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The prevalence of arm lymphedema after radiation treatment in patients with breast cancer

Kamonrat Sueangamiam[1] and Kanisa Rongsriyam[2]

[1]Department of Radiological Technologist, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand and [2]Department of Radiology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Original Article

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Author for correspondence:
Kanisa Rongsriyam, Department of Radiology, Navamindradhiraj University, 681 Samsen Road, Dusit, Bangkok 10300, Thailand.
Tel: 66 (81) 8168789. Fax: 66(2)244-3255.
E-mail: kanisa_r@hotmail.com

Abstract

Aim: To evaluate the prevalence and risk factors of arm lymphedema in patients with breast cancer.

Materials and methods: Between 2006 and 2017, we investigated patients with breast cancer after breast surgery who received adjuvant radiotherapy at the breast or chest wall, and/or adjuvant radiotherapy at regional lymph nodes, and standard systemic chemotherapy depending on disease stage and risk factors. We assessed arm lymphedema using arm circumference measurement differences on the treated side compared with the opposite arm (≥2 cm measurements at any one position). Associations between arm lymphedema and potential risk factors were identified using statistical analysis.

Results: In 308 patients, arm lymphedema prevalence was 6·2%. Patients having ≥20 lymph nodes removed (hazard ratio (HR) = 3·29; 95% confidence interval (CI): 1·12–8·87), undergoing regional lymph node irradiation (HR = 1·81; 95% CI: 1·09–13·28), and no arm and shoulder exercises after treatment (HR = 3·16; 95% CI: 1·89–5·26) had a higher risk of arm lymphedema.

Findings: Arm lymphedema is a serious breast cancer complication and is a preventable morbidity. Planning arm and shoulder exercises in line with adjuvant treatments and increasing clinical awareness of early indications could help lower the risk of occurrence.

Introduction

Globally, breast cancer is the most common cancer and the number one cause of cancer death in women.[1,2] In Thailand, the disease is also a leading cancer, with an age-standardised incidence rate of approximately 28·5 females per 100,000 per annum.[3] Currently, most breast cancer treatments are a combination of surgery, radiotherapy and systemic therapy, which lead to higher survival rates.[4–8]

One important complication of breast cancer treatment is arm lymphedema which is a swelling condition of the arm resulting from obstruction or disruption of lymphatic drainage in the axillary lymphatic system.[9,10] The condition negatively affects physical, daily functional, social, emotional and quality of life aspects of women.[11,12]

The cumulative incidence of arm lymphedema after breast cancer treatment is approximately 3–70%, depending on the extent of axillary surgery, the use of radiotherapy, the measurement criteria used and the length of follow-up.[13–19]

Previous studies have identified possible factors increasing the risk of arm lymphedema, including patient age, obesity, dissected numbers and levels of axillary lymph nodes, type of breast cancer treatment, radiation technique, tumour size and arm exercises after post-breast cancer treatment.[19–28] In this study, we sought to determine the prevalence and risk factors associated with the occurrence of arm lymphedema in breast cancer patients after surgery, adjuvant radiotherapy and standard adjuvant systemic treatments according to breast cancer stage and risk factors.

Methods

This retrospective cross-sectional study included data from 308 patients who were diagnosed with breast cancer after receiving surgery, adjuvant radiotherapy and standard adjuvant systemic treatments according to disease stage and risk factors at the Department of Radiation Oncology, Faculty of Medicine, Vajira Hospital, Navamindrahiraj University between January 2006 and December 2017. The research protocol was approved by an institutional ethics committee (Ref; COA98/2559). Data were also gathered from patient's medical records.

Inclusion and exclusion criteria

Inclusion criteria were patients who had a stage I–III breast cancer diagnosis (according to the American Joint Committee on Cancer, 7th edition[29]) and had undergone surgery, including breast-conserving surgery, mastectomy with sentinel lymph node biopsy or axillary dissection followed by standard systemic treatment, with all patients undergoing adjuvant radiotherapy. Patients were excluded if they had a history of cancer in other organs, incomplete medical records, a history of previous radiation treatment in axillary areas and arm lymphedema before radiation treatment.

Variables

Potential risk factor variables were (1) age, (2) body mass index (BMI), (3) underlying diabetic disease, (4) side of treatment arm, (5) tumour size, (6) type of lymph node excision, (7) number of lymph node excisions, (8) number of positive lymph nodes, (9) staging, (10) type of breast surgery, (11) regional lymph node irradiation, (12) chemotherapy treatment, (13) targeted therapy treatment and (14) arm exercises.

Treatment

All patients underwent breast-conserving surgery or mastectomy as necessary based on tumour characteristics, surgeon recommendation and patient choice. Systemic therapy was delivered at the discretion of the oncologist involved in each case. Typically, cyclophosphamide–doxorubicin regimens and taxane were administered. Most patients started chemotherapy after recovering from surgery, and radiation therapy was delivered after the completion of chemotherapy. For radiation therapy, an axillary field was added if there were four or more nodes positive.

Follow-up and measurement of lymphedema

All patients were followed up to receive breast and arm examinations every 3 months during the first 2 years, then every 6 months until death. Arm lymphedema was determined as a difference in arm circumference on the treated side compared to the opposite arm of ≥2 cm at any one position, when examined twice by a doctor and averaged.

Statistical analysis

Data were analysed using SPSS statistical package for Windows (version 22·0; IBM Corp., Armonk, NY, USA). Data were described using frequency distributions, measures of central tendency and dispersion. Risk factor variables were included in univariate analyses. Variables that were statistically significant in univariate analyses underwent multivariate analyses using the Cox proportional hazards model. All p-values were two-sided and a p-value < 0·05 was considered statistically significant.

Results

From 2006 to 2017, 308 breast cancer patients meeting study inclusion criteria were recruited. The median length of follow-up since breast cancer diagnosis was 4·4 years (range: 1–14·2 years). The prevalence of arm lymphedema after breast cancer treatment by patient, tumour and treatment characteristics is shown (Table 1). The mean age at breast cancer diagnosis was 52·1 years (standard deviation (SD) = 10·3 years). The mean BMI was

Table 1. Patient, tumour, treatment characteristics and occurrence and lymphedema prevalence of the breast cancer patients

Characteristics	Total *n* (%)	Lymphedema (%)
Age (mean (SD)), years	52·1 (10·3)	
<60 years	240 (77·9)	7 (2·9)
≥60 years	68 (22·1)	12 (17·6)
Body mass index (mean (SD)), kg/m2	25·3 (4·6)	
BMI < 30	236 (76·6)	14 (5·9)
BMI ≥ 30	40 (13·0)	4 (10)
Unknown	32 (10·4)	1 (3·1)
Underlying diabetes disease		
No	140 (45·5)	9 (6·4)
Yes	77 (25·0)	10 (13)
Unknown	91 (29·5)	0 (0)
Side of treatment		
Non-dominant side	145 (47·1)	7 (4·8)
Dominant side	163 (52·9)	12 (7·4)
Tumour size (mean (SD)), cm	3·1 (2·0)	
≤5 cm	271 (88·0)	19 (7)
>5 cm	34 (11·0)	0 (0)
Unknown	3 (1·0)	0 (0)
Axillary surgery		
SLNB	91 (29·5)	1 (1·1)
AXND	214 (69·5)	18 (8·4)
No LN dissection	3 (1·0)	0 (0)
Number of nodes excision, median (range)	12(1–48)	
<20	242 (78·6)	9 (3·7)
≥20	63 (20·4)	15 (15·9)
No LN dissection	3 (1·0)	0 (0)
Number of positive nodes, median (range)	1(0–27)	
<4	142 (46·1)	5 (3·5)
≥4	163 (52·9)	14 (8·6)
No LN dissection	3 (1·0)	0 (0)
Staging		
Until IIA	144 (46·8)	5 (3·5)
Above IIB	164 (53·2)	14 (8·5)
Breast surgery		
Conservative	127 (41·2)	4 (3·1)
Mastectomy	181 (58·8)	15 (8·3)
Chemotherapy treatment		
No	46 (14·9)	3 (6·5)
Yes	262 (85·1)	16 (6·1)
Hyperfractionated radiation treatment		
No	283 (91·9)	16 (5·7)
Yes	25 (8·1)	3 (12·0)

(*Continued*)

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Table 1. (*Continued*)

Characteristics	Total *n* (%)	Lymphedema (%)
Regional lymph node irradiation		
No	131 (42·5)	2 (1·5)
Yes	177 (57·5)	17 (9·6)
Targeted therapy treatment		
No	266 (86·4)	16 (6·0)
Yes	42 (13·6)	3 (7·1)
Arm and shoulder exercises		
No	23 (7·5)	12 (52·2)
Yes	233 (75·6)	6 (2·6)
Unknow	52 (16·9)	1 (1·9)

25·3 kg/m2 (SD = 4·6), of which 13% were obese (BMI ≥ 30 kg/m2). The prevalence of arm lymphedema was 6·2%.

Hazard ratios (HRs) for all individual factors considered as potential risk factors for arm lymphedema are shown (Table 2). In considering patient characteristics, patients >60 years old and performing arm and shoulder exercises after complete treatment showed an increased risk in developing arm lymphedema (HR = 3·36, 95% CI: 1·11–10·16 and HR = 0·08, 95% CI: 0·03–0·20, respectively). In terms of tumour characteristics, a statistically significant increased risk in developing arm lymphedema was observed when patients were staged above IIB (HR = 3·91, 95% CI: 1·40–10·97) and having at least four positive lymph nodes (HR = 3·92, 95% CI: 1·40–11·00). Furthermore, in terms of breast cancer treatment characteristics, mastectomy (HR = 3·22, 95% CI: 1·06–9·74), axillary lymph node dissection (HR = 7·21, 95% CI: 1·01–54·45), removal of ≥20 lymph nodes (HR = 4·69, 95% CI: 1·89–17·16) and regional lymph node irradiation (HR = 7·5, 95% CI: 1·73–32·56) all increased the probability of developing arm lymphedema.

Variables that were statistically significant in univariate analyses underwent multivariate analyses (Table 2). The removal of ≥20 lymph nodes, regional lymph node irradiation, and no arm and shoulder exercises after complete treatment were independently associated with an increased risk of arm lymphedema with an adjusted HR of 3·29 (95% CI: 1·12–8·87) for the removal of ≥20 lymph nodes, 1·81 (95% CI: 1·09–13·28) for regional lymph node irradiation, and 3·16 (95% CI: 1·89–5·26) to no arm and shoulder exercises after complete treatment.

Discussion

The prevalence of patients with arm lymphedema after breast cancer treatment was 6·2%. While several studies have reported this prevalence ranges between 3% and 70%, comparisons across studies are difficult because of variability in arm lymphedema definition and measurement techniques, follow-up times, and patient characteristics.[13–19] In a recent meta-analysis, the overall estimated incidence of the condition after breast cancer treatment was 16·6%.[13] The reason for such a low prevalence rate in our study may have been due to the fact we used only one method of arm lymphedema assessment. From other studies, incidences were high when assessed by more than one diagnostic method[13] and also from a lack of diagnostic criteria for breast cancer-related arm lymphedema.[13] Another reason for a possible underestimation may have been due to the median follow-up time; in this study, this was 4·4 years, thus the longer a woman's exposure to risk factors, the greater the chance of developing arm lymphedema. With a 20-year follow-up, Petrek et al.[25] reported that the ongoing risk of developing the condition was approximately 1% per year for at least 20 years.

Current data on whether arm lymphedema incidence varies by age are inconsistent. A higher incidence of arm lymphedema in older patients was observed in some studies,[16,23,24,27] possibly due to a progressive loss of lymphvenous anastomosis due to ageing processes.[17–19,19–28] This finding was not observed in our study; patients >60 years old showed no increased probability of developing arm lymphedema after adjusting for others characteristics.

BMI is a modifiable risk factor for arm lymphedema; previous studies have shown that patients with a higher BMI were at a higher risk of arm lymphedema.[19,24,26,28,30] The mechanism whereby excess weight increases the risk of the condition remains unclear; however, extra demands on both the vascular and lymphatic system to transport fluid could impair lymphatic transport capacity and impair lymphatic functions thereby promoting adipose deposition.[30,31] In contrast, our study failed to show an association between higher BMI and increased risk of arm lymphedema development; therefore, more studies are required to explore such associations.

The majority of studies show that arm lymphedema risk increases with more extensive treatments, in particular breast surgery,[13,19,25–28] lymph node removal[24,32,33] and adjuvant treatment.[7,13,19,21,24,32,33] Several studies have demonstrated arm lymphedema rates of 24% to 49% after mastectomy and 4% to 28% after lumpectomy, with a history of axillary lymph node surgery.[19,25–28] The Axillary Lymphatic Mapping Against Nodal Axillary Clearance trial demonstrated that lymphedema was observed in approximately 5% of patients who had SLNB versus 13% of those who had ALND.[34] Radiation therapy is an independent risk factor for the development of arm lymphedema with reported rates of 2% to 5%, even in the absence of lymph node surgery.[35,36] Radiation to the axilla is associated with 2 to 4·5 times greater risk of lymphedema and 8 to 10 times greater risk when a patient receives ALND and radiation treatment.[37,38] For systemic treatment, there are conflicting studies about chemotherapy as possible risk factors for arm lymphedema. Some studies indicate that adjuvant chemotherapy is a potential risk factor for arm lymphedema.[7,13,19,21,24,32,33] DiSipio et al.[13] did a meta-analysis of 72 studies published from 2000 to 2012 to assess the incidence rates of BCRL, and a meta-analysis of 29 studies published from 2000 to 2012, to assess the risk factors. This study demonstrated that about 75% of the studies reviewed indicated chemotherapy as a risk factor for developing arm lymphedema.[13] Our study also demonstrated that having >20 lymph nodes removed during axillary dissection increased the HR 3.3-fold, and having regional lymph node irradiation increased the HR 1.81-fold. We failed to confirm an association between arm lymphedema development and type of breast surgery, type of lymph node dissection and adjuvant systemic treatment. The reason for this may be due to improvements in treatment techniques to minimise lymphatic disruption and the improved selection of systemic treatments in recent years.[39]

From our multivariate analyses, staging at diagnosis did not increase the risk of developing arm lymphedema. This agreed with the systematic review; staging was classified as a weak or inconclusive independent risk factor for developing arm lymphedema.[13]

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Table 2. Factors affected lymphedema: univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Characteristics	p-Value	HR	95%CI	*p*-Value	HR	95%CI
Age (<60 years versus ≥60 years)	0·001	3·36	(1·11–10·16)	0·205	2·02	(0·68–5·95)
BMI (<30 kg/m2 versus ≥30 kg/m^2)	0·244	1·98	(0·63–6·23)			
Underlying diabetes disease (no versus yes)	0·119	0·62	(0·33–1·13)			
Side of treatment (non-dominant versus dominant)	0·276	1·45	(0·74–2·82)			
Tumour size (≤5 cm versus >5 cm)	0·450	0·04	(0–152·49)			
Axillary surgery (SLNB versus AXND)	0·049	7·21	(1·01–54·45)	0·772	1·44	(0·12–16·66)
Number of nodes removed (<20 versus ≥20)	0·001	4·69	(1·89–17·16)	0·032	3·29	(1·12–8·87)
Number of positive nodes (<4 versus ≥4)	0·009	3·92	(1·40–11·00)	0·707	1·21	(0·12–4·21)
Staging (until IIA versus above IIB)	0·010	3·91	(1·40–10·97)	0·960	0·01	(0·02–2·5)
Breast surgery (conservative versus mastectomy)	0·038	3·22	(1·06–9·74)	0·881	0·89	(0·20–4·06)
Chemotherapy treatment (no versus yes)	0·826	1·15	(0·33–3·96)			
Hyperfractionated radiation treatment (no versus yes)	0·943	0·95	(0·27–3·37)			
Regional lymph node irradiation (no versus yes)	0·007	7·50	(1·73–32·56)	0·046	1·81	(1·09–13·28)
Targeted therapy treatment (no versus yes)	0·159	2·53	(0·70–9·16)			
Arm and shoulder exercises (yes versus no)	0·000	4·75	(1·48–15·43)	0·003	3·16	(1·89–5·26)

Arm and shoulder exercise after breast cancer treatment is an important independent risk factor for arm lymphedema. We observed that arm and shoulder exercises decreased the risk of developing arm lymphedema by 0·08 and 0·15 times, based on univariate and multivariate analyses, respectively. Consistent with others study, arm and shoulder exercises reduced breast cancer treatment complications and side effects, including arm lymphedema, functional limitations and upper limb disability.[40–43]

Conclusions

Arm lymphedema-related breast cancer treatment is a significant morbidity affecting many breast cancer patients. Patients having >20 lymph nodes removed during axillary dissection, regional lymph node irradiation, and no arm and shoulder exercises had a higher risk of arm lymphedema. Thus, this condition is a possible preventable morbidity. Planning arm and shoulder exercises post-adjuvant treatment of patients with breast cancer and increasing health professional awareness of the early diagnosis of arm lymphedema could help reduce morbidity in these patients. Future studies should focus on the arm and shoulder exercises that can prevent arm lymphedema after breast cancer treatment.

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Conflict of Interest. All authors declared no conflict of interest.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees of faculty of Medicine, Vajira Hospital, Navamindrahiraj University (Ref; COA98/2559).

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