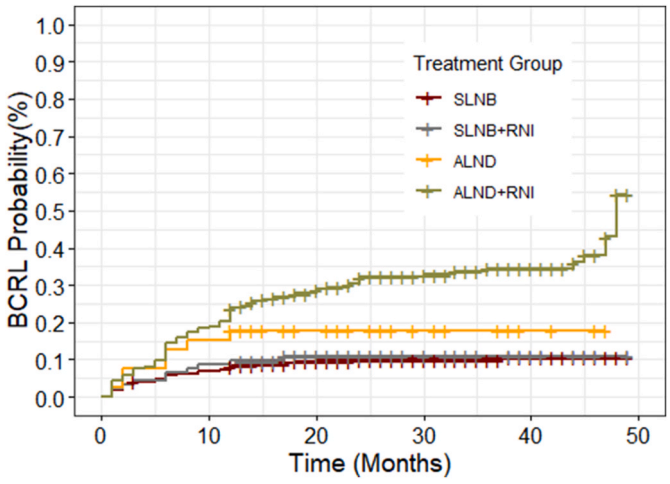

Fig. 1. The cumulative incidence of BCRL stratified by treatment groups. BCRL, breast cancer-related lymphedema; SLNB, sentinel lymph node biopsy; RNI, regional nodal irradiation; ALND, axillary lymph node dissection.

UED in patients receiving SLNB (HR = 0.831, p = 0.654). Although the ALND-only group had lower UED than the ALND + RNI group, the advantage was not significant after Bonferroni correction (HR = 0.266, p = 0.030). For patients with RNI, the type of axillary surgery made a difference, as the SLNB + RNI group had a significantly decreased risk of UED compared with the ALND + RNI group (HR = 0.260, p = 0.001) (Table 5).

The incidence and severity of BCRL and UED according to the treatment strategies are presented in Fig. 2A and B. The proportions of moderate to severe BCRL in the four groups increased sequentially and were 1.7%, 2.2%, 7.7% and 10.7% in the SLNB + WBI, SLNB + RNI, ALND + WBI and ALND + RNI groups, respectively. In the SLNB + WBI group, 61 patients developed mild BCRL, 11 developed moderate BCRL, and 2 developed severe BCRL. In the SLNB + RNI group, 8 and 2 patients developed mild and moderate BCRL, respectively, while none of the patients had severe BCRL. In the ALND + WBI group, there were 4 patients with mild BCRL, 2 with moderate BCRL, and 1 with severe BCRL. In the ALND + RNI group, 106 patients had mild BCRL, 37 had moderate BCRL, and 15 had severe BCRL. The proportion of patients with severe UED in the ALND + RNI group was higher than that in the other groups. There were 53, 6, 3 and 86 patients who had mild UED, which corresponded to having problems but working on the Quick-DASH questionnaire, in the SLNB + WBI, SLNB + RNI, ALND + WBI and ALND + RNI groups, respectively. There were 14, 1, 0 and 30 patients who developed severe UED, which corresponded to inability to work in the Quick-DASH questionnaire, which accounted for 1.9%, 1.1%, 0% and

Table 3
Multivariable BCRL cox proportional hazards regression model results.

Treatment group comparison	HR	95%CI	P value
SLNB VS SLNB + RNI	1.781	0.690–4.600	0.233
ALND + RNI VS SLNB + RNI	0.426	0.208–0.872	0.020
ALND + RNI VS ALND	0.381	0.136–1.066	0.066

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RNI, regional nodal irradiation.

Table 2
Factors associated with BCRL according to cox regression analysis.

Variable	Univariate Analysis			Multivariate Analysis		
	Odds	95%CI	P value	Odds	95%CI	P value
Surgery			< 0.001			0.349
Mastectomy	Ref.			Ref.		
Lumpectomy	0.357	0.278–0.457		0.822	0.546–1.238	
Tumor laterality			0.064			0.047
Left	Ref.			Ref.		
Right	1.266	0.987–1.624		1.289	1.003–1.656	
Tumor location			0.063			0.142
Lateral	Ref.			Ref.		
Median or central	0.781	0.602–1.014		0.819	0.627–1.069	
Tumor size (cm)	1.152	1.032–1.286	0.012	0.920	0.803–1.053	0.225
Axillary surgery			< 0.001			0.023
SLNB	Ref.			Ref.		
ALND	3.416	2.626–4.444		1.937	1.095–3.426	
No. of positive nodes			< 0.001			0.664
0	Ref.			Ref.		
1	2733	2.017–3.703	< 0.001	1.712	0.641–4.571	0.283
2	3.099	2.180–4.406	< 0.001	1.780	0.640–4.952	0.269
3	3.738	2.484–5.625	< 0.001	1.944	0.681–5.548	0.214
No. of dissected nodes	1.063	1.050–1.077	< 0.001	1.024	1.001–1.047	0.039
Chemotherapy			0.001			0.911
No	Ref.			Ref.		
Yes	1.851	1.300–2.636		1.024	0.680–5.548	
Herceptin			0.097			0.952
No	Ref.			Ref.		
Yes	1.286	0.955–1.733		1.009	0.741–1.375	
SCV radiation			< 0.001			0.797
No	Ref.			Ref.		
Yes	2.933	2.253–3.818		0.850	0.245–2.947	
IMNI			< 0.001			0.612
No	Ref.			Ref.		
Yes	2.435	1.898–3.125		1.101	0.760–1.595	
Fractionation			< 0.001			0.043
CFRT	Ref.			Ref.		
HFRT-WBI	0.459	0.346–0.609		1.558	0.748–3.248	0.236
HFRT-RNI	1.925	1.340–2.764		1.527	1.049–2.224	0.027

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; SCV, supraclavicular; IMNI, internal mammary node irradiation; CFRT, conventional fractionated radiotherapy; HFRT, hypofractionated radiotherapy; WBI, whole breast irradiation; RNI, regional nodal irradiation.

Table 4
Factors associated with UED according to logistic regression analysis.

Variable	Univariate Analysis			Multivariate Analysis		
	Odds	95%CI	P value	Odds	95%CI	P value
Surgery			< 0.001			0.109
Mastectomy	Ref.			Ref.		
Lumpectomy	0.352	0.258–0.480		0.638	0.368–1.105	
Tumor location			0.083			0.144
Lateral	Ref.			Ref.		
Median or central	0.755	0.549–1.038		0.780	0.560–1.088	
Tumor size (cm)	1.165	1013–1.341	0.032	0.944	0.798–1.117	0.503
Axillary surgery			< 0.001			0.013
SLNB	Ref.			Ref.		
ALND	3.050	2.228–4.175		2.436	1.209–4.908	
No. of positive nodes			< 0.001			0.378
0	Ref.			Ref.		
1	2.338	1.609–3.396	< 0.001	1.880	0.617–5.726	0.266
2	3.055	1.981–4.710	< 0.001	2.359	0.731–7.618	0.151
3	3.703	2.186–6.272	< 0.001	2.587	0.765–8.748	0.126
No. of dissected nodes	1.051	1.033–1.069	< 0.001	0.987	0.956–1.018	0.401
Chemotherapy			0.030			0.631
No	Ref.			Ref.		
Yes	1.545	1.042–2.289		0.893	0.562–1.418	
SCV radiation			< 0.001			0.842
No	Ref.			Ref.		
Yes	2.673	1.951–3.660		1.172	0.246–5.577	
IMNI			< 0.001			0.679
No	Ref.			Ref.		
Yes	2.316	1.699–3.158		1.109	0.680–1.806	
Fractionation			< 0.001			0.207
CFRT	Ref.			Ref.		
HFRT-WBI	0.496	0.357–0.690	< 0.001	2.495	0.884–7.045	0.084
HFRT-RNI	1.373	0.823–2.293	0.225	1.118	0.654–1.910	0.684

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; SCV, supraclavicular; IMNI, internal mammary node irradiation; CFRT, conventional fractionated radiotherapy; HFRT, hypofractionated radiotherapy; WBI, whole breast irradiation; RNI, regional nodal irradiation.

Table 5
Univariable UED logistic regression model results.

Treatment group comparison	HR	95%CI	P value
SLNB VS SLNB + RNI	0.831	0.370–1.868	0.654
ALND + RNI VS SLNB + RNI	0.260	0.117–0.577	0.001
ALND + RNI VS ALND	0.266	0.080–0.879	0.030

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RNI, regional nodal irradiation.

6.2% in the SLNB + WBI, SLNB + RNI, ALND + WBI and ALND + RNI groups, respectively.

4. Discussion

BCRL and UED are common treatment-related adverse effects for breast cancer patients that remain barriers to improving the long-term quality of life of patients [1,2]. Our study is one of the first studies focusing on the incidences of BCRL and UED and the associated risk factors among Chinese patients in the context of modern treatment strategies. In our study, the cumulative incidence rates of BCRL in the SLNB + WBI, SLNB + RNI, ALND + WBI, and ALND + RNI groups were 9.9%, 10.8%, 18.0%, and 32.5%, respectively, and the cumulative incidences of UED were 8.9%, 7.5%, 7.7%, and 23.9%, respectively. We identified ALND as the major cause of BCRL and UED, while chemotherapy and RNI were not associated with upper extremity adverse events.

Our results are consistent with the recently updated 10-year follow-up of the AMAROS study. Significantly more BCRL was observed and treated in the ALND group at every measured time point than in the ART group. Overall, 44.2% of the patients reported lymphedema at any time point after ALND compared with 28.6% of the patients after ART. Meanwhile, there were no statistical differences in shoulder mobility and quality of life between the two arms. In terms of local control, both groups had a very low axillary recurrence rate although the expected statistical effect was not achieved due to the small number of events (10-year cumulative incidence in ALND vs. ART: 0.93% vs. 1.82%, HR = 1.71) [16]. Considering the breast cancer incidence and the ameliorated prognosis of breast cancer patients over the last decade in China, it is necessary to establish our evidence to support less ALND in cN0/SLN + population.

Different studies have reached inconsistent conclusions about the relationship between taxane-containing chemotherapy and BCRL. In a large retrospective study by Byun et al. a taxane-based regimen was a risk factor for BCRL ($p < 0.001$) [17]. Single-centre retrospective studies by Zhu et al. and Aoishi et al. came to the same conclusion (both $p < 0.05$) [18,19]. However, the results from two large prospective studies did not support this point of view. The study including a cohort of 1121 patients by Swaroop et al. found no significant difference between the taxane and non-taxane group (HR 1.14, $p = 0.62$) or between the taxane chemotherapy group and the no chemotherapy group (HR 1.56, $p = 0.40$), even though the mild swelling rate in the taxane chemotherapy group was significantly higher (both $p < 0.05$) [20]. Armer et al. analysed 486 patients treated with neoadjuvant chemotherapy and found that the occurrence of BCRL was not related to the inclusion of taxane but to the duration of neoadjuvant chemotherapy [21]. The heterogenous conclusions of the above two studies showed that the correlation between taxane and BCRL might be affected by the assessment of BCRL and the duration of chemotherapy in addition to the taxane. The majority of the analysed population in our study received epirubicin and cyclophosphamide followed by docetaxel, and no relationship of taxane inclusion with upper extremity adverse events was found, which implies the uncertainty of the impact of taxane to the occurrence of BCRL in the Chinese population, and is to be confirmed with larger sample and prospective studies.

Different to the conclusions of most previous studies, RNI was not a significant risk factor for upper extremity adverse effects in our study.

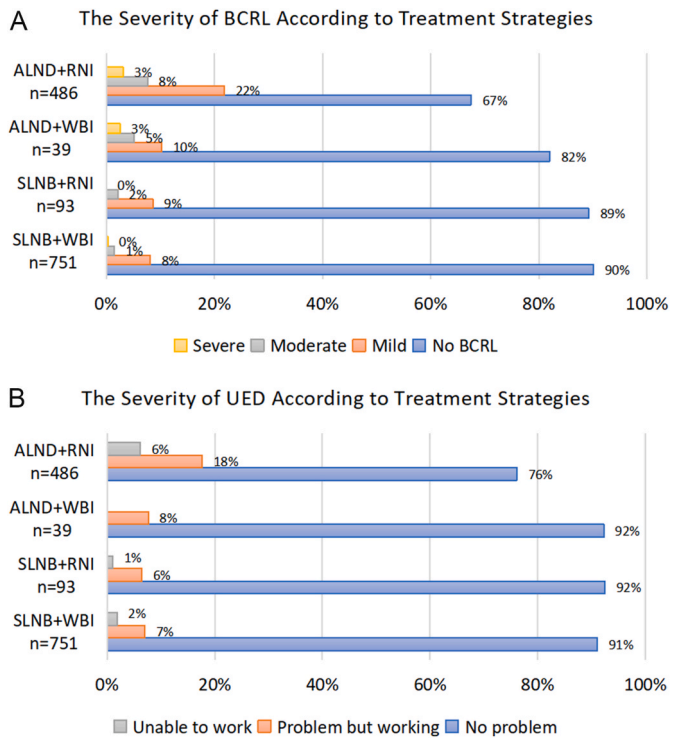

Fig. 2. A The incidence and severity of BCRL stratified by treatment groups. BCRL, breast cancer-related lymphedema; SLNB, sentinel lymph node biopsy; WBI, whole breast irradiation; RNI, regional nodal irradiation; ALND, axillary lymph node dissection.
B The incidence and severity of UED stratified by treatment groups.
UED, upper extremity dysfunction; SLNB, sentinel lymph node biopsy; WBI, whole breast irradiation; RNI, regional nodal irradiation; ALND, axillary lymph node dissection.

The effect of RNI was compared in four treatment groups, which demonstrated that on the premise of the same axillary surgery type, the addition of RNI did not significantly increase the incidence of upper extremity adverse effects. In addition, since RNI was given to most patients with positive ALNs in our centre, we compared the SLNB + RNI group and the ALND + RNI group. The SLNB + RNI group was found to be significantly better than the ALND + RNI group in terms of both BCRL and UED.

However, when comparing the four treatment strategies, the HR value of the ALND vs. ALND + RNI group was 0.266 (95% CI 0.080–0.879, p = 0.030) for UED. Although the difference was not statistically significant after adjusting the significance threshold with Bonferroni correction, it is worth mentioning the potential risk of the application of RNI in patients who had undergone ALND. This also suggests that the axillary surgery type should be considered when evaluating the risk of upper extremity adverse events associated with RNI. In Boyages et al.'s prospective study of subclinical BCRL, the SLNB + RNI group had a significantly higher risk compared to the SLNB group (33.3% vs. 12.9%, p = 0.03), but RNI was not found to impact BCRL on the basis of ALND (30.8% vs. 25.0%, p = 0.69) [22]. Shaitelman's meta-analysis showed that the addition of RNI had no significant effect on patients in the SLNB group but brought a significantly higher risk of BCRL to the ALND group [23]. In the large prospective study by Naoum et al. the addition of RNI did not increase the risk of BCRL in either the SLNB or ALND groups [4]. Our results indicate that the extent of axillary surgery and RNI should be integrated so as to prevent upper extremity adverse effects in patients with early breast cancer, with a focus on ALND as the leading risk factor.

We found that HFRT including RNI was associated with increased risk of BCRL (p = 0.027), while HFRT of WBI only or CFRT with RNI was not. In total, 100 patients (7.3%) underwent RNI-HFRT in our study, most of them were enrolled in the clinical trial HARVEST (NCT03829553), which aims to evaluate the efficacy and safety of RNI-HFRT by intensity-modulated radiation therapy in node-positive breast cancer.

The non-inferiority of the 3-week WBI-HFRT scheme has been confirmed by the START trial, and has been successively recommended by international guidelines and consensus [24,25]. There is growing evidence to date to confirm the non-inferiority of HFRT-RNI to CFRT. Wang et al. reported the safety and efficacy of the 3-week PMRT scheme containing RNI in the Chinese population [26]. Wang et al. conducted another multicenter randomized trial to compare HFRT and CFRT after BCS, in which 3.8% of patients received RNI, and there were no significant differences in toxicities including BCRL and shoulder mobility at a median follow-up of 73.5 months [27]. The DBCG randomized trial (NCT02384733) found that 40Gy/15fr did not result in more BCRL than 50Gy/25fr in node-positive early breast cancer patients (3-year rates in 50Gy vs. 40Gy: 11.6% vs. 11.8%, p = 0.96) [28]. The FAST-Forward nodal substudy (ISRCTN19906132) also revealed that BCRL at 3 years was 8% for 40Gy/15fr, 12% for 26Gy/5fr, 11% for 27Gy/5fr [29]. The percentage of HFRT-RNI is only 7.3% in our study population, which leads to a high chance of bias. As 79 of these 100 patients were enrolled in the prospective trial, their follow-up case report form includes upper arm adverse events. Although the current study is based on retrospective questionnaires, it is postulated that these patients had a higher chance to recall and record any BCRL events than other retrospective populations. The HARVEST trial will continue to follow up, which will help to clarify the impact of RNI-HFRT on BCRL.

The main limitation of our study is its retrospective nature and that BCRL and UED were defined using questionnaires. Bias cannot be avoided due to the subject assessment, although these two questionnaires have been used in many studies of BCRL and UED. Several objective BCRL detection methods have been applied. In the AMAROS trial, an increase in arm circumference 15 cm above and below the medial epicondyle by more than 10% compared with the contralateral arm was defined as BCRL [3]. The DBCG trial (NCT02384733) also used the same measurement [28]. The prospective study by Naoum et al. used a perometer, an optoelectronic volumetry, to scan the limb and calculate the volume, and defined BCRL as a relative volume change > 10% [4]. Arm circumference measurement is a simple, inexpensive and objective BCRL detection method, but is time-consuming and laborious for large-scale and long-term monitoring. The perometer is accurate, objective and time-saving way but relatively expensive. The nature of the above two methods makes them more feasible in the prospective trial but not in the retrospective study. Our study used patients' self-reporting in form of questionnaires, which is feasible for retrospective study, but at the cost of inferior objectivity of the BCRL assessment. Statistically, the incidences of BCRL in the four groups of our study are generally comparable to that in the prospective study of Naoum et al. [4], our results need to be confirmed by well-designed prospective studies with larger sample sizes and a more robust assessment of BCRL. Another limitation is that local-regional control and survival data were not reported in the current study as follow-up is not yet mature for early breast cancer, which needs to be completed by subsequent follow-up.

In conclusion, the treatment strategy of regional lymph nodes in early breast cancer has involved towards de-escalation of axillary surgery followed by RNI based on individual risk in recent decades. In this context, our findings demonstrate that ALND significantly increases the risk of BCRL and UED while RNI does not. Thus, replacing ALND with tailored radiotherapy would be an effective preventive strategy in early breast cancer patients.

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Author contributions

S-YZ, C-YC, W-XQ contributed to the design of the research, to the analysis of the data and to the writing of the manuscript. GC, CX, RC, X-FQ and K-WS contributed to the material preparation and data collection. LC and J-YC were in charge of overall direction. S-YZ and C-YC contributed equally to this work and should be considered co-first authors. All authors contributed to the final manuscript.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics statement

This is a retrospective observational study. The Ethical Committee of RuiJin Hospital has confirmed that no ethical approval is required.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Declaration of Competing interest

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

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