Survival and Prognostic Factors of Stage I-III Breast Cancer

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Objective: *To determine the survival duration of stage I-III breast cancer patients, and to determine prognostic factors for overall survival and disease-free survival in stage I to III breast cancer patients treated with surgery and adjuvant therapy.*
Material and Method: *This retrospective cohort study was conducted by reviewing 166 files of stage I-III breast cancer patients treated with surgery and adjuvant therapy in the Oncology Unit, Department of Medicine, Rajavithi Hospital from January 1st 1998 to December 31st 2007.*
Results: *There were 166 patients whose median age was 48 years. The 5-year overall survival rates for stage I, stage II and stage III were 100.0%, 89.0% and 80.8% respectively (p = 0.11). Multivariate analysis showed that pathological lymph node pN2 status was a significant poor prognostic factor for overall survival (HR = 4.32, 95%CI 1.24-15.04; p = 0.022). The one-, three- and five-year disease-free survival (DFS) rates were 96.7%, 81.4% and 76.7% respectively. Multivariate analysis revealed that pathological pN2 (HR = 4.43, 95%CI 1.44-13.57; p = 0.009), pN3 (HR = 5.16, 95%CI 1.54-17.30; p = 0.008) and progesterone receptor status negative (HR = 5.53, 95%CI 1.85-16.59; p = 0.002) were poor prognostic factors for disease-free survival.*
Conclusion: *The most important prognostic factor affecting disease-free survival and overall survival of stage I-III breast cancer patients was axillary lymph node metastasis. Progesterone receptor status negative influenced disease relapse. Patients with multiple unfavorable risk factors such as lymph node metastasis and progesterone receptor status negative showed poor DFS, and therefore more aggressive adjuvant chemotherapy is required for these patients.*

Keywords: *Breast cancer, Survival, Prognostic factor*

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In 2008, breast cancer ranked as the fifth most lethal cancer, after lung, stomach, liver, and colon cancers, causing 460,000 deaths[1]. The Globocan database for 2002 indicates that the age-standardized rate (ASR) of breast cancer incidence was 67.8 per 100,000 in more-developed regions (Europe, Australia, New Zealand, North America and Japan) and 21.1 per 100,000 in Asia[2]. In Thailand, breast cancer is also the most common cancer in Thai women (ASR = 20.9), and the highest incidence of female breast cancer is found in Bangkok (ASR = 34.1)[3]. In the USA, data from Surveillance Epidemiology and End Results (SEER) from 17 SEER geographical areas during the period 1999-2005 showed that the 5-year survival rate of breast cancer all stages was 89.1%. The five-year survival rate for localized disease, regional disease, distant metastasis and unstaged were 98.3%, 83.5%, 23.3% and 57.7% respectively[4].

Prognostic factors for breast cancer patients are important for identifying groups with a high risk of recurrent disease and for improving overall survival duration in early-stage breast cancer. Previous studies have shown that tumor size, histological grading, lymph node involvement, hormonal receptor status, HER2 status and lymphovascular invasion influenced both overall and disease-free survival in breast cancer patients[5-8]. Identifying prognostic factors of breast cancer patients could indicate proper treatment modality for patients with different types of risk factors. However, only a few studies of prognostic factors for survival in breast cancer have been conducted in Thailand. Rajavithi Hospital is one of the tertiary care hospitals to which many cancer patients are referred for cancer treatment. This has prompted the authors to do a retrospective study of stage I-III breast cancer patients after curative surgery treated in the Department of Medicine in order to determine prognostic values for overall and disease- free survival of various pre-

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treatment characteristics and types of treatment in Thai patients.

Material and Method

The present study was a retrospective cohort study conducted by examining selected medical files of patients with breast cancer stage I, II and III after surgery who were treated in the Oncology Unit, Department of Medicine, Rajavithi hospital during the ten-year period January 1st 1998 to December 31st 2007 as approved by the Ethics Committee on Research Involving Human Subjects, Rajavithi Hospital, Bangkok, Thailand. Patients' status was followed throughout this period from medical records.

Nine variables retrospectively studied as potential prognosis variables included: age, histological grade, lymphovascular invasion, hormonal receptor status (estrogen receptor (ER) and progesterone receptor (PR)), TNM stage, primary tumor (T), regional lymph node (N), and HER2 status. One potential therapeutic prognostic variable also included in the analyses was the type of adjuvant treatment received including adjuvant chemotherapy, adjuvant radiotherapy and adjuvant hormonal therapy. Exclusion criteria were patients with locally advanced disease with inoperable breast cancer and metastatic disease. TNM staging was used in the present study[9].

All stage I, II, III breast cancer patients received standard surgery. Most of the patients received standard treatments based on disease stage including neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiation and adjuvant hormonal treatment. Regimens of neoadjuvant and adjuvant chemotherapy used in the present study included doxorubicin-based chemotherapy, cyclophosphamide/methotrexate/5-fluorouracil (CMF) and taxanes.

Overall survival time was calculated from the date of diagnosis to the time to death which was defined as time to death or time to last follow-up before death. Disease-free survival time was calculated from the date of diagnosis to the time to recurrence which was defined as time to the first incidence of recurrence, death by any cause or time to last follow-up before death.

Statistical analysis

Overall survival time was estimated using the method of Kaplan and Meier[10]. Twelve variables were included for analyses to identify prognostic factors for overall and disease-free survival. Comparisons of cumulative survival were obtained by univariate analyses using the log-rank test[11] and multivariate analyses were performed using Cox proportional hazard regression. A p-value < 0.05 was considered statistically significant.

Results

Patients and tumor characteristics

From 1st January 1998 to 31st December 2007, 166 patients with stage I-III breast cancer were identified who had been treated with surgery alone or surgery plus adjuvant or neoadjuvant treatment. Fifty-six percent of the patients were from Bangkok and its perimeter. Patient characteristics are listed in Table 1. The median age of patients was 48 years. The most common histological type was invasive ductal carcinoma (95.2%). Invasive lobular carcinoma was found in 2 patients (1.2%). Four patients had mucinous colloid carcinoma, one patient had infiltrating lobular and ductal carcinoma, and one patient had atypical medullary carcinoma. Histological gradings 1, 2, 3 and unknown were found in 11.4%, 28.3%, 28.3% and 32% of patients respectively.

Estrogen receptor and progesterone receptor status were positive in 54% and 36% of patients respectively, and ER negative and PR negative were found in 39% and 54% of patients respectively, while unknown ER and PR status were found in 7% and 10% of patients. HER2 positive (immunohistochemistry (IHC) positive 3+) status was found in 30% of patients and HER2 negative (IHC 0-1+) was found in 26%. Equivocal HER-2 (IHC 2+) and unknown HER-2 status were found in 7% and 37% of patients, respectively.

The most frequently-occurring primary tumor size found was T2 (64%). About half of the patients had negative regional lymph node (pN0). Regional lymph node status pN1, pN2 and pN3 were found in 28%, 11% and 10% respectively. TNM Stage I, II and III were found in 10%, 62% and 28% of patients.

Treatment modalities

With regard to surgical procedures, 160 patients (96.4%) underwent modified radical mastectomy (MRM) and 4 patients (2.4%) had breast conservative surgery with axillary lymph node dissection. One patient had only wide excision and another one had mastectomy without lymph node dissection.

Three patients (1.8%) received only pre-operative chemotherapy, including CMF regimen for 6 cycles (1 patient) and doxorubicin/cyclophosphamide (AC) regimen for 4 cycles (2 patients). Nine patients

Table 1. Patient characteristics

Variables	Total	
	n	%
Age at diagnosis		
< 40	33	19.9
40-49	59	35.5
50-59	43	25.9
≥ 60	31	18.7
Median age	48	
Histological type		
Invasive ductal carcinoma	158	95.2
Invasive lobular carcinoma	2	1.2
Others	6	3.6
Histological grading		
Grade 1	19	11.4
Grade 2	47	28.3
Grade 3	47	28.3
Unknown	53	32.0
Lymphovascular invasion		
No	18	10.8
Yes	16	9.6
Unknown	132	79.5
ER status		
Negative	65	39.2
Positive	89	53.6
Unknown	12	7.2
PR status		
Negative	89	53.6
Positive	60	36.1
Unknown	17	10.2
HER 2 status		
IHC = 0	36	21.7
IHC = 1+	6	3.6
IHC = 2+	12	7.2
IHC = 3+	50	30.1
Unknown	62	37.3
Primary tumor (T)		
T1	21	12.7
T2	106	63.9
T3	26	15.7
T4	13	7.8
Regional lymph node (N)		
pN0	83	50.0
pN1	47	28.3
pN2	19	11.4
pN3	17	10.2
TNM Staging		
I	16	9.6
II	103	62.0
III	47	28.3

ER = estrogen receptor, PR = progesterone receptor

(5.4%) received pre-operative chemotherapy followed by adjuvant chemotherapy. The patients who received pre-operative chemotherapy were T3 lesion (5 patients), T4 lesion (6 patients) and T2 lesion (1 patient). Pre-operative chemotherapy regimens included cyclophosphamide/doxorubicin/5-fluorouracil (CAF), AC, CMF, and paclitaxel. One hundred and forty-three patients received adjuvant chemotherapy (85.8%). Adjuvant chemotherapy regimens which were used in the present study included CMF regimen (68%); CAF regimen (14.5%); AC regimen (14.5%); and 4 patients (3%) received other regimens [1 patient received 5-fluorouracil/epirubicin/cyclophosphamide (FEC), 1 patient received paclitaxel, and 2 patients received intravenous doxorubicin combined with oral cyclophosphamide].

Forty-three patients (26%) received adjuvant radiotherapy. Seventy percent of patients received adjuvant hormonal therapy including tamoxifen in the majority of cases, and only one patient received adjuvant aromatase inhibitor.

Clinical outcome

Survival analysis

The median follow-up time of the present study was 58 months (range, 7-185 months). At the date of analysis, 18 patients had died (10.8%): 16 patients had died from breast cancer, and 2 from non-treatment-related heart failure. The median overall survival duration was not reached (Fig. 1). The 1-year, 3-year and 5-year survival rates of all 166 patients were 98.0%, 92.1% and 92.1%, respectively (Table 2). The 5-year survival rate of stage I, stage II and stage III breast cancer were 100.0%, 89.0% and 80.8% respectively ($p = 0.11$).

Univariate survival analysis

Univariate survival analysis by Kaplan Meier and log-rank test showed that significant factors for longer survival were primary tumor T1 ($p = 0.044$) and no regional lymph node involvement pN0 ($p = 0.027$) (Table 2). The other tested variables, including age, TNM staging, histological grading, lymphovascular invasion, hormonal receptor status, HER2 status and adjuvant treatment were not statistically significant factors affecting shorter or longer survival.

Multivariate analysis

Survival duration was further modeled with multivariate Cox regression analysis employing a proportional hazard rate hypothesis. Primary tumor and

Table 2. Univariate overall survival analyses of possible prognostic factors in stage I –III breast cancer

Variable	n	1Y- SR %	3Y-SR %	5Y-SR%	Cumulative survival (%)	p-value
Over all	166	98.0	92.1	92.1	81.9	
Age						0.767
< 40	33	100.0	92.6	92.6	92.6	
40-49	59	98.0	90.7	90.7	81.7	
50-59	43	100.0	95.1	88.1	79.3	
≥ 60	31	93.3	89.6	79.1	79.1	
TNM Staging						0.108
Stage I	16	100.0	100.0	100.0	100.0	
Stage II	103	100.0	95.6	89.0	80.8	
Stage III	47	92.6	80.8	80.8	80.8	
Histological grading**						0.066
Grade 1 + Grade 2	66	100.0	96.0	86.5	86.5	
Grade 3	47	95.3	85.0	80.5	63.7	
Lymphovascular invasion						0.361
No	18	100.0	100.0	100.0	100.0	
Yes	16	100.0	92.9	82.5	82.5	
Unknown	132	97.6	92.3	87.4	80.8	
Estrogen receptor						0.628
Negative	65	93.3	91.2	86.0	78.2	
Positive	89	100.0	92.1	88.2	82.5	
Unknown	12	100.0	100.0	100.0	100.0	
Progesterone receptor**						0.069
Negative	89	91.1	84.9	83.0	75.8	
Positive	60	98.2	95.9	95.9	90.3	
HER2 status						0.809
0	36	93.5	90.1	84.5	84.5	
1+	6	100.0	100.0	100.0	50.0	
2+	12	100.0	90.0	90.0	90.0	
3+	50	97.8	91.1	83.8	76.2	
Unknown	62	100.0	93.6	91.0	87.7	
Tumor size						0.044
T1	21	100.0	100.0	100.0	100.0	
T2	106	100.0	95.6	88.9	79.7	
T3 + T4	39	91.1	77.5	77.5	77.5	
Lymph node status						0.027
pN0	83	100.0	97.2	91.1	88.1	
pN1	47	100.0	94.9	91.2	79.5	
pN2	19	88.9	70.6	70.6	70.6	
pN3	17	92.9	84.4	84.4	84.4	
Adjuvant hormonal therapy						0.638
No	50	92.5	89.5	85.0	85.0	
Yes	116	100.0	93.2	88.9	81.5	
Chemotherapy*						0.255
No	11	100.0	100.0	100.0	100.0	
Yes	155	97.1	91.6	86.9	80.7	
Adjuvant radiotherapy						0.807
No	123	96.3	93.4	87.6	79.9	
Yes	43	91.8	88.5	88.5	88.5	

1Y-SR = 1-year survival rate, 3Y-SR = 3-year survival rate, 5Y-SR = 5-year survival rate, chemotherapy* = pre-operative chemotherapy (1.8%), pre-operative chemotherapy plus adjuvant chemotherapy (5.4%) and adjuvant chemotherapy alone (85.8%), ** number may not be added up the total number due to missing data (unknown)

regional lymph node involvement factors were included in the proportional Cox regression analysis, and only lymph node pN2 status was found to be a significant poor prognostic factor for survival (HR = 4.32, 95%CI 1.24-15.04; p = 0.022) (Table 3).

Disease-free survival

Recurrent disease was found in 36 instances including 4 loco-regional (2.4%) and 32 distant-metastasis occurrences (19.3%). Distant metastases were found in the lung of 22 patients (13.3%), the bone of 15 patients (9%), the liver of 11 patients (6.6%), the skin of 7 patients (4.2%) and the brain of 5 patients (3%). The median duration of disease-free survival (DFS) was not reached. However, the DFS rates of all patients at 1, 3 and 5 years were 96.7%, 81.4% and 76.7% respectively (Table 4).

Univariate analysis for disease-free survival

Univariate survival analysis by Kaplan Meier and log-rank test showed that the statistically significant factors for longer DFS time were histological grade 1 plus 2 (p = 0.013), progesterone receptor status positive, (p < 0.001) (Fig. 2) and no regional lymph node involvement pN0, (p = 0.042) (Fig. 3). The other tested variables including age, TNM staging, lymphovascular invasion, estrogen receptor status, HER2 status, primary tumor size, and adjuvant treatment were not statistically significant in determining shorter or longer DFS time (Table 4).

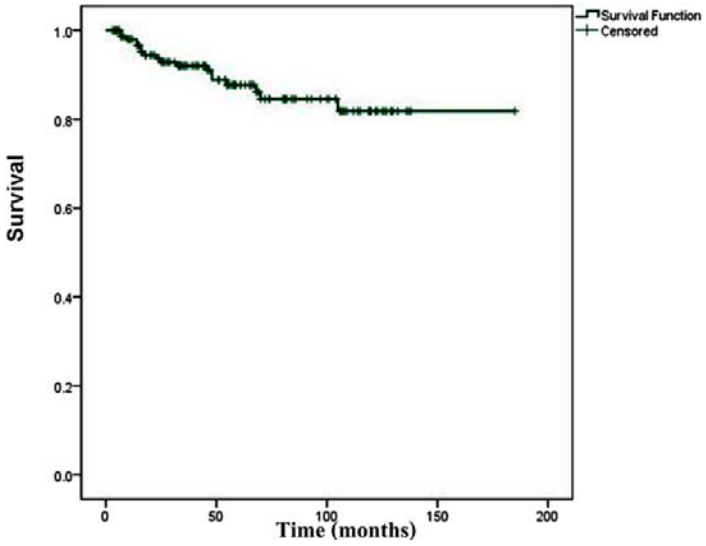

Fig. 1 Overall survival curve, median duration overall survival was not reached. The one-, three-, and five- year survival rates for all stage I-III breast cancer were 98.0%, 92.1% and 92.1% respectively

Table 3. Multivariate analyses of the relationship between prognostic factors and survival time of early stage breast cancer by Cox proportional hazard model

Variable	HR	95%CI	p-value
Tumor size			
T1 + T2	Ref[1]		
T3 + T4	2.15	0.75-6.20	0.155
Regional lymph node			
pN0	Ref[1]		
pN1	1.56	0.47-5.13	0.465
pN2	4.32	1.24-15.04	0.022
pN3	1.50	0.27-8.26	0.644

HR= Harzard Ratio, 95% CI of HR = 95% confidence interval

Table 4. Univariate disease-free survival analysis of possible prognostic factors in stage I-III breast cancer

Variable	n	1Y-DF SR %	3Y-DF SR %	5Y-DF SR %	Cumulative DFS (%)	p-value
Over all	166	96.7	81.4	76.7	68.9	
Age						0.951
< 40	33	93.1	85.3	75.3	75.3	
40-49	59	92.0	82.6	82.6	69.5	
50-59	43	80.9	78.3	72.0	64.0	
≥ 60	31	96.7	80.5	76.0	70.6	
TNM Staging						0.063
Stage I	16	92.9	84.4	84.4	84.4	
Stage II	103	95.8	85.0	80.5	70.7	
Stage III	47	80.0	71.5	64.3	58.5	
Histological grading**						0.013
Grade 1 + Grade 2	66	92.8	82.3	77.2	73.1	
Grade 3	47	97.7	67.7	56.4	40.4	
Lymphovascular invasion						0.377
No	18	100.0	85.7	85.7	85.7	
Yes	16	86.2	77.5	64.6	64.6	
Unknown	132	91.0	82.0	76.6	68.2	
Estrogen receptor						0.467
Negative	65	88.6	79.9	71.0	62.3	
Positive	89	93.7	82.2	80.3	72.5	
Unknown	12	85.7	85.7	85.7	85.7	
Progesterone receptor**						< 0.001
Negative	89	86.3	78.3	65.0	57.3	
Positive	60	98.2	93.5	93.5	86.3	
HER2 status						0.989
0	36	90.0	82.6	77.7	68.0	
1+	6	83.3	83.3	83.3	41.7	
2+	12	90.9	77.9	77.9	77.9	
3+	50	91.0	81.2	73.8	59.0	
Unknown	62	92.7	80.7	74.0	71.1	
Tumor size						0.306
T1	21	94.4	88.1	88.1	88.1	
T2	106	94.9	82.3	76.5	64.2	
T3 + T4	39	82.0	75.3	70.6	70.6	
Lymph node status						0.042
pN0	83	96.0	87.3	83.4	80.7	
pN1	47	87.8	78.6	75.5	60.8	
pN2	19	81.9	75.0	56.3	56.3	
pN3	17	80.7	66.0	66.0	49.5	
Adjuvant hormonal therapy						0.139
No	50	92.7	74.3	67.0	61.9	
Yes	116	92.8	83.8	79.9	71.7	
Chemotherapy*						0.393
No	11	78.8	78.8	78.8	52.5	
Yes	155	92.1	81.6	76.6	69.9	
Adjuvant radiotherapy						0.808
No	123	91.9	80.4	77.9	69.3	
Yes	43	89.5	83.9	73.2	67.9	

1Y-DF SR = 1 year disease free survival rate, 3Y-DF SR = 3 year disease free survival rate, 5Y-DF SR = 5 year disease free survival rate, DFS = Disease free survival, chemotherapy* = pre-operative chemotherapy (1.8%), pre-operative chemo therapy plus adjuvant chemotherapy (5.4%) and adjuvant chemotherapy alone (85.8%), ** number may not be added up the total number due to missing data (unknown)

Multivariate analysis for disease free survival

Disease-free survival duration was further modeled with multivariate Cox regression analysis employing a proportional hazard rate hypothesis.

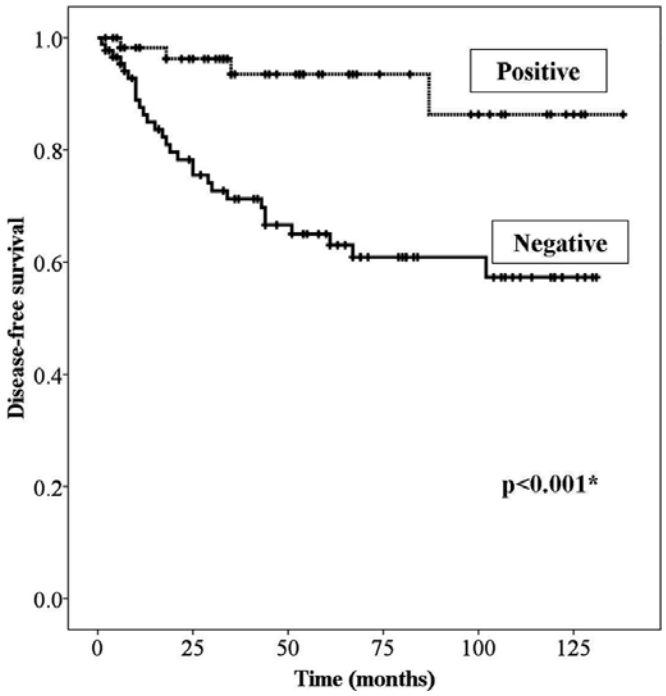

Fig. 2 Comparison of disease-free survival curves of patients by progesterone receptor status ($p < 0.001$). Disease-free survival difference between progesterone receptor positive, and negative groups was shown

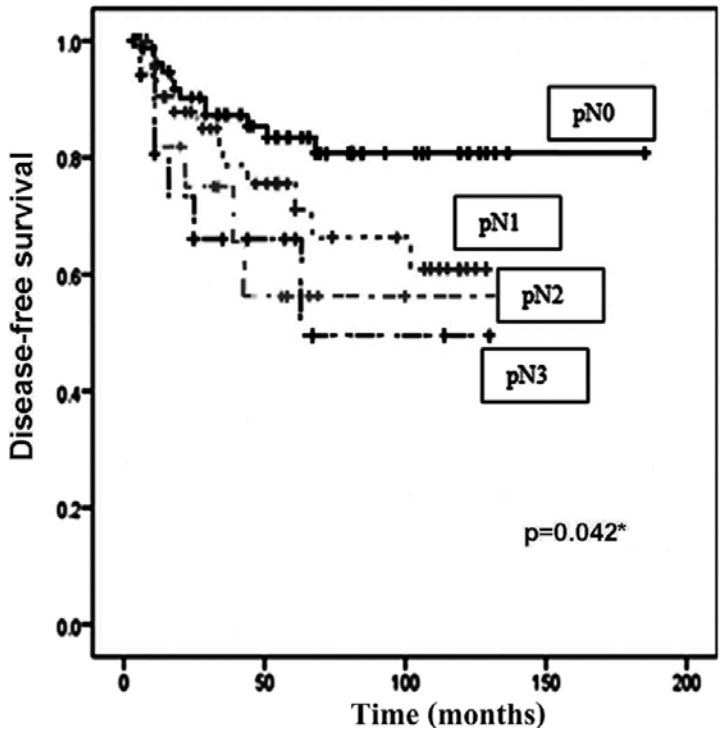

Fig. 3 Comparison of disease-free survival curves of patients by pathological lymph node involvement ($p = 0.042$). Disease-free survival difference between pathological pN0, pN1, pN2 and pN3 groups was shown

Table 5. Multivariate analyses of the relationship between prognostic factors and disease free survival time of early stage breast cancer by Cox proportional hazard model

Variable	HR	95%CI	p-value
Histological grading			
Grade 1 + Grade 2	Ref[1]		
Grade 3	1.78	0.78-4.07	0.174
Progesterone receptor			
Positive	Ref[1]		
Negative	5.53	1.85-16.59	0.002
Lymph node status			
pN0	Ref[1]		
pN1	1.97	0.76-5.13	0.165
pN2	4.43	1.44-13.57	0.009
pN3	5.16	1.54-17.30	0.008

HR = Harzard ratio, 95%CI of HR = 95% confidence interval

Histological grade, progesterone receptor and regional lymph node involvement factors were included in the proportional Cox regression analysis. Progesterone receptor negative was found to be a poor prognostic factor for disease-free survival (HR = 5.53, 95%CI 1.85-16.59; p = 0.002). Lymph node status pN2 and pN3 were also found to be poor prognostic factors for disease-free survival (HR = 4.43, 95%CI 1.44-13.57; p = 0.009 and HR = 5.16, 95%CI 1.54-17.30; p = 0.008, respectively) (Table 5).

Discussion

The median age of patients in the present study was 48 years old which was comparable with that of patients reported on in other publications in Thailand and in Asia (49-50 years old)[5,12,13]. The most common histological type was invasive ductal carcinoma (95.2%) which is comparable with findings in Thailand and Hong Kong populations (82%-93%)[5,13]. Sixty-two percent of patients in the present study were diagnosed with stage II disease as the common stage diagnosed group which is similar to data collected from US breast cancer patients from 1999-2005 which showed that 60% of breast cancer cases were diagnosed at the localized stage[4]. Other studies from Thailand and Hong Kong also demonstrated that stage II breast cancer was the most common stage of breast cancer (around 47%)[5,13]. Grade 2 and 3 were common histological gradings (28%) found in the presented study which was comparable with findings in reports from Thailand and other Asian countries (30-48%)[5,6,12,13]. Estrogen and progesterone receptors were positive in 54% and 36% respectively in the present study which is in keeping with results from other reports in Thailand and other Asian countries (ER 53-55%; PR 41-43%)[6,12,13]. Thirty percent of patients were HER2 positive which is comparable with the results reported by Slamon et al[14]. However, it should be noted that HER2 testing in the present study was done in only 63% of our patients.

Five-year survival and DFS rates were 92.1% and 76.7%, respectively. Another study of early breast cancer (stage I and II) treated with breast conservative surgery and radiotherapy reported 5-year survival and DFS rates of 95% and 88%, respectively[6] which is comparable with the present results. Five-year stage-specific survivals of patients in the present study were 100% for stage I, 89% for stage II and 80.8% for stage III, which is in keeping with data from the SEER data (females of all races and ages between the years 1999 and 2005) which demonstrated that the 5-year survival rate was 98.3% for localized disease and 83.5% for regional disease[4]. Other studies from Thailand and other Asian countries reported that the 5-year stage-specific survival rates of breast cancer were 97-100% for stage I, 84-95% for stage II and 64-66% for stage III[5,6,13]. The 5-year survival rate of patients in stage III in the present study was 15% higher than that of the patients in other studies in Thailand[5] and Hong Kong[13] in the same period of time (1997-2007). Although the stage-specific survival of patients in the present study was comparable to that of patients in other studies, the shorter survival associated with a later stage of diagnosis of the disease emphasizes the importance of the need for early diagnosis. Only 10% of the present study presented with stage I disease

(the majority presented with stage II and III) which is lower than the figure reported from Hong Kong, where 22% of patients were diagnosed at stage I disease[13]. Although breast cancer screening facilities are available in Thailand, the centers for screening are not widely distributed in the country and Thailand does not have a population-screening program. Therefore, another way to improve the quality of care for breast cancer in Thailand would be to start a population-screening program.

Prognostic factors of breast cancer have been studied and have demonstrated that tumor size, lymph node status, staging, histological grade, vascular invasion, ER, PR and HER2 status have an impact on survival and disease recurrence[6-8,15-17]. The presented study, using univariate analysis, showed that tumor size and lymph node status had an impact on overall survival. However, using multivariate analysis, pathological N2 status (HR = 4.32, p = 0.022) was the only factor that had a statistically significant impact on overall survival. This result, which is in agreement with a report from Korea, suggested that number of lymph node, T stage, nuclear grade and HER2 status significantly affected early breast cancer patients' survival when multivariate analysis was used[6]. The fact that multivariate analysis in the present report did not demonstrate that T stage, nuclear grade and HER2 status were prognostic factors could be due to the limited number of patients and the fact that not all patients were tested for HER2 status.

In evaluating the impact of pathological factors on DFS, high histological grade, high lymph node involvement and progesterone receptor status negative were significantly poor prognostic factors when univariate analysis was used. Multivariate analyses also confirmed that pN2, pN3 (HR = 4.43, p = 0.009; HR = 5.16, p = 0.008) and absence of progesterone receptor (HR = 5.53, p = 0.002) were poor prognostic factors for disease-free survival. The identification of lymph node metastasis as a poor prognostic factor in the present study was confirmed by the results of the multivariate analysis for distant disease after mastectomy for stage I-II breast cancer from the European randomized trials which showed that lymph node-positive status (HR= 1.8, p < 0.0001) was one of the poor prognostic factors affecting DFS[7]. However, the European study also showed that large tumor size (HR = 2.4, p = 0.002), high histological grade (HR = 1.51, p = 0.004) and vascular invasion (HR = 1.73, p = 0.0001) were poor prognostic factors; this was not found in the current study. In addition, the study from Korea also showed that histological grade, tumor size, staging, and high lymph node involvement were poor prognostic factors according to univariate analysis results, and only histological grade, tumor size and number of lymph node were bad prognostic factors affecting DFS of stage I-II breast cancer patients according to multivariate analysis results[6]. It can be concluded that high lymph node involvement is a strong predictor for DFS in stage I-III breast cancer from multivariate analysis from Asian and European studies, and from this present study.

Absence of progesterone receptor was a poor prognostic factor for disease-free survival, demonstrated by univariate and multivariate analyses in the present study. This finding was also found in a previous study which showed that the presence of progesterone receptors was a prognostic factor in stage II breast cancer patients receiving adjuvant therapy. That study also demonstrated that the presence of progesterone receptors was more significant than that of estrogen receptors for predicting time to recurrence in multivariate models[16].

In evaluating the impact of treatment on overall and disease-free survival, adjuvant chemotherapy, hormonal therapy and radiotherapy were not prognostic factors for either overall survival or DFS in the present study. This could be due to the fact that all of the patients received adjuvant treatment, 93% of the patients received adjuvant chemotherapy and 70% received adjuvant hormonal therapy. Therefore, it was not possible to reach any conclusion about survival duration differences.

Regarding regimens of adjuvant chemotherapy in the present study, the majority of the patients who received adjuvant CMF (68%) and doxorubicin-based (29%) treatment had a 5-year overall survival rate of 86.9 % which was comparable to that reported in the study by the GEICAM group from Spain which showed that 5-year overall survival rates of patients who received adjuvant CMF and FAC were 69% and 75% respectively[17].

As multivariate analysis in the present study showed, patients with high lymph nodes involvement had significantly poor DFS and overall survival outcome (HR 5.16 and 4.32). A regimen of adjuvant chemotherapy is one of the factors which could have an impact on the survival of the node-positive breast cancer patients. According to data from 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 and 11% further reduction in the annual odds of death with anthracycline-containing regimens; these results were statistically significant[18]. In the present study the 5-year DFS and 5-year overall survival rates of stage III breast cancer were 64.3% and 80.8% which was comparable with the adjuvant FAC (5-fluorouracil/doxorubicin/cyclophosphamide) regimen in node-positive early breast cancer patients but inferior to the higher-potency TAC (docetaxel/doxorubicin/cyclophosphamide) regimen which had better 5-year DFS and overall survival rates of 75% and 87% respectively[19]. Adjuvant weekly paclitaxel after 4 cycles of doxorubicin and cyclophosphamide (AC) was studied in the node-positive or high risk node-negative early breast cancer and showed high 5-year DFS and overall survival rates of 81.5% and 89.7% respectively[20]. Therefore, to improve outcome in our patients, anthracycline-containing regimens should be used for stage I-III breast cancer patients with lymph node-positive status. In high risk patients with pN2 and pN3 diseases who had good performance status, regimens containing taxanes e.g. weekly paclitaxel after AC or TAC regimens, should be offered.

Regarding HER2 status, 37% of patients did not have HER2 receptor testing. This was probably due to the specific time period of study, as the use of anti-HER2 therapy, such as trastuzumab, was still neither widely available nor affordable; therefore HER2 testing was not performed. Adjuvant trastuzumab plus adjuvant chemotherapy in HER2 positive breast cancer patients showed a significant reduction in DFS occurrence rates and death rates with HR 0.52, $p < 0.001$ and HR 0.61, $p < 0.001$, respectively[21]. In addition to using more effective adjuvant chemotherapy regimens in high-risk early breast cancer patients as described previously, adjuvant trastuzumab should also be provided concurrently to patients with HER2 positive.

In conclusion, the present study demonstrated that stage I-III breast cancer patients after curative surgery who were treated with adjuvant treatment had good overall survival and DFS rates. The important prognostic factors for overall and disease-free survival by univariate and multivariate analyses were regional lymph node status, progesterone receptor status, histological grade, and tumor size. In order to improve survival outcome, patients with poor prognostic factors especially pN2 and pN3 should be treated with higher-potency adjuvant chemotherapy regimens. HER2 testing should be routinely done and adjuvant-targeted therapy for HER2-overexpression patients should be provided if affordable. Finally, a breast cancer population-screening program should be initiated in Thailand to identify the early stage I breast cancer patients, who have the best chance of survival.

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Potential conflicts of interest

None.

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การรอดชีพและปัจจัยพยากรณ์ที่มีผลต่อการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะที่ 1 ถึง 3

สุดสวาท เลาหวินิจ, คิ ฤกษ์ชูชิต, เจษฎา มณีชวขจร

***วัตถุประสงค์**: เพื่อศึกษาหาระยะเวลาการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะที่ 1 ถึง 3 และหาปัจจัยพยากรณ์ที่มีผลต่อการรอดชีพและระยะเวลาการปลอดโรค (disease-free survival) ของผู้ป่วยโรคมะเร็งเต้านมระยะที่ 1 ถึง 3 ที่รักษาด้วยการผ่าตัดและการรักษาเสริม*

***วัสดุและวิธีการ**: เป็นการศึกษา retrospective cohort โดยการทบทวนเวชระเบียนของผู้ป่วยมะเร็งเต้านมระยะที่ 1 ถึง 3 จำนวน 166 ราย ที่รักษาด้วยการผ่าตัดและการรักษาเสริมที่งานโรคมะเร็ง กลุ่มงานอายุรศาสตร์ โรงพยาบาลราชวิถี ระหว่างวันที่ 1 มกราคม พ.ศ. 2541 ถึงวันที่ 31 ธันวาคม พ.ศ. 2550*

***ผลการศึกษา**: ค่ามัธยฐานของอายุของผู้ป่วย 166 ราย เท่ากับ 48 ปี อัตราการรอดชีพที่ 5 ปี ของผู้ป่วยระยะที่ 1, ระยะที่ 2 และระยะที่ 3 เท่ากับ ร้อยละ 100 ร้อยละ 89.0 และร้อยละ 80.8 ตามลำดับ (p = 0.11) การวิเคราะห์ชนิด multivariate พบว่าการกระจายไปต่อมน้ำเหลือง pathological pN2 เป็นปัจจัยพยากรณ์โรคที่ไม่ดีต่อการรอดชีพ (HR = 4.32, 95%CI 1.24-15.04; p = 0.022) อัตราการปลอดโรคที่ 1 ปี 3 ปี และ 5 ปี เท่ากับ ร้อยละ 96.7 ร้อยละ 81.4 และร้อยละ 76.7 ตามลำดับ การวิเคราะห์ชนิด multivariate พบว่า pathological pN2 (HR = 4.43, 95%CI 1.44-13.57; p = 0.009), pN3 (HR = 5.16, 95%CI 1.54-17.30; p = 0.008) และ progesterone receptor เป็นลบ (HR = 5.53, 95%CI 1.85-16.59; p = 0.002) เป็นปัจจัยพยากรณ์โรคที่ไม่ดีต่อการปลอดโรค*

***สรุป**: ปัจจัยพยากรณ์โรคที่สำคัญที่สุดที่มีผลต่อการปลอดโรค และการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะที่ 1 ถึง 3 คือการกระจายของโรคไปยังต่อมน้ำเหลือง การที่ชิ้นเนื้อมี progesterone receptor เป็นลบ มีผลต่อการกลับมาของโรค ดังนั้นผู้ป่วยที่มีปัจจัยพยากรณ์โรคที่ไม่ดีหลายอย่างเช่น การกระจายของโรคไปต่อมน้ำเหลือง และ progesterone receptor เป็นลบซึ่งมีระยะเวลาการปลอดโรคที่ไม่ดี ดังนั้นการรักษาเสริมด้วย ยาเคมีบำบัดที่มีประสิทธิภาพสูงจึงมีความจำเป็นในผู้ป่วยกลุ่มนี้*