Survival and Prognostic Factors of Metastatic Breast Cancer

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Background: *Prognostic factors for survival of metastatic breast cancer (MBC) patients are important for identifying risks and deciding on patient treatment; however, few studies of prognostic factors in MBC have been performed in Thailand.*
Objective: *To determine the survival duration and prognostic factors for overall survival in metastatic breast cancer.*
Material and Method: *This retrospective cohort study was conducted by reviewing 232 files of MBC patients treated in the Oncology Unit, Department of Medicine, Rajavithi Hospital from January 1st 2005 to December 31th 2013.*
Results: *There were 232 patients whose median age was 51.5 years. The 1-year, 3-year and 5-year overall survival rates for MBC patients were 53.2%, 18.7% and 7.3% respectively, and the median overall survival time of all MBC patients was 13.43 months. Multivariate analysis showed that large tumor size T4 (HR = 1.89, 95% CI 1.04-3.44; p = 0.038), ECOG performance status 3-4 (HR = 2.44, 95% CI 1.48-4.00; p<0.001) and treatment with best supportive care only (HR = 5.95, 95% CI 3.56-9.96; p<0.001) were significant prognostic factors for poor overall survival in MBC. Breast cancer subtype analysis showed that luminal-A subtype was associated with a high rate of late recurrence (beyond 2 years) (p = 0.016) and HER-2 enriched subtype was related to a high rate of early relapse (before 2 years (p = 0.001)).*
Conclusion: *The important prognostic factors for overall survival in MBC were tumor size, ECOG PS and type of first-line treatment. In order to improve survival outcomes, patients with large tumor size should be treated with intensive chemotherapy and targeted therapy if HER-2 status positive. It is essential that early breast cancer patients have an awareness of recurrent diseases in order to identify good performance status in MBC patients suitable for active treatment.*

Keywords: *Metastatic breast cancer, Survival, Prognostic factor*

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Breast cancer is the most common cancer among women in the world. It is estimated that 1.67 million new cases of breast cancer will be diagnosed in 2012, and that there will be 522,000 deaths from this disease worldwide[1]. It remains the leading cause of death of women aged between 45 and 54 years old in the United States[2]. In Thailand, it is also the most common cancer in Thai women (age-standardized incidence rates = 28.5)[3].

Metastatic breast cancer (MBC) or advanced-stage breast cancer with distant metastases can be diagnosed at first presentation or as a recurring disease after prior early breast cancer. Although MBC is an incurable disease, proper systemic treatment can control its progression, prolong survival, and improve quality of life. The median overall survival time of MBC is approximately two years, but individuals' survival can range from a few months to many years[4,5]; therefore, it is important to try to achieve improved treatment outcomes.

The study of prognostic factors for MBC patients is important in order to identify high- or low-risk groups and select the proper management for these patients. Tumor size, nodal involvement, histological grade, lymphovascular invasion, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) status, Eastern Cooperative Oncology Group (ECOG) performance status, and disease-free interval (DFI) are all independent risk factors of survival and relapse in MBC[6-9].

Breast cancer subtypes also can predict the metastatic behavior of breast cancer and survival prospects[10]. The molecular subtypes of breast cancer have been modified and classified by immunohistochemical surrogates as luminal A, luminal

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B, luminal/HER-2, HER-2 enriched, basal-like and triple-negative (TN)[10,11].

Bone metastases are more likely to occur in patients with ER positive breast cancer [11,12]. Slimane et al have demonstrated that hormone-receptor-negative breast cancer patients are associated with early central nervous system (CNS) relapse[13]. Early breast cancer patients with triple-negative (TN) subtypes (ER/PR/HER-2 negative) developed CNS metastasis in 6% to 7% of cases[14,15]. In addition, the incidence of CNS metastasis among early-stage HER-2 positive breast cancer patients was 7.8% to 9%[15,16].

Only a few studies of prognostic factors for survival in MBC 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 prompted the authors to perform a retrospective cohort study of stage IV breast cancer patients treated in the Department of Medicine, Rajavithi Hospital, in order to determine overall survival rates of MBC patients and prognostic values for overall survival of various pre-treatment characteristics, especially prior early-stage breast cancer status, molecular subtypes and types of treatment in Thai patients.

Material and Method

This was a retrospective cohort study conducted by examining selected medical files of MBC patients who were treated in the Oncology Unit, Department of Medicine, Rajavithi Hospital over a 9-year period from January 1st, 2005 to December 31th, 2013. The protocol of this research was reviewed and approved by the Ethics Committee of Rajavithi Hospital. (No. 183/2013). Patient status was followed until February 28th, 2014 from medical records.

The inclusion criteria were MBC patients with histological diagnosis of invasive breast cancer who were treated in the Oncology Unit, Department of Medicine, Rajavithi Hospital. The exclusion criteria were patients who had other malignancy and patients who attended the Oncology Unit for less than 2 visits or were lost to follow-up.

Breast cancer molecular subtypes are identified by ER, PR and HER-2 status in Thai women[17]. In the present study tumors were classified into subtypes as follows: luminal-A (ER positive and/or PR positive and HER-2 negative), luminal/HER-2 (ER positive and/or PR positive and HER-2 positive), HER-2 enriched (ER negative, PR negative, HER-2 positive), and triple-negative breast cancer (TNBC) (ER negative and PR negative and HER-2 negative)[10,11,17]. ER positivity and PR positivity were defined as any positive nuclear staining (i.e. $\geq$1%), and HER-2 positive cases were defined as immunohistochemistry (IHC) score of 3+ or immunohistochemistry score of 2+ plus fluorescent in situ hybridization (FISH) with amplification ratio $\geq$2.0[11]. However, in the present study, 7 patients with HER-2 IHC score of 3+ were confirmed by FISH test: 6 had FISH test positive and one patient's result was negative. The patient with IHC 3+ and FISH negative was classified as HER-2 negative. Only one of 23 patients with HER-2 IHC score 2+ was confirmed by FISH test and the result was negative. All patients with HER-2 IHC score 2+ were classified as HER-2 negative.

Treatment for MBC patients in the present study was chosen based on tumor and disease characteristics, response to previous anti-cancer drugs, and prior treatment of the individual patients.

Eleven variables retrospectively studied as potential prognostic factors comprised age, ECOG performance status, histological grade, lymphovascular invasion, tumor size (T), regional lymph node (N), hormonal receptors status (ER and PR), HER-2 status, breast cancer subtype, and history of prior early breast cancer. The potential therapeutic prognostic variable also included in the analyses was the type of first-line palliative treatment, including palliative chemotherapy, palliative hormonal therapy or best supportive care (BSC). These 12 variables were included to determine the risk of death for patients with MBC.

Palliative chemotherapy regimens consisted of anthracycline-based, paclitaxel, docetaxel, capecitabine, vinorelbine, gemcitabine and ixabepilone. Palliative hormonal therapy comprised tamoxifen, anastrozole, letrozole, exemestane, fulvestrant and megestrol acetate. Targeted therapy (anti-HER-2) trastuzumab and lapatinib were also given in a few cases.

Overall survival for MBC was calculated from the date of MBC diagnosis to the time of death by breast cancer or other causes or to the last follow-up. In MBC patients who had prior early breast cancer, the disease-free interval was the period of time between first diagnosis of breast cancer in the early-stage group and first event of recurrence or metastasis.

Statistical analysis

Overall survival time, progression-free survival time and disease-free interval were estimated by the Kaplan-Meier method[18]. Twelve variables were included for analysis in order to determine prognostic

factors for overall survival. Comparisons of cumulative overall survival rates were obtained by univariate analysis using the log-rank test[19], and multivariate analysis was performed using Cox proportional hazards regression models. A *p*-value <0.05 was considered statistically significant.

Results

Patients and tumor characteristics

From 1st January 2005 to 31st December 2013, 232 patients with MBC treated at the Oncology Unit, Department of Medicine, Rajavithi Hospital were identified and studied, and their characteristics (at diagnosis of metastatic breast cancer) are listed in Table 1. The median age of all patients was 51.5 years, and the most common histological type was invasive ductal carcinoma (97.8%). Four patients had invasive lobular carcinoma and one had mucinous carcinoma. Histological gradings 1, 2, 3 and unknown were found in 5.2%, 32.3%, 38.4% and 24.1% of patients respectively.

The most frequently found primary tumor size in the study was T2 at 43.1%. Regional lymph node status of N1, N2 and N3 were 23.7%, 24.6% and 33.2% respectively.

Estrogen receptor and progesterone receptor were positive in 59.1% and 42.7% of patients respectively. HER-2 positivity was found in 32.8% of patients, and 61.2% of patients were HER-2 negative. Patients were classified as subtypes luminal-A (48.7%), luminal/HER-2 positive (14.3%), triple-negative (18.5%) and HER-2 enriched subtypes (18.5%). Most of the MBC patients were previously diagnosed early-stage breast cancer cases (72.8%) and 27.2% of patients were first-diagnosis cases of metastatic disease. Patients with prior early-stage breast cancer who underwent surgery accounted 80.2% of cases: 68.5% had modified radical mastectomy, and 11.7% underwent breast conservative surgery. Neoadjuvant plus adjuvant chemotherapy, adjuvant radiation and adjuvant hormonal therapy were prescribed in 60.3%, 39.7% and 35.3% of patients respectively. The most commonly used adjuvant chemotherapy regimens were anthracycline-based (55%). Only 2.2% of early-stage breast cancer patients with HER-2 positive received anti HER-2 trastuzumab in addition to adjuvant chemotherapy.

About seventy percent of patients had good ECOG performance status ≤1. Common metastatic sites were lung (61.6%), bone (51.7%), liver (42.0%), skin (25%), brain (16%), local recurrence (10%), and pleural effusion (7%).

Patients who had prior early-stage breast cancer before developing MBC had median disease-free interval of 25.87 months (range 0.0-225.7). The majority of patients with prior early-stage breast cancer (53%) developed MBC within 2 years of initial diagnosis.

Most of the MBC patients (162, 69.9%) received first-line palliative treatment with chemotherapy, while 37 (15.9%) received hormonal treatment and 33 patients (14.2%) were given best supportive care only (Table 1). One hundred and sixty-two patients received first-line palliative chemotherapy treatment including anthracycline-based (39.5%), paclitaxel (22.8%), docetaxel (11.1%), capecitabine (8%), CMF (4.3%) and others (14.3%). Eighty-eight patients received second-line palliative chemotherapy treatment including paclitaxel (37.5%), capecitabine (20.5%), docetaxel (12.5%) and others (29.4%). Sixty patients received third-line palliative chemotherapy treatment including capecitabine (41.7%), paclitaxel (26.7%), anthracyclines-based (10%), and others (21.6%).

Thirty-seven patients underwent first-line palliative hormonal treatment including tamoxifen (48.7%), aromatase inhibitors (letrozole, anastrozole, exemestane) (43.2%) and megestrol acetate (8.1%). Fifty-two patients received palliative hormonal therapy including tamoxifen (53.8%), aromatase inhibitors (letrozole, exemestane) (32.7%) and megestrol acetate (13.5%) as the second line of treatment. Thirty patients were given palliative hormonal therapy as the third line of treatment including tamoxifen (40.0%), aromatase inhibitors (letrozole, anastrozole, exemestane) (43.3%), megestrol acetate (13.4%) and fulvestrant (3.3%).

The median progression-free survival (PFS) time of patients who received first- and second-line palliative chemotherapy were 5.10 months (range 0.0-29.6) and 5.13 months (range 0.2-41.3) respectively.

Clinical outcomes

Survival analysis

The mean and median follow-up times of this study were 22.11 months (SD. 22.62) and 16.33 months (range 0.00 to 200.67) respectively. At the time of analysis, 190 patients (81.9%) had died while 42 patients (18.1%) were still alive. The causes of death were cancer-related death (158 patients, 83.2%) and treatment-related death (7 patients, 3.6%).

The 1-year, 3-year and 5-year survival rates from diagnosis of MBC were 53.2%, 18.7% and 7.3% respectively. The median overall survival time of all 232 MBC patients was 13.43 months (95% CI, 10.21 to 16.66

Table 1. Patient characteristics at diagnosis of MBC

Characteristics	Total (n = 232)
Age (year) median (min-max)	51.5 (28-88)
Histological grading	
Grade 1	12 (5.2)
Grade 2	75 (32.3)
Grade 3	89 (38.4)
Unknown	56 (24.1)
Lymphovascular invasion	
Yes	55 (23.7)
No	26 (11.2)
Unknown	151 (65.1)
Estrogen receptor	
Positive	137 (59.1)
Negative	95 (40.9)
Progesterone receptor	
Positive	99 (42.7)
Negative	127 (54.7)
Unknown	6 (2.6)
HER-2 status	
Positive	76 (32.8)
Negative	142 (61.2)
Unknown	14 (6.0)
Tumor size	
T1	24 (10.3)
T2	100 (43.1)
T3	34 (14.7)
T4	74 (31.9)
Lymph node status	
N0	43 (18.5)
N1	55 (23.7)
N2	57 (24.6)
N3	77 (33.2)
Breast cancer subtype	
Luminal-A	113 (48.7)
Luminal/HER-2	33 (14.3)
TNBC	43 (18.5)
HER-2 enriched	43 (18.5)
ECOG PS	
ECOG PS 0-1	164 (70.7)
ECOG PS 2	37 (15.9)
ECOG PS 3-4	31 (13.4)
Prior early-stage breast cancer	
Yes	169 (72.8)
No (MBC at 1st diagnosis)	63 (27.2)
Type of 1st-line palliative treatment	
Chemotherapy	162 (69.9)
Hormonal treatment	37 (15.9)
Best supportive care	33 (14.2)

Values are presented as n (%), median (min-max)
HER-2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; ECOG PS = Eastern co-operative oncology group performance status; MBC = metastatic breast cancer

months) (Table 2, Fig. 1).

The median overall survival time (MST) of MBC patients with prior history of early-stage breast cancer was 13.77 months (range 10.01-17.53) compared

Table 2. Univariate overall survival analysis of possible prognostic factors in metastatic breast cancer

Variables	n	1Y-SR%	3Y-SR%	5Y-SR%	Median (95% CI) (months)	*p*-value
Overall survival	232	53.2	18.7	7.3	13.43 (10.21, 16.66)	
Histological grading						0.007*
Grade 1	12	71.3	38.2	38.2	24.90 (11.65, 38.15)	
Grade 2	75	52.8	17	8.5	12.93 (8.43, 17.44)	
Grade 3	89	43.1	12	0	10.43 (8.19, 12.68)	
Unknown	56	66.1	28.7	7.9	24.37 (17.71, 31.03)	
Estrogen receptor						0.001*
Positive	137	57.7	23.4	11.8	18.26 (10.53, 26.00)	
Negative	95	46.9	12.6	0	11.40 (8.52, 14.27)	
Progesterone receptor						0.040*
Positive	99	56.6	22.3	4.1	17.50 (7.86, 27.13)	
Negative	127	49.8	15.3	1.6	11.63 (9.06, 14.20)	
Unknown	6	66.7	33.3	33.3	16.00 (0.00, 51.60)	
HER-2 status						0.621
Positive	76	47.8	16.4	6.8	11.20 (7.81, 14.58)	
Negative	142	56.3	18.2	6.7	15.86 (10.50, 21.22)	
Unknown	14	50	34.3	12.9	9.83 (0.00, 28.47)	
Tumor size						0.030*
T1	24	70.6	33.8	27	24.36 (8.08, 40.65)	
T2	100	61.3	18.5	6.6	16.30 (11.85, 20.74)	
T3	34	38.2	18.9	0	10.13 (6.09, 14.17)	
T4	74	43.7	13.2	5.7	10.90 (8.45, 13.34)	
Lymph node status						0.034*
N0	43	67.2	31	22.6	26.60 (16.24, 36.95)	
N1	55	49.5	14.5	7.2	11.63 (4.96, 18.3)	
N2	57	59.8	31	0	16.30 (8.35, 24.24)	
N3	77	42.4	16.4	3	11.00 (8.93, 13.06)	
Breast cancer subtype						0.054
Luminal-A	113	59.5	22.9	10.6	19.03 (12.23-25.83)	
Luminal/HER-2	33	47.5	21.1	11.3	11.20 (5.85-16.55)	
TNBC	43	46.5	12.2	0.0	11.47 (5.77-17.66)	
HER-2 enriched	43	47.9	13.2	4.4	11.40 (7.45-15.35)	
ECOG PS						<0.001*
ECOG PS 0-1	164	61.1	22.9	10.3	17.50 (13.39, 21.60)	
ECOG PS 2	37	44.2	9.1	0	9.40 (5.06, 13.73)	
ECOG PS 3-4	31	20.8	6.9	0	1.83 (0.00, 4.05)	
Prior early-stage breast cancer						0.444
Yes	169	54.2	19.7	7.7	13.77 (10.01, 17.53)	
No (MBC at 1st diagnosis)	63	50.1	15.8	5.3	12.93 (8.03, 17.84)	
Type of 1st-line palliative treatment						<0.001*
Chemotherapy	162	61.2	21.6	9.6	17.83 (13.39, 22.27)	
Hormonal treatment	37	61.9	23.4	3.9	17.50 (7.01, 27.99)	
Best supportive care	33	3.1	0	0	1.40 (0.71, 2.09)	

1Y- SR = 1-year survival rate; 3Y- SR = 3-year survival rate; 5Y- SR = 5-year survival rate; HER-2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; ECOG PS = eastern co-operative oncology group performance status; MBC = metastatic breast cancer

* = Significant at $p<0.05$

to 12.93 months (range 8.03-17.84) in patients with first-diagnosis MBC, but these figures were not significantly different (Table 2).

The prior early breast cancer patients who developed MBC later than 2 years after first diagnosis had similar median survival times to those who developed recurrent disease within 2 years (13.43 vs. 13.77 months, ($p = 0.274$)).

Breast cancer subtypes

Survival rate analyses of all MBC patients classified by breast cancer subtypes in the present study showed that luminal A, luminal/HER-2, TNBC and HER-2 enriched subtypes had survival durations of 19.0, 11.2, 11.4 and 11.4 months respectively (Table 2, Fig. 2).

TNBC and HER-2 enriched breast cancer subtypes had shorter survival times compared to those of patients with luminal A subtype, with crude HR of 1.56 (95% CI, 1.07-2.27) ($p = 0.021$) and HR 1.49 (95% CI, 1.01-2.19) ($p = 0.046$) respectively. However, breast cancer subtype was not a prognostic factor according to multivariate analyses (Table 3).

Correlation of incidence of metastasis to different organs with breast cancer subtypes were studied and triple-negative breast cancer subtype had a relatively high rate of brain metastasis (26.8%) compared with luminal A subtype (9.9%). Luminal A and luminal/HER-2 subtypes exhibited high rates of bone metastasis, at 58% and 54% respectively, compared to HER-2 enriched subtype at 41.9%. Liver metastasis was found in 46.5% of patients with HER-2 enriched subtypes but only 38.6% of those with luminal A; however, these differences were not statistically significant. Therefore, although sites of metastases had some correlation with breast cancer subtypes, no statistically significant association was found.

Breast cancer subtype analyses also showed an association with disease-free interval of early-stage breast cancer patients who later developed MBC. Sixty-four percent of luminal-A subtype patients had late relapse (after 2 years) (63.8% vs. 36.2%, $p = 0.016$); in contrast, HER-2 enriched subtype patients had a high rate of early relapse (within 2 years) (72.7% vs. 27.3%, $p = 0.001$).

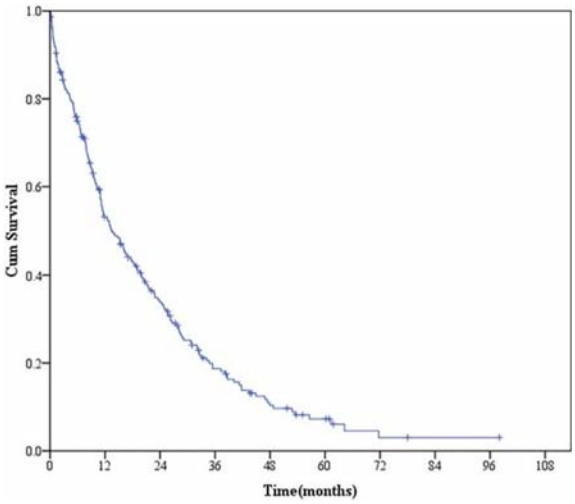

Fig. 1 Overall survival curve showing median duration of overall survival was 13.43 months. The one-, three-, and five-year survival rates for stage IV breast cancer were 53.2%, 18.7% and 7.3% respectively.

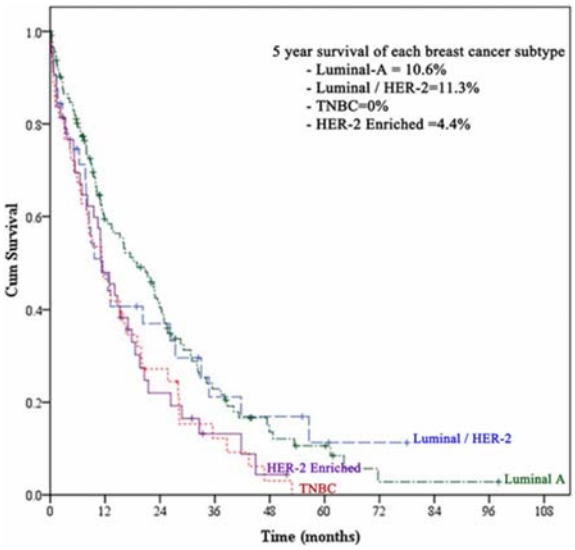

Fig. 2 Comparison of overall survival curves of patients by breast cancer subtype ($p = 0.054$). Overall survival differences between breast cancer subtype luminal A, luminal/HER-2, triple negative breast cancer (TNBC), and HER-2 enriched groups are shown with median survival times of 19.0, 11.2, 11.4 and 11.4 months respectively.

Univariate survival analysis

Univariate survival analysis by Kaplan-Meier and log-rank test showed 7 significant factors for shorter survival for MBC patients: high histological grading ($p = 0.007$), crude HR 1.33 (0.96 to 1.86); estrogen receptor negative ($p = 0.001$), crude HR 1.61 (1.20 to 2.14); progesterone receptor negative ($p = 0.04$); T4 tumor size ($p = 0.03$), crude HR 2.13 (1.21 to 3.76); N3 lymph node status ($p = 0.034$), crude HR 1.89 (1.22 to 2.93);

Table 3. Multivariate analyses of the relationships between prognostic factors and survival time of metastatic breast cancer

	n	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Histological grading					
Grade 1+2	87	1		1	
Grade 3	89	1.33 (0.96 to 1.86)	0.087	1.37 (0.97 to 1.95)	0.075
Unknown	56	0.77 (0.53 to 1.13)	0.180	0.79 (0.53 to 1.16)	0.229
Negative estrogen receptor	95	1.61 (1.20 to 2.14)	0.002	1.70 (0.81 to 3.57)	0.158
Tumor size					
T1	24	1		1	
T2	100	1.67 (0.96 to 2.90)	0.070	1.38 (0.77 to 2.45)	0.278
T3	34	2.22 (1.19 to 4.13)	0.012	1.72 (0.89 to 3.34)	0.106
T4	74	2.13 (1.21 to 3.76)	0.009	1.89 (1.04 to 3.44)	0.038*
Lymph node status					
N0	43	1		1	
N1	55	1.72 (1.08 to 2.72)	0.022	1.61 (1.00 to 2.60)	0.051
N2	57	1.58 (0.99 to 2.52)	0.054	1.29 (0.78 to 2.15)	0.322
N3	77	1.89 (1.22 to 2.93)	0.004	1.41 (0.86 to 2.31)	0.170
Breast cancer subtype					
Luminal-A	113	1		1	
Luminal/HER-2	33	1.05 (0.67 to 1.63)	0.841	1.03 (0.64 to 1.67)	0.893
TNBC	43	1.56 (1.07 to 2.27)	0.021	0.88 (0.38 to 2.01)	0.755
HER-2 enriched	43	1.49 (1.01 to 2.19)	0.046	0.60 (0.26 to 1.38)	0.230
ECOG PS at stage IV BC					
ECOG PS 0-1	164	1		1	
ECOG PS 2	37	1.82 (1.22 to 2.72)	0.003	1.34 (0.86 to 2.09)	0.194
ECOG PS 3-4	31	3.34 (2.23 to 5.01)	<0.001*	2.44 (1.48 to 4.00)	<0.001*
Type of 1st-line palliative treatment					
Chemotherapy	162	1		1	
Hormonal treatment	37	1.19 (0.81 to 1.77)	0.374	1.13 (0.72 to 1.78)	0.601
Best supportive care	33	9.39 (6.06 to 14.54)	<0.001*	5.95 (3.56 to 9.96)	<0.001*

HR = harzard ratio; 95% CI = 95% confidence interval; HER-2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; ECOG PS = eastern co-operative oncology group performance status
* = significant at $p<0.05$

ECOG PS 3-4 ($p<0.001$), crude HR 3.34 (2.23 to 5.01); and best supportive care treatment ($p<0.001$) (Fig. 3), crude HR 9.39 (6.06 to 14.54). HER-2 enriched and TNBC subtypes of breast cancer showed a trend towards shorter survival ($p = 0.054$) with crude HR 1.49 (1.01 to 2.19) and 1.56 (1.07 to 2.27) respectively (Table 2 and 3). Other tested variables, including age group, lymphovascular invasion, HER-2 status and prior early-stage breast cancer, were not statistically significant factors affecting shorter or longer survival (Table 2).

Multivariate analysis

Survival duration was further modeled with multivariate Cox regression analysis employing a proportional hazard rate hypothesis. Tumor size, lymph node status, histological grade, hormone receptor status (ER/PR), breast cancer subtypes, ECOG performance status and type of first-line palliative treatment were included in proportional Cox regression analysis.

After adjustment for the confounding effects of MBC, only three significant prognostic factors were found: MBC patients who had greater tumor size (T4), ECOG PS 3-4, and treatment with best supportive care only were poor prognostic factors for metastasic breast cancer (Table 3); however, grade 3 histological grading, negative estrogen receptor and lymph node positive showed trends towards worse prognoses.

Discussion

The median age of patients with MBC in the present study was 51.5 years old which was comparable

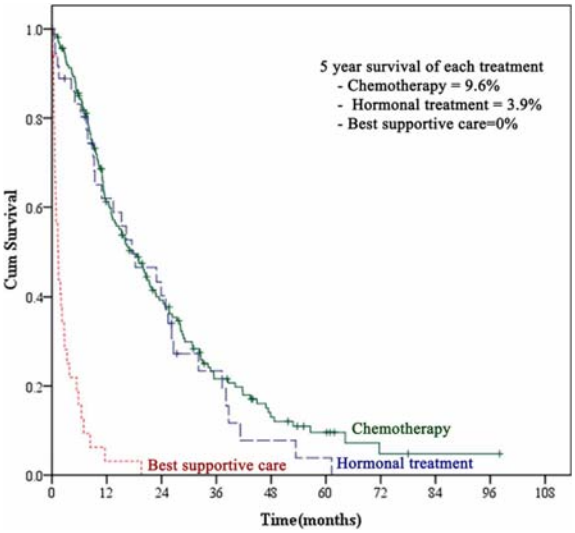

Fig. 3 Comparison of overall survival curves of patients by type of first-line palliative treatment (p<0.001). Overall survival differences between first-line chemotherapy, hormonal treatment, and best supportive care groups are shown.

with that of patients reported in other publications (49 to 62 years old)[8,11,20,21]. The most common histological type was invasive ductal carcinoma (97.8%), and this is comparable with reports in Thai and Hong Kong populations (82 to 93%)[20,21]. Tumor histological gradings 2 (32.3%) and 3 (38.4%) were commonly found in the present study, in line with findings in reports from Thailand and other Asian countries (30 to 48%)[20,21]. Estrogen and progesterone receptors and HER-2 status were positive in 59.1%, 42.7% and 32.8% respectively in the present study which is in keeping with results from various reports in Thailand and other Asian countries (ER 38 to 53%; PR 25 to 41%; HER-2 7.3 to 20%)[20,21].

In the present study, median survival time of MBC was 13.43 months, while 1- and 5-year survival rates were 53.2% and 7.3% respectively. These results are comparable with those of others studies which found median survival times of between 16 and 31 months[8,20] and 5-year survival rates of 5 to 27%[7,20]. MBC patients with liver metastases had poorer outcomes with median survival time of 4 months and 1-year survival rate of 27.6%[22]. The survival duration of MBC patients in this study was slightly shorter than in others, and this could be explained by the fact that nearly half (42%) of the patients in the present study who had poor survival outcome had liver metastases. In addition, fourteen percent of patients in the present study did not receive active treatment in accordance with their poor ECOG performance status and preferred to have only best supportive care. Finally, most patients with HER-2 positive subtypes could not afford to receive anti-HER-2 trastuzumab treatment.

Breast cancer subtypes of MBC patients with prior early-stage breast cancer in the present study demonstrated significant differences in timing of disease recurrence. Luminal-A subtype patients were associated with a significant late recurrence (beyond 2 years) at 64% (p = 0.016). In contrast, HER-2 enriched subtype patients had a high rate of early relapse (before 2 years) at 73% (p = 0.001). These results were consistent with those of previous studies which demonstrated that ER-negative tumors were associated with early relapse, ER-positive tumors were associated with persistent late relapse, and HER-2 subtype demonstrated a high rate of early relapse[13,23,24].

Brain metastases were found in 16% of MBC subjects in this present study which is comparable with the findings of previous reports[25,26]. However, the incidence of brain metastasis was higher (26.8%) in TNBC subtypes in the present report. These results were comparable with a report of the study of risk factors of developing brain metastases which showed that triple-negative tumor subtype in early breast cancer was a significant unfavorable factor for developing brain metastases (3-year brain metastasis-free survival of 0.78, 95% CI 0.64 to 0.93)[27].

High rates of bone metastasis in luminal-A and luminal/ HER-2 subtypes (54% and 58%) were observed in the present study, similar to the results of previous studies which found that bone metastasis was a common site among ER-positive MBC (69%)[12], luminal A and luminal/HER2-positive subtypes (65 to 66%)[11].

Previous studies on prognostic factors for survival in metastatic breast cancer have demonstrated that tumor size, lymph node status, staging, histological grading, lymphovascular invasion, ER, PR and HER-2 status had an impact on survival and disease recurrence[6-8]. The present study demonstrated that histological grade, ER, PR, tumor size, lymph node status, ECOG performance status and type of first-line palliative treatment had an impact on overall survival in univariate analyses. Multivariate analyses, on the other hand, showed that T4 (HR = 1.89, 95% CI 1.04 to 3.44; p = 0.038), ECOG performance status 3, 4 (HR = 2.44, 95% CI 1.48 to 4.00; p<0.001) and receiving only best supportive care (HR = 5.95, 95% CI 3.56 to 9.96; p<0.001) were the factors that had statistically

significant impacts on overall survival. These results are in agreement with those of other reports which suggested that T stage (HR = 1.24 95% CI 1.02 to 1.50; $p = 0.027$) and ECOG performance status ($p = 0.04$) significantly affected MBC patients' survival prospects[7,8]. In addition, tumor histological grade 3 and N1 lymph node status showed a trend towards being worse prognostic factors. This study did not demonstrate that estrogen receptor, HER-2 status or breast cancer subtype were prognostic factors, and this could be due to the limited number of patients, and HER-2 testing. The authors would like to emphasize that prior early-stage breast cancer status of diagnosed MBC patients, proposed as a prognostic factor for survival, was not proven to be a predictive factor for survival of MBC patients in this report.

In conclusion, the important prognostic factors for overall survival were T4 tumor size, poor ECOG performance status and type of first-line palliative treatment. In order to improve survival outcomes for MBC, patients with T4 disease should be treated with higher-potency chemotherapy regimens and anti HER-2 targeted therapy for HER-2 positive patients. Patients' knowledge and awareness of disease recurrence programs need to be raised in order to identify MBC early enough to improve the final outcomes of treatment. Early-stage breast cancer patients with HER-2 enriched subtype should be treated with high-potency adjuvant chemotherapy and adjuvant trastuzumab with close surveillance especially in the first 2 years after adjuvant treatment. Surveillance programs for early-stage breast cancer patients with TNBC and luminal-A subtypes should focus on brain and bone metastases.

What is already known on this topic?

Prognostic factors for survival of metastatic breast cancer have been studied worldwide; however there is a paucity of data from Thailand.

Prior early-stage breast cancer status and molecular subtypes of breast cancer have not been studied as prognostic factors in metastatic breast cancer in Thai patients.

What this study adds?

Survival rates of metastatic breast cancer patients in Rajavithi Hospital were comparable to those found in other reports although there was only limited use of anti HER-2 treatment. Fourteen percent of metastatic breast cancer patients could not receive active treatment due to poor performance status, and this could be due to lack of awareness of breast cancer, leading to delayed diagnosis. Disease-free survival of early breast cancer was related to breast cancer subtypes, but prior early-stage breast cancer status of MBC patients was not a prognostic factor for survival.

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Potential conflicts of interest

None.

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การรอดชีพและปัจจัยพยากรณ์ที่มีผลต่อการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะแพร่กระจาย

สุดสวาท เลาหวินิจ, วินัย พอล, กุลธิดา มณีนิล

ภูมิหลัง: การศึกษาปัจจัยพยากรณ์ที่มีผลต่อการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะแพร่กระจายมีความสำคัญในการสืบค้นปัจจัยเสี่ยงและการพิจารณาวิธีรักษาของผู้ป่วย อย่างไรก็ตามการศึกษาปัจจัยพยากรณ์นี้ในประเทศไทยยังมีน้อย

วัตถุประสงค์: เพื่อศึกษาระยะเวลาการรอดชีพและปัจจัยพยากรณ์ที่มีผลต่อการรอดชีพของผู้ป่วยโรคมะเร็งเต้านมระยะแพร่กระจาย

วัสดุและวิธีการ: เป็นการศึกษา retrospective cohort โดยการทบทวนเวชระเบียนของผู้ป่วยมะเร็งเต้านมระยะแพร่กระจายจำนวน 232 ราย ที่มารับการรักษาที่งานโรคมะเร็ง กลุ่มงานอายุรศาสตร์ โรงพยาบาลราชวิถี ระหว่างวันที่ 1 มกราคม พ.ศ. 2548 ถึงวันที่ 31 ธันวาคม พ.ศ. 2556

ผลการศึกษา: ค่ามัธยฐานของอายุของผู้ป่วย 232 ราย เท่ากับ 51.5 ปี อัตราการรอดชีพที่ 1 ปี, 3 ปี และ 5 ปี ของผู้ป่วยมะเร็งเต้านมระยะแพร่กระจายเท่ากับร้อยละ 53.2, ร้อยละ 18.7 และร้อยละ 7.3 ตามลำดับ ค่ามัธยฐานของระยะเวลาการรอดชีพของผู้ป่วยทั้งหมดเท่ากับ 13.43 เดือน การวิเคราะห์ชนิดพหุปัจจัย พบว่าปัจจัยพยากรณ์โรคที่ไม่ดีต่อการรอดชีพของมะเร็งเต้านมระยะแพร่กระจายอย่างมีนัยสำคัญทางสถิติ ได้แก่ ขนาดก้อนเนื้องอกที่ใหญ่ T4 (HR = 1.89, 95% CI 1.04-3.44; p = 0.038), ECOG performance status 3-4 (HR = 2.44, 95% CI 1.48-4.00; p<0.001) และการรักษาแบบประคับประคองอย่างเดียว (HR = 5.95, 95%CI 3.56-9.96; p<0.001) การศึกษาชนิด subtypes ของมะเร็งเต้านมพบว่ากลุ่ม luminal-A subtype มีอัตราการกลับมาของโรคหลังการวินิจฉัยครั้งแรกยาวนานกว่า 2 ปีที่สูง (p = 0.016) ขณะที่กลุ่ม HER-2 enriched subtype มีอัตราการกลับมาของโรคก่อนระยะเวลา 2 ปีที่สูง (p = 0.001)

สรุป: ปัจจัยพยากรณ์โรคที่สำคัญที่มีผลต่อการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะแพร่กระจาย ได้แก่ ขนาดของก้อนเนื้องอก ECOG performance status ชนิดของการรักษาขนานแรก ดังนั้นผู้ป่วยที่มีขนาดก้อนเนื้องอกที่ใหญ่ควรได้รับการรักษาด้วยยาเคมีบำบัดที่มีประสิทธิภาพสูงและให้การรักษาด้วยยามุ่งเป้าในรายที่มี HER-2 เป็นบวกเพื่อเพิ่มระยะเวลาการรอดชีพของผู้ป่วยมะเร็งเต้านมระยะแพร่กระจาย อนึ่งผู้ป่วยมะเร็งเต้านมระยะแรกควรได้รับการส่งเสริมให้ตระหนักถึงอาการของการกลับมาของโรคมะเร็งเต้านม เพื่อที่จะสามารถวินิจฉัยโรคมะเร็งเต้านมระยะแพร่กระจายได้เร็วขณะที่ผู้ป่วยยังมี performance status ที่ดีและสามารถรับการรักษาด้วยยาที่มีประสิทธิภาพสูงได้