นิพนธ์ต้นฉบับ ▪ Original Article

ผลการผ่าตัดเพื่อรักษามะเร็งเต้านมด้วยวิธี Modified Radical Mastectomy ในโรงพยาบาลศรีนครินทร์

อนงค์พร วงศ์พุทธะ, ปุณวัฒน์ จันทรจำนง, ดำเนิน วชิโรดม, องอาจ โสมอินทร์
ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

Outcome of Modified Radical Mastectomy of Breast Cancer in Srinagarind Hospital

Anongporn Wongbuddha , Punnawat Chandrachamnong , Dumnern Vachirodom , Ongart Somintara
Department of Surgery, Faculty of Medicine, Khonkaen University.

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หลักการและวัตถุประสงค์: การรักษามะเร็งเต้านมขึ้นกับระยะของโรค ซึ่งมะเร็งเต้านมในระยะที่ 1-3 การรักษาที่เป็นที่ยอมรับในปัจจุบันวิธีหนึ่งก็คือการผ่าตัดเต้านมด้วยวิธี Modified radical mastectomy (MRM) และอัตราการรอดชีวิตของผู้ป่วยก็ขึ้นกับระยะของโรค การศึกษานี้จึงมีจุดประสงค์หลักเพื่อศึกษาอัตราการรอดชีวิตในระยะเวลา 5 ปี และอัตราการเกิดโรคซ้ำในเวลา 3 ปี ของผู้ป่วยมะเร็งเต้านมที่ได้รับการรักษาด้วยวิธี MRM ในโรงพยาบาลศรีนครินทร์ ดังนั้นการศึกษานี้จึงมีวัตถุประสงค์รองเพื่อดูผลข้างเคียงหลังการผ่าตัด และ ปัจจัยที่อาจจะมีผลต่ออัตราการรอดชีวิตของผู้ป่วยนั่นเอง

วิธีการศึกษา: เก็บข้อมูลผู้ป่วยแบบ retrospective study ในผู้ป่วย มะเร็งเต้านมที่ได้รับการผ่าตัดโดยวิธี MRM จากเวชระเบียนของโรงพยาบาลศรีนครินทร์ ที่เข้ารับการรักษาในโรงพยาบาลตั้งแต่ 1 มกราคม 2547- 1 ธันวาคม 2550

ผลการศึกษา: ผู้ป่วยมะเร็งเต้านมที่ได้รับการรักษาด้วยวิธี MRM ทั้งหมด 215 ราย พบว่าอายุโดยเฉลี่ย 51.1 ปี โดยพบช่วงอายุที่พบมากที่สุดคืออายุ 41-50 ปี ตำแหน่งที่พบมะเร็งเต้านมมากที่สุดอยู่ที่ด้านบนและด้านนอกของเต้านมซึ่งพบด้านซ้ายและด้านขวาได้ไม่แตกต่างกัน ส่วนใหญ่ผู้ป่วยมะเร็งเต้านมจะอยู่ในระยะที่สอง ผลการรักษาอัตราการรอดชีวิตที่ห้าปีของผู้ป่วยมะเร็งเต้านมทั้งหมดเท่ากับร้อยละ 83.6 และอัตราการรอดชีวิตโดยปราศจากโรคที่สามปีของผู้ป่วยมะเร็งเต้านมทั้งหมดเท่ากับร้อยละ 78.9 โดยผลข้างเคียงหลังจากการผ่าตัดที่พบบ่อยที่สุดคือ น้ำเหลืองคั่งใต้แผลผ่าตัด

สรุป: อัตราการรอดชีวิตที่ห้าปีของผู้ป่วยมะเร็งเต้านมทั้งหมดเท่ากับร้อยละ 83.6 และอัตราการรอดชีวิตโดยปราศจากโรคที่สามปีของผู้ป่วยมะเร็งเต้านมทั้งหมดเท่ากับร้อยละ 78.9

Background and Objective: Modified Radical Mastectomy (MRM) is one option for the surgical treatment of breast cancer which is widely used in Srinagarind Hospital. This study aimed to evaluate the outcome of Modified Radical Mastectomy by studying the 5-year survival rate and 3-year disease-free survival rate, complication and risk factor of survival of breast cancer patients at Srinagarind Hospital.

Material and Method: We reviewed the case records of 215 consecutive breast cancer patients who underwent MRM at Srinagarind Hospital, Faculty of medicine, Khonkaen University between January 2004 and December 2007

Result: Of all the 215 patients over the study period, the mean age was 51.1 years old. The most common site of tumor was located by the upper outer quadrant (46.5%). Most patients had Stage II breast cancer: 117 patients (54.4%). The most common operative surgical complication was seroma collection in seven percent of patients. The 5-year survival rate was 83.6% and the 3-year disease-free survival rate was 78.9%.

Conclusion: The 5-year survival rate of breast cancer who underwent MRM was 83.6% and the 3-year disease-free survival rate was 78.9 %.

Keywords: Breast cancer, Modified Radical Mastectomy, 5-year survival rate, 3-year disease-free survival rate.

*Corresponding author : Ongart Somintara, Department of Surgery, Faculty of Medicine, Khonkaen University.
E-mail: ongaso@kku.ac.th

คำสำคัญ: มะเร็งเต้านม, การผ่าตัดด้วยวิธี Modified Radical Mastectomy, อัตราการรอดชีวิตที่ห้าปีของผู้ป่วยมะเร็งเต้านม, อัตราการรอดชีวิตโดยปราศจากโรคที่สามปีของผู้ป่วยมะเร็งเต้านม.

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Introduction

According to worldwide epidemiologic study, breast cancer is the most frequently diagnosed malignancy in female, accounting for over two million cases each year[1]. It is also the leading cause of cancer death in women worldwide. In the United States, breast cancer is the most common female cancer, and the second most common cause of cancer death in women[2]. Breast cancer accounts over 260,000 cases each year and is responsible for over 40,000 deaths in the United States[3].

In Thailand, prevalent rate of breast cancer is 35.7: 100,000[1] which is the most common malignancy. Breast cancer is treated with a multidisciplinary approach involving surgical oncology, radiation oncology, and medical oncology, which has been associated with a reduction in breast cancer mortality[4]. Generally, patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) to the breast and regional nodes with or without radiation therapy (RT). And the operation procedure for breast experienced a long period of time[5]. Modified radical mastectomy (MRM) is one of the standard treatment. Survival rate of breast cancer is up to staging.

According to study Srinagarind Hospital in 1998-2002 showed that the overall 5-year survival rate is 63%, stage I breast cancer was 100%, stage II was 85%, stage III was 39% and stage IV was 9%[6]. Molecular subtype was not included in the study for it was not available and hormonal therapy was not widely used.

This study was purposed to continue studying the result of MRM in treatment of breast cancer in other aspect of 5-year survival rate, 3-year disease-free survival rate, complication and factor affected the treatment.

Materials and Methods

The retrospective study of 215 breast cancer patients who underwent MRM at Srinagarind Hospital between 2004 and 2007. The record was collected , including sex, age at presentation , BMI, method of tissue diagnosis, tumor size, tumor location ,TNM staging, histological subtype , hormone receptor, grading, LVI, hormonal subtype, treatment modality; including neoadjuvant and adjuvant chemotherapy, hormonal therapy, radiation therapy , trastuzumab, complications, the 5-year survival rate and 3-year disease-free survival rate.

The stage IV breast cancer patients, patients who did not have pathological report and patients who had previous breast surgery included MRM, breast conserving surgery, mastectomy with sentinel lymph node dissection were excluded from this study.

The retrospective descriptive study was analyzed by SPSS version 17: continuous data was presented in frequency, mean and percentage. The 5-year survival rate and the 3-year disease-free survival rate were estimated by using the Kaplan-Meier method; $p \leq 0.05$ were considered statistically significant.

Associations with survival rate after modified radical mastectomy were further evaluated by using univariate and multivariate Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals.

Results

Two hundred and fifteen breast cancer patients who underwent MRM at Srinagarind hospital between 2004 and 2007 were included in this study. Table 1 shows the socio-demographic characteristics of the patients who had MRM. They were aged from 28-73 years with a mean of 51.13 years and age group between 41-50 years was the peak age (90 patients, 41.9%). The majority of patients (249, 99.1%) were females. The mean body mass index (BMI) was 23.81 and the peak BMI group were obese (BMI≥25; 80 patients, 40.8%).

Table 2 show the clinical and pathological characteristics of patients. Breast cancer occurred in the right side were 107 (49.8%) patients while in the left side were 108 (50.2%) patients but not seen bilateral tumor in this study. Most tumors were located in the upper outer quadrant 100 (46.5%)

patients, upper inner quadrant 43 (20.0%) patients, lower outer quadrant 28 patients (13.0%) , lower inner quadrant 20 (9.4%) patients and subareolar 22 10.23%) patients. Mean tumor size was 3.73 cm, tumor sizes ranged between 0.5-15cm. Clinically, axillary node involvement was seen in 107 (49.8%) and absent in 108 (50.2%) patients.

There were 215 (100%) patients who had tissue diagnosis; methods of tissue diagnosis were core needle biopsy 82 (38.1%) patients, excisional biopsy 78 (36.8%) patients, FNA 43 (20.0%) patients and incisional biopsy 12 (5.6%) patients. The most common histological type was invasive ductal carcinoma 196 (91.1%) patients. The second most common histological type mucinous carcinoma 10 (4.7%) patients, lobular carcinoma 5 (2.3%) patients, medullary carcinoma 3 (1.4%) patients and only one patient had papillary carcinoma. Immunohistochemistry results were available for the tumors of 167 (77.7%) patients. Of these, 100 (59.9%) were estrogen receptor (ER) positive, 69 (41.3%) were progesterone receptor (PR) positive and 15 (9.4%) were HER 2 positive. There were 113 patients who can classified into the molecular subtype including luminal A 4 (3.6%) patients, luminal B 71 (62.8%)patients, ERb-B2 overexpression 10 (8.8%) patients and Basal-like 28 (24.8%) patients. By tumor grading, grade 2 was the most common type 77 (35.8%)patients. There were 29 (13.5%) patients with lymphovascular invasion.

Two hundred and two patients (94.0%) received chemotherapy and 59 (27.4%) patients received neoadjuvant chemotherapy. The regimen FAC was the most commonly used 50 (24.8%) patients, FEC 40 (19.8%) patients, AC plus T 24 (11.9%) patients, AC 20 (9.9%) patients and other 52 (25.7%) patients included FEC+T, CMF, EC, TAC and TC. 143 (66.5%) patients received hormonal therapy ,47 (21.9%) patients received radiotherapy and only 4 (1.9%) patients received trastuzumab.

There were 32 patients (14.88%) who had postoperative complications. The most common post-operative complication was seroma formation:15 patients (7.0%), wound infection 5 (2.3%) patients, lymphedema 5 (2.3%), hematoma 4 (1.9%), skin flap necrosis 2 (0.9%) and only one patient had frozen shoulder.

The 5-year survival rate was 83.6%, stage I breast cancer 97%; stage II breast cancer 92.2% and stage III 60.3% as show in figure 1. The 3-year disease-free survival rate was 78.9%; stage I breast cancer 90.9%, stage II breast cancer 87.0 % and stage III breast cancer 57.4%. as shown in Figure 2

Univariate analysis showed tumor size(T), nodal status(N), surgical margin positive, lymphovascular invasion(LVI) and HER-2 positive affected the survival outcome.

When comparing T1 to T3 and T4, T3 was about 4.7 times as likely to increase risk of mortality in 5 years (HR 4.7; p<0.005; 95%CI 1.58-14.10) compared to T1 and T4 was about 5.1 times as likely to increases risk of mortality in 5 years compared to T1 (HR 5.11; p<0.003; 95%CI 1.74-14.97)

In nodal status, when comparing N0 to N1, N2 and N3, N1-3 showed statistically significance in

Table 1 Demographic characteristics of breast cancer patients who had MRM in Srinagarind hospital in 2004-2007

Characteristic	Mean	No (%) (n=215)
Age(years)	51.1	
Age group (years)		
<30		3 (1.4)
31-40		24 (11.2)
41-50		90 (41.9)
51-60		58 (27.0)
61-70		31 (14.4)
>70		9 (4.2)
Sex		
Female		249 (99.1)
Male		2 (0.9)
Body mass index(kg/m^2)	23.8	

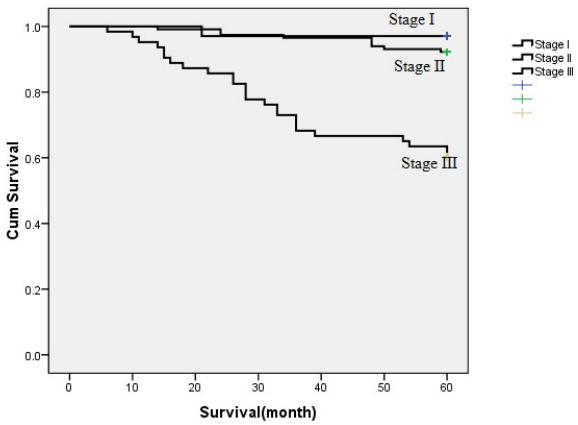

Figure 1 Kaplan-Meier plot showing five-year survival rate

Table 2 Clinico-pathological characteristic of breast cancer patients who had Modified Radical Mastectomy in Srinagarind hospital in 2004-2007

Characteristic	Mean	No (%) (n=215)
Tumor size (cm.)	3.73 (0.5-15)	
Tumor side		
Right		107 (49.8)
Left		108 (50.2)
Tumor location		
Upper outer quadrant		100 (46.5)
Upper inner quadrant		43 (20.0)
Lower outer quadrant		28 (13.0)
Lower inner quadrant		20 (9.3)
Subareolar		22 (10.2)
Axillary lymph node involvement		
Yes		107 (49.8)
No		108 (50.2)
Histology type		
Invasive ductal carcinoma		196 (91.1)
Mucinous carcinoma		10 (4.7)
Lobular carcinoma		5 (2.3)
Medullary carcinoma		3 (1.4)
Papillary carcinoma		1 (0.5)
Immunochemistry ER		
Positive		100 59.9()
Negative		67 (40.1)
Immunochemistry PR		
Positive		69 (41.3)
Negative		98 (58.7)
Immunochemistry HER 2 neu		
Positive		15 (9.4)
Equivalent		29 (18.2)
Negative		116 (68.4)
Ki-67≥14%		110 (93.2)

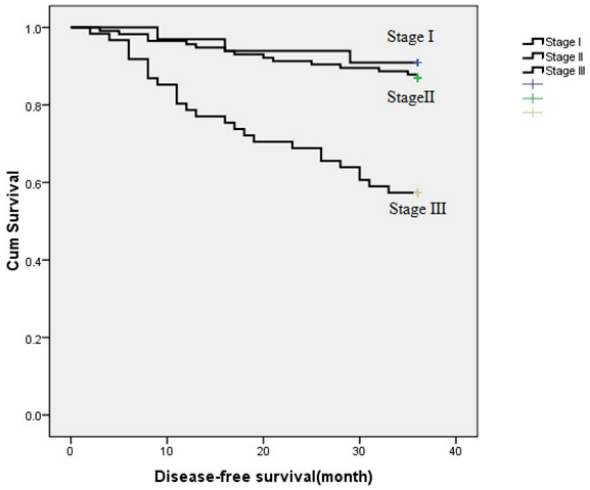

Figure 2 Kaplan-Meier plot showing three-year disease-free survival rate

increased rate of mortality in 5 years; N1 (HR 7.53; p<0.00; 95%CI 2.53-22.40), N2 (HR 9.92; p<0.00; 95%CI 2.90-33.93) and N3 (HR16.08 ; p<0.00; 95%CI 4.70-55.04)

Positive surgical margin positive, LVI and HER-2 positive were also associated with increased mortality rate in 5 years; HR 3.13 (p<0.018; 95% CI1.21-8.07), HR 2.34 (p<0.028;95%CI 1.09-5.00) and HR 6.223 (p<0.001; 95% CI 2.40-16.08)

Factors associated with improving 5-years survival rate included ER positivity (HR 0.477: p<0.048; 95%CI 0.23-0.99) and PR positive (HR 0.405; p<0.037; 95%CI 0.173-0.948). Patients age, BMI, histological grading, Ki-67. (Table 3)

Multivariable analysis showed that T3, N1, N2 and N3 increased risk of death in 5 years. T3; HR3.91 (p<0.02; 95%CI 1.17-13.02), N1; HR 9.45 (p<0.001; 95%CI 2.49-35.87), N2; HR 14.09 (p<0.001; 95%CI 2.97-66.87) and N3; HR 26.11 (p<0.001; 95%CI 5.46-124.92). On the other hand, ER positive decreased risk of death in 5 years; HR 0.23 (p< 0.004; 95%CI 0.09-0.62) (Table 4)

Discussion

MRM is the one of the standard treatment in breast cancer. In this study, most patients were between the ages of 41 and 50 years, had invasive ductal carcinoma. The overall 5-year survival rate is 83.6%: stage I 97%, stage II 92.2% and stage III 60.3%. We compare with previous study from Srinagarind hospital, there is no different survival rate of the stage I and stage II patients but significant increase in

Table 3 Univariate analysis associations with 5-year survival after MRM

Variable		HR	P-value	95% CI
Age	<40/>40	1.250	0.674	0.441-3.542
BMI	<22.9/>23	0.844	0.626	0.425-1.674
T	T1/T2	1.149	0.797	0.399-3.307
	T1/T3	4.724	0.005	1.582-14.108
	T1/T4	5.115	0.003	1.748-14.971
N	N0/N1	7.537	<0.001	2.536-22.404
	N0/N2	9.928	<0.001	2.905-33.935
	N0/N3	16.088	<0.001	4.702-55.045
Margin	Free/ positive	3.132	0.018	1.214-8.076
Grading	G1/G2	1.554	0.481	0.455-5.304
	G1/G3	1.231	0.759	0.327-4.641
LVI	Positive/ negative	2.343	0.028	1.097-5.003
ER	Positive/ negative	0.477	0.048	0.230-0.993
PR	Positive/ negative	0.405	0.037	0.173-0.948
Ki-67	High/ Low(<14%)	0.778	0.735	0.182-3.327
HER 2	Positive/ negative	6.223	<0.001	2.408-16.087

Table 4 Multivariate analysis associations with 5-year survival after MRM

Variable	HR	P-value	95% CI
Age >40 yr	0.448	0.186	0.136-1.474
T2	1.241	0.699	0.416-3.705
T3	3.914	0.026	1.176-13.027
T4	1.593	0.462	0.461-5.505
N1	9.455	0.001	2.492-35.875
N2	14.092	0.001	2.970-66.870
N3	26.117	<0.001	5.460-124.929
Positive surgical margin	3.062	0.099	0.809-11.592
LVI positive	0.985	0.974	0.408-2.382
ER positive	0.238	0.004	0.090-0.627
PR positive	1.123	0.836	0.374-3.366

survival rate of stage III patients is notable. This could be due to development of treatment such as protocol of chemotherapy. Besides, hormonal therapy has not been important role of adjuvant therapy in Srinagarind hospital until the year 2002.

We also correlate our study with the study of American Cancer Society[7] showing 100% survival rate of stage I patients, 93% for stage II and 72% for stage III which is not definitely different from our study.

However overall survival rate of the three studies cannot be compared statistically because this study collected the information of the patients stage I, II and III. The patients with stage IV are not included for the aim of study. Additionally, we exclusively examine the patients who underwent MRM only which is different from previous study performed in patients in stage I-IV and surgical treatment for them is not only MRM but also other types such as breast conservative surgery and mastectomy with sentinel lymph node resection.

The key points illustrated in this study included numbers of factors affect survival rate of breast cancer patients that such as tumor size, nodal status, surgical margin, histological type and grading and lymphovascular invasion. Additionally HER-2 positive is patients were found to decrease survival rate. On the other hand if patients had ER positive and PR positive were increase survival rate.

Post-operative lymphedema was found in 5 (2.3%) patients which much lower than the study of Jan WA et al (40 patients; 26 %)[8]. No evidence of postoperative paresthesia due to damage of the intercostobranchial nerve plexus and winged scapula are found in this study. This could partly be due to incomplete record in some patients.

Molecular subtypes were identified in 113 patients; luminal A 3.5%, luminal B 62.8% , Erb-B2 overexpression 8.8% and basal-like 24.8%. Comparison with Chuthapisith S et al[9]; luminal A 59.3% , luminal B 12.3% , Erb-B2 overexpression 13.3% and basal-like 15.2%. , the result of luminal A and luminal B were different which could be that this study collects data in the early time of molecular subtypes in Srinagarind Hospital, so there may be some error in interpretation. Further study should be performed.

Conclusion

In this study, stage II breast cancer was the most common stage. The most common complication of MRM was seroma formation. The overall 5-year

survival rate and the 3-year disease-free survival rate were not definitely different from this study. But the results of this study are based on retrospective data which was easily affected by some bias. Hence, prospective cohort study need for further evaluation this operation procedure.

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