Breast Cancer (2018) 25:309–314
https://doi.org/10.1007/s12282-018-0830-3

ORIGINAL ARTICLE

The incidence and risk factors of related lymphedema for breast cancer survivors post-operation: a 2-year follow-up prospective cohort study

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Received: 25 September 2017 / Accepted: 3 January 2018 / Published online: 3 February 2018

Abstract

Purpose To investigate the incidence rate, severity and risk factors of related lymphedema in breast cancer survivors.

Methods A 2-year follow-up prospective study of 387 women who had operation from four hospitals from January 1, to December 31, 2014 was conducted. Limb volume was measured by circumference and symptoms were measured using questionnaires pre-treatment and 1, 3, 6, 12, 18, 24 months after surgery separately. The incidence rates and the severity of lymphedema were evaluated, respectively. Risk factors for the development of breast cancer-related lymphedema (BCRL) were analyzed using log-rank test and Cox regression.

Results The incidences of BCRL were 4.4, 10.1, 15.2, 28.6, 31.2 and 32.5% at 1, 3, 6, 12, 18, 24 months after surgery, respectively, measured by Norman questionnaire. The rates measured by arm circumference were 2.5, 6.7, 13.4, 21.4, 26.3 and 29.4%, respectively. About 114 (29.4% of 387) women were diagnosed with BCRL, and 78 of them got mild lymphedema. Axillary lymph node dissection (ALND) (HR = 5.2, 95% CI 1.6–17.3), radiotherapy (HR = 3.9, 95% CI 2.0–7.5), modified radical mastectomy (MRM) (HR = 2.1, 95% CI 1.3–3.4), the number of positive lymph nodes (HR = 1.1, 95% CI 1.0–1.2) and body mass index (BMI) (HR = 1.1, 95% CI 1.0–1.1) were independent risk factors for BCRL.

Conclusions BCRL is a common complication for breast cancer patients after surgery. It can be fairly diagnosed only 1 month post-operation and the cumulative incidence of BCRL seems to be increasing over time, especially in the first year after surgery. ALND, radiotherapy, MRM, the number of positive axillary lymph nodes and BMI were found to be independent risk factors in the development of BCRL in this study.

Keywords Breast cancer · Lymphedema · Incidence · Risk factors

Introduction

With the development of treatment, the mortality from breast cancer was significantly decreased. It is more and more important to release the side effects resulting from treatments on breast cancer to improve the quality of life of breast cancer long-time survivors. Breast cancer-related lymphedema (BCRL) is one of the most common and distressing complication of post-operative breast cancer survivors. Upper limb swelling, pain, immobility and so on could be caused by BCRL, which affect the quality of life seriously [1–3]. BCRL continues to challenge clinicians worldwide and it has remained a potentially life-time and irreversible complication that is leaving chronic physical, psychological and emotional consequences for breast cancer patients. Quality of life (QOL) is impaired remarkably in women with BCRL via inducing pain, heaviness, tightness, decreased range of motion, restriction at work or home, personal care functions and by imposing anxiety, depression, and emotional distress on these patients. Some reports showed that lymphedema may also shorten survival. Due to the lack of uniform diagnostic methods, the diagnostic criteria and

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observation interval, the reported incidence of BCRL was quite different (0–94%) in previous researches [4, 5].

The pathogenesis mechanism of BCRL was still unknown. In this study, a 2-year follow-up prospective cohort study of BCRL was performed, to obtain a more detailed and accurate incidence of BCRL in Chinese breast cancer survivors with current treatment patterns and select the risk factors of BCRL, then to provide better options for BCRL prevention and treatment.

Methods

Study population

In our study, the women with first diagnosis of primary breast cancer, who had surgical treatment at the four hospitals (including Second Affiliated Hospital of Soochow University, Jiangsu Province Hospital, the First People's Hospital of Changzhou, and Affiliated Hospital of Jiangsu Uinversity) from January 1 to December 31 in 2014 were included. The women with the following conditions were excluded: (1) second primary tumors at the time of diagnosis or follow-up; (2) distant metastasis at the time of diagnosis or follow-up; (3) tumor recurrence at time of follow-up; (4) bilateral breast cancer; (5) upper limbs or neck with the history of major trauma, surgery, or infection; (6) lack of clinical data and follow-up data. Informed consents were obtained from all the patients participating in this study. The study was performed after it was approved by the ethics committee of The Second Affiliated Hospital of Soochow University hospital.

Data collection

This study was designed for 2 years follow-up. The follow-up was completed by doctors and medical students who had unified training previously though face-to-face interviews or telephone interviews. Clinical information, including age, complication, type of pathology, tumor staging, axillary node status, number of axillary nodes removed, type of surgery, body mass index (BMI), and the situation of radiotherapy, chemotherapy and endocrinotherapy were obtained. Body mass index (BMI) was calculated before surgery treatment. To assess the baseline of limb volume, which we got pre-treatment, we record the assessment data before surgery, 1, 3, 6, 12, 18 and 24 months post-surgery, respectively, using circumferences and questionnaires.

Assessing lymphedema

Arm circumference measurement [6, 7] is one of the most common techniques utilized to assess the BCRL. This study mainly refers to the BSABP B-04 Trial, considering the differences in body size between China and abroad, 10 cm above and below the olecranon were selected as the measurement points, and an absolute change of 2 cm at any point was defined as criteria for BCRL. According to the standard evaluation criterion of LENT SOMA [8], the severity of BCRL was graded mild when circumference change was $\leqq 4$ cm, moderate when $\leqq 6$ cm, and severe when change was more than 6 cm.

The questionnaire was designed from the report of Norman SA et al. [9]. At every in-person interview, the woman was first asked: "between the date of breast cancer diagnosis and today, did your right and left hands/lower arms/upper arms seemed to differ in size". To assess the size of the difference, women who noticed any difference in size between the 2 limbs got 1 point and then were asked: "Would you say that, on average, the difference in the size of your hands/lower arms/upper arms was (1) very slight, you are the only person who would notice this, get 1 point, (2) noticeable to people who know you well but not to strangers, get 2 points or (3) very noticeable, get 3 points". The score points are added. The diagnosis of BCRL was evaluated as, 1–3 mild edema, 4–6 moderate edema, 7–9 severe edema.

Statistical analysis

SPSS 23.0 software was used to calculate the BCRL incidence and composition ratio at each follow-up time point by two diagnostic methods. Log-rank univariate analysis and the cox model multivariate analysis were applied to analyze the result by circumference measurement 24 months after operation. Descriptive values are expressed as mean ± standard deviation (SD). $P < 0.05$ was considered to be the statistically significant difference.

Results

Sample description

The patients with bilateral breast cancer, multiple tumors, death, serious loss of data were excluded, and 387 patients were left for the final analysis. The median age of the patients was 50 (24–81) years, BMI 17.58–35.56 kg/m^2, in which 47.5% of patients' BMI < 24 kg/m^2. 107 patients had a history of mammary gland disease, 36 people had a family history of breast cancer, 112 with hypertensive, and 70 smoking for more than half a year.

46.0% of the patients with breast cancer had the primary tumor located in the upper quadrant. The T staging of the most patients was T1 or T2. 202 patients (52.2%) were N0, in addition, 86 patients were N1, 75 patients were N2. 254 patients were stage I or II after surgey. More than 16 axillary

lymph node dissections during surgery was accounted for 59.4% of the patients, among which 47.8% were axillary lymph node positive. 327 patients were pathologically proven with invasive breast cancer. The number of patients with estrogen receptor (ER) positive is 262, and progesterone receptor (PR) positive is 243. 142 patients were HER-2 positive, which means that they had 3+ in immunohistochemical test or 2+, in that case, it should be proved by situ hybridization tests. 53 patients, who had 2+ in the immunohistochemical test but did not do situ hybridization test, were divided into the HER-2 unknown group.

Most of the breast cancer surgical methods included modified radical mastectomy (MRM) and breast conserving surgery (BCS), in which the numbers were 273 and 109, respectively. 323 patients had axillary lymph node dissection (ALND) treatment and 64 patients underwent sentinel lymph node biopsy (SLNB). There were 245 patients who received radiation therapy, all of them had three-dimensional conformal radiation therapy or intensity modulated radiation therapy (IMRT) technology based on CT scaning. 46 patients experienced chest wall irradiation only, 14 people just received the whole breast radiation and tumor bed boost. The radiation therapeutic fields included chest wall and supraclavicular fossa in 127 patients. Besides, another 58 patients had accepted the whole breast + supraclavicular fossa radiotherapy with tumor bed boost. The median dose was 50 (45–56) Gy and a tumor bed boost of 10.0 (8.4–9.6) Gy. 334 patients received chemotherapy, including neoadjuvant chemotherapy and post-operative adjuvant chemotherapy.

BCRL incidence

Most patients with mild lymphedema underwent a slow progress after surgery. The incidence of lymphedema was slightly higher using the Norman questionnaire than those of the circumference measurement, and the incidence of moderate and severe edema was higher with Norman questionnaire than those of the circumference measurement. There were 7 people who was diagnosed as moderate lymphedema immediately after surgery, which meant acute onset, while with circumference measurement, only 4 people had acute onset. Details are shown in Table 1, Fig. 1.

Table 1 BCRL incidence

Diagnosed method	Time post-surgery (Month)/*N* (%)					
	1	3	6	12	18	24
Norman questionnaire	17 (4.4%)	39 (10.1%)	59 (15.2%)	111 (28.6%)	121 (31.2%)	126 (32.5%)
Mild	10	22	35	70	69	69
Moderate	7	14	18	28	35	38
Severe	0	2	6	13	17	19
Circumference	10 (2.5%)	26 (6.7%)	52 (13.4%)	83 (21.4%)	102 (26.3%)	114 (29.4%)
Mild	6	14	34	55	68	78
Moderate	4	12	15	22	26	27
Severe	0	0	3	6	8	9

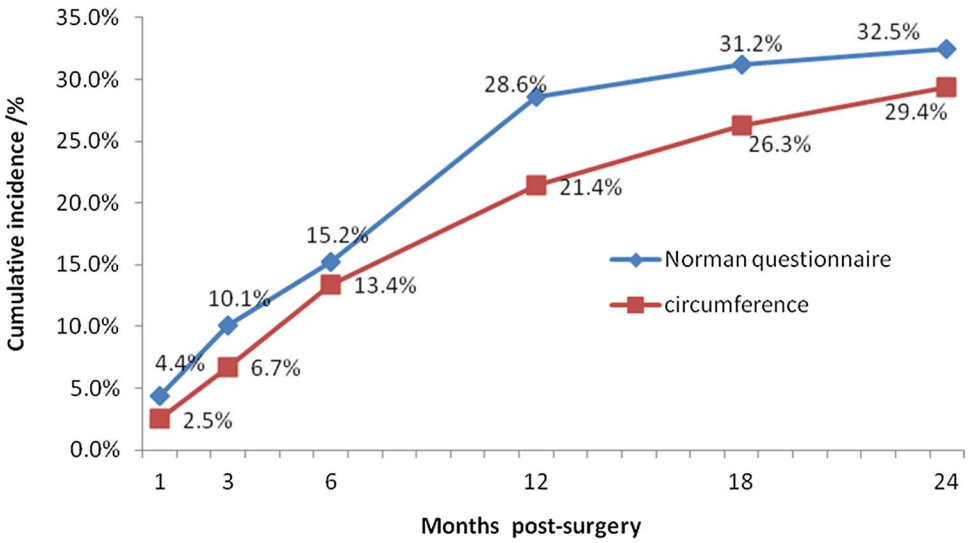

Fig. 1 Cumulative incidence showing range of development times for BCRL up to 24 months post-surgery

Risk factors

Risk factors for lymphedema in the upper limb of breast cancer included BMI, type of pathology, the number of lymph node dissection, number of positive lymph nodes, postoperative N and TNM staging, surgical approach, treatment of axillary lymph node, whether to accept radiotherapy or chemotherapy, which were obtained by the univariate log-rank analysis. 10 risk factors were included in the multivariate analysis, then we found that the relative risk of BCRL after ALND was 5.2 ($P = 0.007$, 95% CI 1.6–17.3), compared with SLNB, the relative risk of radiotherapy was 3.9 ($P < 0.001$, 95% CI 2.0–7.5), the relative risk of MRM was 2.1 ($P = 0.004$, 95% CI 1.3–3.4), whereas axillary lymph node dissection also increases the risk of BCRL. Axillary lymph node positive number and obese patients were more likely to have BCRL, the relative risks were 1.1 ($P = 0.002$, 95% CI 1.0–1.2) and 1.1 ($P = 0.03$, 95% CI 1.0–1.1), respectively. Details are shown in Table 2.

Radiation therapy was an independent risk factor of BCRL. We analyzed the differences of radiotherapy dosages and areas, and then we found that areas including supraclavicular fossa could increase the risk of BCRL ($P < 0.001$).

Discussion

The pathogenesis of BCRL is still unclear, most of the researchers believe that surgery, radiotherapy and other treatments lead to upper limb lymphatic vessels obstruction, and then a lot of protein-rich lymph resides in the interstitial space. By the same time intravascular colloid osmotic pressure reduces relatively. And then the liquid from the capillaries flows into the interstitial space which finally induces the high-protein edema [10].

There are many diagnostic methods that are used to record the lymphedema, but the most commonly used methods include the subjective symptom assessment and the objective measurements of physical signs. It is believed that the objective measures are more reliable and consistent than subjective symptom assessment [11], but it is still hard to determine which approach is closer to the facts [12]. The objective measurements include circumference measurement, water displacement method, perometry, and bioelectrical impedance analysis (BIS). BIS was recommended as an early diagnostic and detection tool for BCRL, but it is not used widely now because of its large and costly equipment [11, 13–15]. In this study, both subjective and objective diagnostic methods were used. Similar to the results reported in other literatures, the incidence of lymphedema measured by the subjective symptom assessment method was slightly higher than that of objective physical signs [16–18]. BCRL generally occurred from the far-end. As the Norman questionnaire assessment, we measured the palm of the hand, forearm and upper arm, while as the circumference measurement method, we can not measure in palm, that may be likely to cause underestimate the incidence. In addition, in this study, we measured the ipsilateral limb preoperation and postoperation to eliminate the thickness difference of the dominant and non-dominant limb. It was intuitive to get the dynamic observation of upper limb volume changes in patients. However, the patient's weight changes can also affect the measurement results. So, if we want to get more accurate results, it is proposed to measure the changes in the contralateral limb at the same time and use the appropriate algorithms to eliminate the impact of weight changes on the upper limb volume.

The average incidence of BCRL reported in a prospective cohort study was 21.4% [19]. Most of the researchers believe that within 2 years after surgery, BCRL incidence increases gradually with time [18, 20]; the same phenomenon was also observed in this study and the incidence of BCRL increased more rapidly during the first year post-operation, detail is shown in Fig. 1. The incidence of BCRL is still in a slow upward trend in the 2 year after surgery, which also was confirmed by Norman SA [20] and Paskett ED [21] in much long-term follow-up. For this reason, the preventive and curative measures given by the health care provider or the patient against BCRL should be adopted for at least 2 years or more after surgery.

The risk factors of BCRL in our study include: ALND [9, 22, 23] MRM [6, 24, 25], radiotherapy [26, 27], chemotherapy [9, 28], BMI [9, 21, 25, 27], the number of axillary lymph node dissection [18, 21, 23], the number of positive lymph nodes. Lymphatic reflow obstruction is the most possible mechanism, and we confirmed it again. ALND, MRM, radiotherapy will increase the damage to the axillary lymphatic reflow, thus increasing the risk of BCRL. As different irradiation ranges caused different impacts, regional lymphatic drainage area of radiation can significantly improve the incidence of BCRL [26].

There is no significant correlation between chemotherapy and BCRL, although many of other literatures showed positive results. Chemotherapy is usually used in advanced beast cancer patients, who got more radical surgery,axillary lymph node resection, radiotherapy or other treatments. So, it is hard to rule out the interference of those factors when evaluating chemotherapy.

It has been shown in our study that high BMI can increase the risk of BCRL, as some meta-analysis has reported the same results [19, 29], but the effect of this factor is still controversial. Geller et al. [30] had shown no significant correlation between BMI and BCRL. Some studies had shown that only BMI > 30 kg/m^2 will increase the risk of BCRL [21]. Other controversial factors, such as hypertension, age, endocrine therapy, are still lacking

Table 2 Risk factors of BCRL

Clinical feature	Total number	BCRL/*N* (%)	Log-rank		Cox		
			Chi square	*P*	HR	95% CI	*P*
BMI (kg/m$^{2)}$							
< 24	205	54 (26.3%)	745.143	< 0.001	1.1	1.0–1.1	0.03
≧ 24	182	60 (33.0%)					
Type of pathology							
LCIS	4	1 (25.0%)	13.728	0.003	1.4	0.7–2.8	0.33
DCIS	33	2 (6.1%)					
IDC	327	107 (32.7%)					
Others	23	6 (26.1%)					
Number of lymph node dissection							
< 16	157	44 (28.0%)	115.347	< 0.001	1.0	0.9–1.0	0.09
≧ 16	230	70 (30.4%)					
Number of positive lymph nodes							
< 1	202	31 (15.3%)	160.992	< 0.001	1.1	1.0–1.2	0.002
≧ 1	185	83 (44.9%)					
N stage							
N0	202	31 (15.3%)	80.531	< 0.001	0.6	0.4–1.1	0.09
N1	86	26 (30.2%)					
N2	75	38 (50.7%)					
N3	24	19 (79.2%)					
TNM stage							
0	29	1 (3.4%)	81.411	< 0.001	1.2	0.8–1.6	0.38
I	104	21 (20.2%)					
IIA	118	21 (17.8%)					
IIB	35	13 (37.1%)					
IIIA	73	37 (50.7%)					
IIIB	2	1 (50.0%)					
IIIC	22	18 (81.8%)					
IV	4	2 (50.0%)					
Surgical types							
BCS	109	13 (11.9%)	24.895	< 0.001	2.1	1.3–3.4	0.004
MRM	273	98 (35.9%)					
Others	5	3 (60.0%)					
Axillary node status							
SLNB	64	4 (6.3%)	18.363	< 0.001	5.2	1.6–17.3	0.007
ALND	323	110 (34.1%)					
Radiotherapy							
No	142	14 (9.9%)	39.705	< 0.001	3.9	2.0–7.5	0
Yes	245	100 (40.8%)					
Chemotherapy							
No	53	5 (9.4%)	11.083	0.001	1.6	0.6–4.0	0.33
Yes	334	109 (32.6%)					

LCIS lobular carcinoma in situ, *DCIS* ductal carcinoma in situ, *IDC* infiltrating ductal carcinoma

$P < 0.05$ was considered as statistically significantly different

more direct and sufficient evidence; therefore, further studies are needed to obtain clear data to provide clearer conclusions and provide a basis for clinical prevention and treatment of BCRL, especially in large, multicenter, long-term prospective cohort studies.

The limitation of this study is that the sample size is relatively small and a further study with a larger sample size is needed.

Conclusion

BCRL is a common complication of breast cancer patients after surgery has occurred as early as the first month after surgery, and the incidence gradually increases over time (< 2 years), especially in the first year, but the majority of patients underwent mild BCRL. ALND, radiotherapy, MRM, axillary lymph node positive number and BMI were independent risk factors. Age, hypertension, the number of axillary lymph node detection, chemotherapy, etc., in this study found no correlation with the occurrence and development of BCRL.

Funding This study was supported by Jiangsu Province's Key Medical Department in 2011 (No. 201112) and Jiangsu Province Health Department Research Project (No. z201305).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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