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Incidence and Risk Factors Analysis of Lymphedema Secondary to Breast Cancer

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Lymphedema, the most significant complication of treatment for breast cancer, can result in substantial psychological and physical morbidity. However, no long-term follow-up lymphedema studies yet exist for Taiwanese breast cancer survivors. This study therefore focused on examining frequency and risk factors of lymphedema secondary to breast cancer in Taiwanese patients. Five hundred and seventy patients who received surgical treatment between 1994 and 2000 at Changhua Christian Hospital were retrospectively investigated in October 2002. The incidence of self-reported edema was 28 percent (161/570), and the incidence of lymphedema with circumference difference greater than 2 cm was 8.1 percent (46/570). Eighty-four percent of patients developed lymphedema within 3 years of surgery, with a mean onset interval of 1.91 years. The accumulative incidence of lymphedema in the 7th follow-up year was 5 percent without radiotherapy and 23.5 percent with radiotherapy. Risk factors were radiotherapy (odds ratio, 7.49; p<0.001) and modified radical mastectomy (MRM) (OR, 2.83; p=0.032). Radiation was significantly associated with lymphedema in the MRM group (p<0.001), but not in the breast conserving surgery group. In the radiation subgroup, supraclavicular or axillary radiotherapy (p=0.022), and MRM (p=0.048) were significantly associated with lymphedema. Lymph nodes resection or metastasis, chemotherapy, year of diagnosis, and radiation dosage were not associated with lymphedema. Lymphedema was significantly associated with radiotherapy, axillary or supraclavicular irradiation, and MRM.

Key Words: lymphedema, breast cancer, radiotherapy, Taiwan

INTRODUCTION

Lymphedema is the result of a functional overload of the lymphatic system in which lymph volume exceeds transport capacities. Secondary lymphedema attributed to breast cancer surgery and/or radiation therapy is the most significant complication of breast cancer. Breast cancer survivors with secondary lymphedema not only have to contend with the physical effects of the disease, but also to experience increased psychosocial maladjustment, psychological and physical morbidity. As the
swelling progresses, patients may suffer from functional
difficulties at home or at work, feel embarrassed or
distressed, and eventually lose interest in social activities.
All of these significantly affect the quality of life (QOL)
of breast cancer survivors.\[4\]

Worldwide incidence of lymphedema varied. There
are 2 million breast cancer survivors in the United States,
of whom between 10 to 20 percent are thought to have
clinically diagnosed lymphedema;\[5\] and 49 percent of
breast cancer patients have been found to suffer from
self-reported lymphedema.\[6\] An incidence rate of 20 percent
was cited in a review article by Eriskson et al in 2001.\[7\] The
risk factors for lymphedema of breast cancer were found to
be axillary node dissection and/or axillary radiation.\[7\]
The actuarial probability of lymphedema of breast cancer
was predicted by age, number of lymph nodes dissected,
and number of positive lymph nodes.\[8\]

Western countries had the highest breast cancer
incidence, which were 3-4 times the rates in Asia in both
time periods (1973-77, 1993-97); but the number of breast
cancer patients in Asia has increased markedly, and the age
of onset breast cancer has lowered.\[9\] Adaptation to a
western lifestyle has been postulated as being one of the
primary reasons for higher breast cancer rates in developed
countries and for increasing breast cancer incidence among
Asian and Asian American women.\[9\] In Taiwan, the
incidence of breast cancer has become higher than cervical
cancer, and the onset age of breast cancer is between 40 to
59 years old, which is 10 years younger than European and
North American women.\[10\] With the above two reasons,
the risk of arm lymphedema has likewise grown. In spite of
the trend, research into lymphedema of breast cancer in
Taiwanese women remained limited. In particular, no
long-term follow-up and large group studies have been
undertaken in Taiwan. The aim of this study is therefore to
define the long-term incidence of upper extremity lymphedema
in breast cancer patients, and to clarify the risk factors
that predispose lymphedema in Taiwan.

**Materials and Methods**

**Patients**

A cohort of 900 women who had been surgically
treated for breast cancer at Changhua Christian Hospital
in central Taiwan between 1 January 1994 and 31 December 2000 were enrolled in this retrospective study. The study was performed during October 2002. Subjects were excluded if 1) they were deceased at the time of the study; 2) they lost follow-up after their surgery, or 3) they refused to answer the questionnaire that formed part of our study or to have their arm circumference measured.

Five hundred and seventy study subjects were divided
into three main groups according to the differing surgical
techniques for breast cancer surgery. The first group was
479 patients who had been treated by modified radical
mastectomy (MRM); the second group was 87 patients
who had been treated for breast conserving surgery (BC);
and the last group was 4 patients who had received simple
mastectomy. The MRM group (84 percent of our patients)
was by far the largest because of the popularity of this
surgical technique - MRM is considered more acceptable
than other procedures for reducing the possible recurrence
of the cancer in the early years. Both the MRM and BC
groups were divided into sub-groups of patients who had
or had not received radiotherapy (Table 1). The minimal
post-operative period was set at 10 months to exclude any
patients who might have temporary lymphedema.

The medical records of 570 eligible women were
reviewed and all completed the questionnaire and had
their arm circumference measured. The end point of follow-
up was defined as when lymphedema was diagnosed, or
in October 2002.

This study was approved by the Research Ethics
Committee of Changhua Christian Hospital. All of the
patients gave their informed, written consent.

**Data Collection**

We collected possible lymphedema risk factors from
patient’s charts: surgical procedures, the number of
removed lymph nodes, the number of metastatic lymph
nodes, radiotherapy area and dosage, and chemotherapy
details.

**Radiotherapy**

For the purpose of this analysis, the radiation delivery
areas were defined as breast, supraclavicular fossa,
axillary, and internal mammary chain field.

**Lymphedema Questionnaire**
We asked our patients to complete a questionnaire in which they were asked if they had noticed: 1) swelling or a heavy sensation of the operated arm, 2) tightness of the operated arm, 3) a tighter feeling than before in their clothing sleeves. Any positive response to the three questions was defined in this study as ‘self-reported edema’.

Circumferential measurement

A senior physiatrist recorded the circumferential measurement of each participant’s arm as they sat with their arm abducted to 90 degrees, palm-down, on a bedside table placed at a level slightly below the axillary. Measurements were made at the metacarpophalangeal joint and the wrist, and repeated for every 10 cm proximally from the tip of the third digit to the maximum height of the arm. In this series of measurements the difference at any measured point was compared with the non-operated arm. A difference greater than 2 cm was accepted as definite lymphedema.[11,12] This finding marked the end of follow-up period, and from which the accumulative incidence of lymphedema was calculated.

Analysis

To estimate the accumulative incidence of lymphedema,[13] we used the Kaplan-Meier technique. The statistical significance of the difference between the curves in Figure 1 was assessed using the two-tailed log-rank test. We used logistic regression analysis to analyze the influence of the categorized and interval covariates on the development of arm lymphedema. We documented the association of risk factors using the chi-square test. Relative risks were reported with a 95 percent confidence interval. A value of p<0.05 was considered as statistically significant. Statistical analysis was conducted using SPSS 13.0 for Windows (SPSS Inc., Chicago, USA).

RESULTS

Five hundred and seventy patients were studied to assess the frequency and risk factors of lymphedema secondary to breast cancer. The mean follow-up interval after breast cancer surgery was 4.3 (range: 0.08-8.82) years. The mean number of removed lymph nodes was 14.37 (median: 14; range: 1 to 43), and the mean number of metastatic lymph nodes was 2.49 (median: 0; range: 0 to 34). The incidence of self-reported edema was 28 percent (161/570), and the incidence of definitive lymphedema was 8.1 percent (46/570). The mean interval following surgery to developing lymphedema was 1.91 years (median: 1.5 years; range: 0.08 to 7 years). In 84 percent of patients, lymphedema occurred within 3 years of surgery, which meets the criterion for classification as early onset lymphedema.[6] The incidence of lymphedema according to surgical techniques was 8.35 percent (40/479) in the MRM group, 20.86 percent (29/139) in the MRM group with radiotherapy, 6.9 percent (6/87) in the BC group, and 9 percent (6/66) in the BC group with radiotherapy. No lymphedema (0/21) occurred in the BC group without radiotherapy (Table 1). There was a significant difference within the MRM group between those patients who received radiotherapy and those who did not (OR, 7.77; 95% CI, 3.72-16.22; p<0.001). Within the BC group, there was no statistical difference between the radiotherapy and no radiotherapy subgroups. (p=0.998) (Table 1).

Multivariate analysis revealed that the significant risk factors for the development of lymphedema were radiotherapy (OR, 7.49; 95% CI, 3.64-15.4; p<0.001), and surgical technique (MRM; OR, 2.83; 95% CI, 1.11-7.32; p=0.032) (Table 2). The accumulative incidence of lymphedema was 5 percent without radiotherapy vs. 23.5 percent with radiotherapy at the 7th follow-up year (Figure 1). The other variables – including the number of metastatic nodes, the existence of more than 15 resected lymph nodes, whether the patient received chemotherapy, whether the patient was diagnosed after 1999 – were not associated with lymphedema (Table 2).

DISCUSSION

The current study assesses the incidence and risk factors of lymphedema in Taiwanese breast cancer patients who were operated between 1994 and 2000 in a medical institute. It was found that the incidence of self-reported edema was 28 percent and definitive lymphedema was 8.2 percent. The symptoms of lymphedema in our questionnaire were also confirmed in the research of Ridner et al, who found that self-reporting of certain
symptoms such as swelling and tightness might be indicative of developing lymphedema.\textsuperscript{[14]} For the group that we assessed, the incidence of self-reported edema was close to that reported by Bani et al,\textsuperscript{[15]} who declared that it was feasible to assess self-reported lymphedema. Approximately 30 percent of our subjects reported subjective lymphedema indicates that the assessment of lymphedema is newer overlooked in breast cancer patients’ life quality.

Table 1. Incidence of subjective arm edema, and lymphedema

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Subjective edema</th>
<th>Lymphedema</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>570</td>
<td>28.0%(161)</td>
<td>8.2%(46)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRM</td>
<td>479</td>
<td>27.8%(133)</td>
<td>8.4%(40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRM+R/T</td>
<td>139</td>
<td>49.6%(69)</td>
<td>20.9%(29)</td>
<td>&lt;0.001</td>
<td>7.77</td>
<td>3.72-16.22</td>
</tr>
<tr>
<td>MRM-R/T</td>
<td>340</td>
<td>18.8%(64)</td>
<td>3.2%(11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC</td>
<td>87</td>
<td>32.5%(27)</td>
<td>7.2%(6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC+R/T</td>
<td>66</td>
<td>38.5%(25)</td>
<td>9.2%(6)</td>
<td>0.998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC-R/T</td>
<td>21</td>
<td>11.1%(2)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple mastectomy</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MRM=modified radical mastectomy; BC=breast conserving surgery; +R/T= with radiotherapy; -R/T= without radiotherapy

Table 2. Factors predictive of arm lymphedema on multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>7.49</td>
<td>3.64-15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.86</td>
<td>0.42-1.78</td>
<td>0.688</td>
</tr>
<tr>
<td>Surgical technique (MRM vs. BC)</td>
<td>2.83</td>
<td>1.10-7.32</td>
<td>0.032</td>
</tr>
<tr>
<td>Resected nodes&gt;15</td>
<td>1.04</td>
<td>0.54-2.00</td>
<td>0.898</td>
</tr>
</tbody>
</table>

OR= odds ratio; CI=confidence interval

Table 3. Univariate analysis of radiation variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>L.E. (number of L.E./total number)</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose(Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>19.9%(28/141)</td>
<td>2.35</td>
<td>0.92-6.01</td>
<td>0.073</td>
</tr>
<tr>
<td>≤50</td>
<td>9.5%(6/63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation area: Supraclavicular or axillary surgery</td>
<td>20.7%(30/145)</td>
<td>3.59</td>
<td>1.20-10.69</td>
<td>0.022*</td>
</tr>
<tr>
<td>MRM</td>
<td>20.4%(28/137)</td>
<td>2.57</td>
<td>1.01-6.55</td>
<td>0.048*</td>
</tr>
<tr>
<td>BC</td>
<td>9.1%(6/66)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L.E.= lymphedema; *: p value <0.05
The incidence of definitive lymphedema in our study was lower than the cited incidence rate of 20 percent in past studies. In the largest study to date, in which 5868 German breast cancer survivors were investigated, the incidence of clinically diagnosed arm lymphedema was 24 percent. The overall incidence of self-reported arm edema was 26 percent ranking from 0 percent (following sentinel node biopsy) to 56 percent (following axillary dissection and axillary radiotherapy). For this study, we used a criterion of 2 cm circumferential difference between both arms. Although this criterion has been adopted by many researchers, it didn’t easily detect low-grade lymphedema and it might not be appropriate for thinner, oriental females. Arm swelling producing only 1 cm circumference difference was not regards as definite lymphedema by this criteria. The lymphoscintigraphy will be one of the assessment guidelines in such condition that less than 2 cm circumference difference. Patrek et al. reported that the incidence of self-reported swelling in their studies was 49 percent, and 30 percent of patients suffered from moderate and severe lymphedema. Patrek defined measured arm enlargement greater than 2 inches (5.08 cm) as severe lymphedema, greater than 0.5 inches (1.27 cm) as moderate lymphedema, and less than 0.5 inches as mild lymphedema. The incidence of lymphedema per se varies depending on different measuring methods. Though sixty-three percent of patients were analyzed in this study, we believed that if more patients’ data were analyzed and the criteria of lymphedema modified, the incidence of lymphedema would be found to be higher.

In our study, latency period from surgery to the on-
A set of lymphedema was 1.91 years in average, and 84 percent of lymphedema happened within 3 years of surgery, similar to other reports that most lymphedema develops within 1-2 years of breast cancer treatment. Patients receiving radiotherapy have a 7.5-fold higher risk of lymphedema than those who did not undergo radiotherapy, and 23.5 percent of radiated patients will suffer from lymphedema once or more at the end of 7th follow-up year. It is important that patients receiving radiotherapy must pay attention to the possible development of lymphedema even after 7 years latency, especially during the first 3 years, even cancer therapy has completed. It is needed particular surveillance for lymphedema in radiated patients.

In our radiation subgroup, radiation over the supraclavicular or axillary lymph nodes areas was significantly associated with lymphedema. Coen et al. found that nodal irradiation was the only significant risk factor for arm lymphedema in patients receiving BC for early-stage breast cancer. Hinrichs et al. reported that radiation to the dissected axilla incurred high rates of lymphedema. This study found no relationship between the radiation dose and lymphedema. In contrast, Hinrichs et al. found that a higher dose (≥60 Gy) led to a higher risk of lymphedema. Although the relationship between lymphedema and radiation dosage could not be effectively analyzed in this study because 40 percent of our patients received the same dose (5040 cGy), there was a trend toward increased lymphedema with the addition of radiation and with axillary and supraclavicular nodal fields radiation. The effect of radiation dose thoroughly investigated in future studies.

The MRM procedure, when compared with BC surgery, showed a considerably increased risk of lymphedema independent of whether or not patients received radiotherapy. Engel et al. however, reported that the type of surgery did not contribute to arm problems. On the contrary, Schünemann et al. studied over 5000 women and found a 39.5 percent prevalence of arm swelling following radical mastectomy, 24 percent after MRM, and 9.3 percent following BC. The more extensive surgical procedure destroys more lymphatic tissue, and leads to higher incidence of lymphedema.

Edwards and Hinrichs et al. found that the number of the removed lymph nodes and metastatic lymph nodes were not correlated with lymphedema, similar to our finding. However, other authors demonstrated that the increased number of the removed lymph nodes and the presence of axillary metastasis would incur the development of lymphedema. At the time that this study took place and for the period that we analyzed, MRM – the more extensive procedure – was the preferred treatment. BC is now more common, however, and if combined with sentinel lymph node biopsy, the long-term risk of lymphedema should be decreased.

Dissection disrupts the lymphatic system and impairs the patency of the remaining channels secondary to scarring. Radiation can lead to scarring and increased lymphostasis, which can be more predominant in the post-operative axillary and supraclavicular nodal areas. Both dissection and radiation have been associated with increasing rates of lymphedema when used alone and having an additive interaction when used together. The mechanism of lymphedema development is complex. Though breast cancer surgery and radiation lowered the lymph transport capacity, some patients remain in the latency stage for life-long. The acute inflammation, infection, immune deficiency and finally proliferation of adipose tissue also play major roles in progressive lymphedema.

In this study, although the incidence of clinically diagnosed lymphedema was found to be lower than 10 percent, the incidence of self-reported edema was close to 30 percent. This indicates that the actual incidence of lymphedema is underestimated in Taiwan. We found that the type of breast cancer treatment was most consistently correlated with lymphedema. The risk of lymphedema must be borne in mind when the advantages and disadvantages of post-mastectomy radiotherapy (PMRT) are considered. With advanced nodal disease, PMRT clearly reduces the risk of both locoregional failure and death. With less advanced diseases, however, the role of PMRT is less clear. The high incidence and debilitating effects of lymphedema must be weighted against the benefits of PMRT for early stage breast cancer patients. More selective surgery and radiotherapy may be warranted to lower the risk of lymphedema.

This study defined the incidence and risk factors of lymphedema secondary to breast cancer in Taiwanese
patients. The limitations of this report are (a) it was a retrospective cohort study, (b) it only analyzed the treatment-related factors for developing lymphedema and (c) the lymphoscintigraphy was not used to evaluate the patients whose circumference difference less than 2 cm.

**CONCLUSION**

The risk factors of lymphedema secondary to breast cancer were radiotherapy and MRM. We believed the actual incidence of clinically diagnosed lymphedema is underestimated because the 2 cm criteria is not suitable for thinner, oriental females. In future studies, adjusting the circumference criteria for oriental women, added lymphoscintigraphy as assessment guideline, and analyzing additional factors such as patients’ age, obesity, and current infection, will lead a better understanding the mechanism of lymphedema happened in breast cancer patients.

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乳癌後次發性淋巴水腫之發生率及危險因子分析

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淋巴水腫是乳癌最顯見的併發症，會影響病人的生理及心理。本篇研究主要在探討台灣乳癌患者術後淋巴水腫的發生率及危險因子分析。總共在2002年10月回溯性收錄了1994年至2000年間於彰化基督教醫院接受手術治療的乳癌患者共570人。病人自述手臂腫脹發生率為28%(161/570)，兩側手臂圍徑差異大於2cm定義為淋巴水腫之發生率是8.1%(46/570)。百分之84的淋巴水腫的病人在手術後3年内發生；平均為術後1.91年發生淋巴水腫。淋巴水腫在術後第七年的累積發生率：在未接受放射線治療的患者為5%；接受放射線治療的患者則為23.5%。致淋巴水腫的危險因子為放射線治療(OR, 7.49; p<0.001)，及改良式乳房根除術(modified radical mastectomy; OR, 2.83; p=0.032)。在分組分析中，改良式乳房根除術組中放射線治療與淋巴水腫的發生有顯著相關(p<0.001)；但在乳房保留手術(breast conserving surgery)組則無顯著相關。接受放射線治療的病人中，鎖骨上或腋下放射線治療(p=0.022)、以及改良式乳房根除術(p=0.048)都跟淋巴水腫有顯著相關。至於淋巴結切除個數或轉移、化學治療、診斷年、以及放射線劑量則跟淋巴水腫沒有顯著相關。我們認爲乳癌後淋巴水腫跟放射線治療、鎖骨上或腋下照射、以及改良式乳房根除術有顯著相關。（台灣復健醫誌2009；37(4):217-225）

關鍵詞: 淋淋巴水腫(lymphedema)，乳癌(breast cancer)，放射線治療(radiotherapy)，台灣(Taiwan)