
SURVIVAL ANALYSIS OF STAGE I-III A BREAST CANCER PATIENTS TREATED WITH MASTECTOMY; 11-YEAR EXPERIENCE IN KING CHULALONGKORN MEMORIAL HOSPITAL

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ABSTRACT

A retrospective review was performed on 357 stage I-III A breast cancer patients who were treated with mastectomy and had been referred to radiation oncology unit, King Chulalongkorn Memorial Hospital, between January 1991 and December 2001. The primary objectives were to report the overall survival and relapse-free survival rates. Survival rates were also stratified by stages, tumor sizes, number of positive axillary lymph nodes and the effect of adjuvant treatment.

The median age in the present study was 49 years. The number of patients were 39, 132, 152 and 34 in stage I, II A, II B and III A respectively. Adjuvant Chemotherapy was given to 247 patients (69.2 %), while adjuvant hormonal therapy was given to 122 patients (34.2 %). Sixty one patients (17.1 %) received both adjuvant chemotherapy and hormonal therapy. Median follow up time was 42.6 months (range 6-136 months).

Five-year overall survival and relapse-free survival rates for the whole group were 72.3% and 58.6%, respectively. The 5-year overall survival rates were 75.2%, 81.0%, 69.0% and 49.8% for stage I, IIA, IIB and IIIA, respectively (P= 0.0001). The corresponding 5-year relapse-free survival rates were 53.9%, 68.1%, 57.5%, and 32.1%, respectively (P= 0.0017). Factors significantly affect overall survival rate composed of stages, T-stage, number of positive lymph nodes and regimens of chemotherapy.

Overall, our results of breast cancer treatment in King Chulalongkorn Memorial Hospital were comparable to the previous reports in medical literatures. This study provided base line data of breast cancer treatment results in Thailand, King Chulalongkorn Memorial Hospital.

Key words: Breast cancer, mastectomy, Stage I-III A, Survival analysis

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INTRODUCTION

Breast cancer has become a major impact on the health problem of Thai women. For several decades, there had been a dramatic increase in the incidence of invasive breast cancer. The estimated incidence rate was increased from 16.3 in 1994 to 7.2 in 1997 per 100,000.^{1,2} In 2000, there were 307 new breast cancer patients treated in King Chulalongkorn Memorial Hospital.³ This figure increased to 374 in 2001.⁴ There was also an increase of new breast cancer patients in Siriraj Hospital.⁵

Surgery is the main treatment for early breast cancer patients. However, postoperative adjuvant therapy is considered an essential part of the management of early breast cancer. Adjuvant chemotherapy typically produces an absolute improvement of about 7-11% in 10-year survival for women aged under 50 with early breast cancer, and of about 2-3% for those aged 50-69.⁶ Similarly, adjuvant tamoxifen treatment substantially improves the 10-year survival of women with positive-estrogen-receptor (ER) tumors and of women whose tumors are of unknown ER status.⁷

Since there is a trend that breast cancer incidence will be the first leading cancer in Thai women and the lack of a large-scaled published data in Thai population, we retrospectively studied our patients as base line data for future comparison. The primary end points were overall survival and relapse-free survival rates. Survival rates were also stratified by stages, tumor sizes, number of positive axillary lymph nodes and the effect of adjuvant treatments.

MATERIAL AND METHOD

Patients

All records of patients with stage I-IIIa operable breast cancer who underwent mastectomy between Jan 1991 to Dec 2001 were retrospectively reviewed. The diagnosis of breast cancer was confirmed histopathologically. Modified radical

mastectomy was performed with level I and II axillary lymph node dissection. Patients with concurrent distant metastasis or previous diagnosis of other cancer were excluded. Neoadjuvant chemotherapy or preoperative irradiation was not eligible. There were 371 patients in this review but only 357 patients were analyzed. Fourteen patients were ineligible; 7 patients refused adjuvant therapy, 4 patients were referred to other hospitals and 3 patients presented with distant organ involvement after metastases work up. Hormonal study, estrogen (ER) and progesterone (PgR) receptors, was evaluated by immunohistochemistry.

Treatment

Since this is a retrospective review, there were mixed groups of adjuvant treatment. Our policy of adjuvant treatment between the reviewed period is summarized in table 1. The details of radiation therapy technique have been reported.⁸ Systemic adjuvant chemotherapy was used in high-risk patients. The regimens were CMF (Cyclophosphamide 600 mg/m², Methotrexate 40 mg/m² and 5 Fluorouracil (5 FU) 600 mg/m² intravenous every three weeks) and FEC (Cyclophosphamide 600 mg/m², Epirubicin 60 mg/m² and 5FU 600 mg/m² intravenous every three weeks) for six cycles. Regarding hormonal therapy, Tamoxifen 20 mg/day was usually prescribed for patients with positive estrogen (ER) and/or progesterone (PgR) receptor. Tamoxifen was given for 5 years and started after completion of adjuvant chemotherapy and/or radiation therapy.

Statistical analysis

Overall survival rate was calculated from the date of surgery to death. Data on patients who were alive or lost to follow-up were censored on the date of last follow-up. Relapse-free survival rate was calculated from the date of surgery to the date of local, regional or distant metastases. Overall survival

and relapse-free survival rates were calculated by the Kaplan-Meier method⁹ and differences between groups were compared by the log-rank test.¹⁰ Subgroup analyses were stratified by stage grouping, T-stage, number of lymph node metastasis and adjuvant treatment. The AJCC 1997 cancer staging system was used in this study.¹¹

RESULTS

Patient characteristics is demonstrated in table 2. Median follow-up time was 42.6 months (range 6-136 months). T1, T2 and T3 tumors were found in 20.2%, 66.9% and 12.9% of the patients, respectively. Regarding nodal status, 43.7% were negative axillary lymph node whereas 56.3% were positive axillary lymph nodes. According to AJCC 1997 stage grouping, there were 10.9%, 37.0%, 42.6% and 9.5% of patients in stage I, IIA, IIB and IIIA, respectively. The correlation between T stage and number of positive axillary lymph nodes is shown

in table 3. The median age in the present study was 49 years.

The adjuvant therapy in the present study is shown in table 4. Adjuvant radiation therapy was given to 55.2% (197/357) of all patients, whereas adjuvant chemotherapy was given to 69.2% of the patients. Of those who received chemotherapy, CMF regimen was used in 61.1% while anthracycline-based regimen was used in 35.2%.

Regarding hormonal receptor status, results of hormonal receptor study were available in 69.5 % (248/357) of cases. Of these patients, ER and/or PgR were positive in 62.1% (154/248). ER and PgR were both negative in 37.9% (94/248). Adjuvant hormonal therapy was given to 34.2% (122/357) of all patients. There were 17.1% (61/357) of patients received both adjuvant chemotherapy and hormonal therapy. Patients who did not received any adjuvant treatment were 12.6% (45/357).

Table 1 Policy of adjuvant treatment scheme in early breast cancer patients who underwent mastectomy between 1991 and 2001 at Radiation Oncology Unit, King Chulalongkorn Memorial Hospital.

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- **Adjuvant radiation therapy**
 1. chest wall alone in
 - close margin less than 2 mm
 - positive resected margin
 - large tumor (T3) without axillary node involvement
 2. chest wall + supraclavicular lymph node field in
 - high risk with axillary node positive less than 4 lymph nodes
 - **Adjuvant chemotherapy in**
 - positive axillary lymph nodes
 - tumor size larger than 1 cm
 - high grade tumor
 - negative ER and PgR
 - **Adjuvant hormonal therapy in**
 - positive ER and/or PgR
-

Table 2 Patient characteristics

	N	(%)
Age		
< 35	30	8.4
35-49	157	44.0
50-69	151	42.3
>70	19	5.3
Pathological T-stage		
T1	72	20.2
T2	239	66.9
T3	46	12.9
T4	-	-
Number of pathological positive lymph nodes		
Negative	156	43.7
N1-3	87	24.4
N4-9	74	20.7
N10 or more	33	9.2
positive node (unspecified number)	7	2
Stage grouping		
I	39	10.9
IIA	132	37.0
IIB	152	42.6
III	34	9.5
Grade		
Unknown	157	44.0
Known grade	200	56.0
G1	17	8.5
G2	113	56.5
G3	70	35.0
Estrogen receptor		
Unknown	118	33.1
Known	239	66.9
Negative	103	43.1
Positive	136	56.9

N = Number of patients

Progesterone receptor		
Unknown	142	39.8
Known		
Negative	113	52.6
Positive	102	47.4
Margin of resection		
> 2 mm	328	91.9
≤ 2 mm	16	4.5
Positive margin	11	3.1
Unknown	2	0.6

Table 3 Correlation between T stage and number of positive axillary lymph nodes

	N0 n (%)	N1-3 n (%)	N4-9 n (%)	N ≥10 n (%)	positive node (unspecified) n (%)	Total n
T1	39 (54.2%)	20 (27.8%)	10 (13.9%)	2 (2.8%)	1 (1.3%)	72
T2	100 (41.8%)	62 (25.9%)	48 (20.1%)	23 (9.6%)	6 (2.6%)	239
T3	17 (36.9%)	5 (10.9%)	16 (34.8%)	8 (17.4%)	0 (0%)	46
Total	156	87	74	33	7	357

Note: N 0 : No axillary lymph node involvement
 N1-3 : one to three positive nodes
 N 4-9 : four to nine positive nodes
 N ≥10 : ten or more than ten positive nodes
 Positive node (unspecified) : Positive lymph node but unspecified number

Table 4 Adjuvant therapy given to the patients

Adjuvant Treatment	N	(%)
Adjuvant radiation		
No	160	44.8
Yes	197	55.2
Adjuvant chemotherapy		
No	110	30.8
Yes	247	69.2
CMF	151	61.1
Anthracycline-based	87	35.2
Other	9	3.6
Adjuvant Hormonal treatment		
No	235	65.8
Yes	122	34.2
- Tamoxifen	118	96.7
- Others	4	3.3
Both chemotherapy and Hormonal treatment	61	17.1
No any adjuvant treatment	45	12.6

Overall survival and relapse-free survival rates (Table 5 and 6)

The 5-year overall survival and relapse-free survival rates for the whole group were 72.3% and 58.6%, respectively (Figure 1 and Figure 2). For stage I, IIA, IIB and IIIA, the 5-year overall survival rates (Table 5) were 75.2%, 81.0%, 69.0% and 49.8%, respectively ($P=0.0001$). The corresponding 5-year relapse-free survival rates were 53.9%, 68.1%, 57.5%, and 32.1%, respectively ($P=0.0017$).

Comparison between negative- and positive-axillary lymph node

The median number of dissected axillary lymph nodes was 15 nodes. According to the number of positive nodes, there were 43.7%, 24.4%, 20.7%

and 9.2% of the patients who had 0, 1-3, 4-9 and ≥ 10 positive nodes, respectively (Table 3). Seven patients (2%) did not have specified number of positive axillary node.

Five-year overall survival rates were 79.7%, 76.6%, 62.9% and 49.1% for patients with NO, N1-3, N4-9 and $N\geq 10$, respectively ($P=0.0024$) (Table 5). The corresponding relapse-free survival rates were 64.7%, 63.4%, 49.8% and 40.8%, respectively ($P=0.0065$) (Table 6).

Comparison of other disease status

Subgroup analyses of patients stratified by adjuvant radiation (no or yes), adjuvant chemotherapy

(no or yes) and chemotherapy regimens (CMF or anthracycline-based) were performed. The 5-year overall and relapse-free survival rates are demonstrated in table 5.

Factors significantly affect overall survival rate composed of stage, T-stage, number of positive lymph node and regimens of chemotherapy. While factors significantly affect relapse-free survival rate composed of stage, number of positive lymph node and adjuvant radiation therapy.

Patients who received adjuvant radiation therapy had statistically significant superior 5-year relapse-free survival rate as compared to those who did not received adjuvant radiation therapy (66.2 % vs 50.2 %). However, 5-year overall survival rates

were comparable (72.1% vs 72.1%).

Five-year overall survival rates in patients who received and did not received adjuvant chemotherapy were 70.3% and 75.8% (P= 0.26), respectively. The corresponding 5-year relapse-free survival rates were 61.2% and 54.4% (p=0.21), respectively.

When stratified by the status of axillary lymph node involvement (Table 6), there was no statistically significant survival difference between the patients who received and those who did not received adjuvant chemotherapy. The survival rates in anthracycline-based chemotherapy subgroup were not superior to CMF regimen subgroup in term of 5-year overall survival or relapse free survival rates.

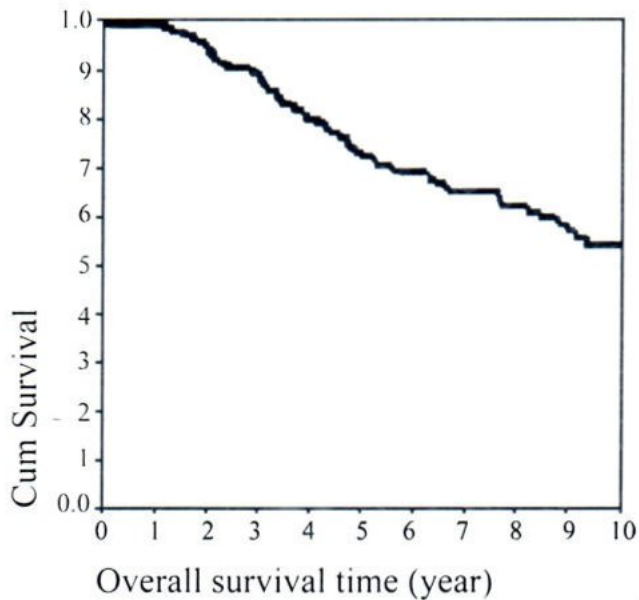


Figure 1 Overall survival curve

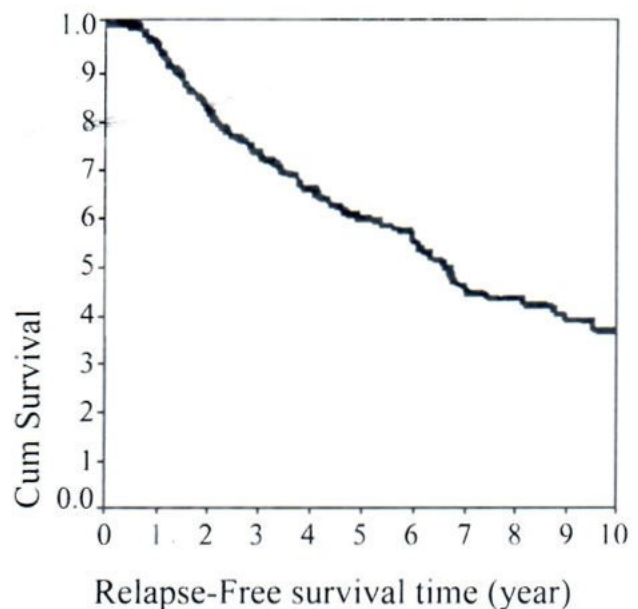


Figure 2 Relapse-free survival curve

Table 5 Five-year overall survival and relapse free survival rates stratified by groups

Group	Number	5-year P-value Overall survival % (SE*)	P-value	5-year relapse -free survival % (SE*)	P-value
Stage					
I	39	75.2 (8.9)	0.0001	53.9 (10.2)	0.0017
IIA	132	81.0 (4.3)		68.1 (4.8)	
IIIB	152	69.0 (4.8)		57.5 (5.0)	
IIIA	34	49.8 (10.4)		32.1 (9.3)	
T-stage					
T1	72	77.8 (6.4)	0.0187	59.8 (7.3)	0.141
T2	239	73.1 (3.6)		61.4 (3.7)	
T3	46	60.2 (9.3)		40.7 (9.4)	
Nodal status					
Negative	156	79.7 (4.1)	0.0024	64.7 (4.7)	0.0065
Positive	201	66.4 (4.2)		54.0 (4.3)	
1-3	87	79.7 (4.1)		63.4 (6.5)	
4-9	74	62.9 (7.4)		49.8 (7.0)	
≥10	33	49.1 (11.2)		40.8 (7.0)	
⊕ unspecified**	7	57.1 (18.7)		42.9 (18.7)	
Adjuvant radiation					
Yes	197	72.1 (4.1)	0.97	66.2 (4.1)	0.0003
No	160	72.1 (4.4)		50.2 (4.8)	
Adjuvant chemotherapy					
Yes	247	70.3 (3.9)	0.263	61.2 (3.8)	0.21
No	110	75.8 (4.7)		54.4 (5.5)	
Chemotherapy regimens					
CMF	151	75.9 (4.5)	0.0059	65.7 (4.7)	0.0548
Anthracycline	87	62.7 (7.7)		57.2 (6.8)	
Other	9	35.0 (19.7)		18.8 (16.7)	

* SE – Standard error

** Positive lymph node but unspecified number

Table 6 Five-year overall and relapse-free survival rates stratified by nodal status and chemotherapy

regimens	N	5-yr Overall survival rate %(SE)*	P-value	5-yr relapse-free survival rate %(SE)*	P-value
LN negative					
Adj Chemo					
Yes	84	80.0 (5.2)	0.799	70.2 (6.5)	0.1592
No	72	78.3 (6.7)		60.4 (6.5)	
LN negative**					
CMF	74	78.0 (7.2)	0.6892	69.7 (7.0)	0.8021
Anthra***	9	75.0 (21.7)		74.1 (16.1)	
LN positive					
Adj Chemo					
Yes	163	66.6 (4.8)	0.924	57.15 (4.6)	0.1977
No	38	65.7 (9.7)		41.0 (10.1)	
LN. positive**					
CMF	77	73.9 (5.9)	0.116	62.4 (6.3)	0.3118
Anthra***	78	60.4 (8.4)		55.1 (7.4)	

* SE - Standard error

** Patients received chemotherapy other than CMF and anthracycline-based regimens were not included

*** anthracycline-based regimen

DISCUSSION

This retrospective study revealed 5-year overall and relapse-free survival rates of 72.3% and 58.6%, respectively. As we know that the most established prognostic factors are the involvement and the number of positive axillary lymph nodes based on adequate dissection of level I and II axillary nodes. When the number of involved nodes increase; relapse rates increase and survival rates decrease.¹² The current study showed statistically significant decrease in overall and relapse-free survival when the number of positive axillary lymph nodes increased.

When T-stage and axillary lymph node were grouped by AJCC 1997 stage grouping,¹¹ we found statistically significant difference in survival rates among different stages. The 5-year overall survival rates reported in the National Cancer Data Base for the year 1989¹¹ were 87%, 78%, 68% and 51% for stage I, IIA, IIB and IIIA, respectively. While the corresponding rates in our study were 75.2%, 81.0%, 69.0% and 49.8%, respectively.

The Early Breast Cancer Trialists¹³ evaluated

the effect of adjuvant polychemotherapy in 2,710 node-negative breast cancer patients. The 5-year disease-free survival rates were 67% and 75% for control and adjuvant chemotherapy groups, respectively. Our current study showed that 5-year relapse-free survival rate in node-negative patients who did not receive chemotherapy was 60.4%, while it was 70.2% in the adjuvant chemotherapy group (table 6).

In the updated report of the Early Breast Cancer Trialists⁶ regarding patients with negative lymph node and under 50 years of age, the five-year survival rates were 83.5% and 86.5% for control and adjuvant chemotherapy groups, respectively. The corresponding survival rates in the 50-69 year-old group were 81.4% and 85.3%. Our result showed that 5-year overall survival rates in node-negative patients were 78.3% and 80% for those who did not receive and those who received adjuvant chemotherapy, respectively. Although patients who received chemotherapy had worse prognostic factor, the 5-years overall survival rates were not inferior. This result underlined the benefit of adjuvant chemotherapy.

For patients with negative axillary lymph node, Fisher et al (NSABP B-23 trial)¹⁴ reported 5-year overall survival rates of 89% for patients treated with CMF and 90% for those treated with AC (doxorubicin plus cyclophosphamide) ($P=0.04$). The 5-year relapse-free survival rates were identical, 87%, for both CMF and AC treated groups. Regardless of chemotherapy regimens, the patients with negative axillary lymph node in our study had a better comparable 5-year overall survival and relapse-free survival. However, this result should be interpreted with caution because of the small number of patients in anthracycline-based subgroup.

Bang¹⁵ reported the study in positive axillary lymph node patients. The patients were randomized between adjuvant AC (doxorubicin plus cyclophosphamide) and CMF. The 5-year overall survival rates for AC group and CMF group were 90% and 86%,

respectively ($P=0.96$). The corresponding 5-year recurrence-free survival rates were 64% and 78% ($P=0.12$).

Levine¹⁶ randomized premenopausal women with node-positive breast cancer between adjuvant intensive CEF (cyclophosphamide, epirubicin and 5-FU) and CMF (classical). The five-year survival rates for CEF and CMF groups were 77% and 70%, respectively ($P=.03$). Whereas 5-year relapse-free survival rates were 63% and 53% ($P=.009$).

French Adjuvant Study Groups¹⁷ reported 565 operable breast cancer patients with positive lymph nodes between adjuvant FEC50 and FEC100 for 6 cycles. The 5-year overall survival rates were 65.3% for FEC50 and 77.4% for FEC100 ($P=0.03$). The 5-year disease-free survival rates were 54.8% and 66.3%, respectively ($P=.03$).

The recent report by Henderson¹⁸ showed that the 5-year overall survival rates were 77% after adjuvant AC (doxorubicin plus cyclophosphamide) and 80% after AC plus paclitaxel. The corresponding disease-free survival rates were 65% and 70%, respectively.

In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence ($=0.006$) and an 11% further reduction in the annual odds of death ($=0.02$) with anthracycline-containing regimens.⁶ Based on the above study, the NCCN guideline suggested that anthracycline-containing regimens are preferred for node positive patients.¹⁹

Our results in patients with positive axillary lymph node showed that 5-year overall survival rate was 65.7% in patients who did not receive adjuvant chemotherapy, while they were 73.9% and 60.4% in patients who received adjuvant CMF and anthracycline-based regimens, respectively. The 5-year relapse-free survival rates were 41.0%, 62.4% and

55.1%, respectively. Since the patients who received anthracycline-based chemotherapy regimen had worse prognostic factors than those who received CMF regimen in our study, this explained the inferior overall survival of anthracycline-based regimen.

CONCLUSION

Overall, our results of breast cancer treatment at Radiation Oncology Unit, King Chulalongkorn Memorial Hospital were comparable to the previous reports in medical literatures. The improvement on diagnostic, pathological and treatment procedures will enhance survival rates in the near future. This study provided a base line data of breast cancer treatment results in Thailand, King Chulalongkorn Hospital.

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