Effect of Age on Recurrence in Hormone Receptor-Positive Breast Cancer, and Factors Significantly Associated with Cancer Recurrence

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ABSTRACT

Objective: Age is an important factor for predicting survival, with worse prognosis among young women compared to middle-aged women. Hormone receptor-positive breast cancer is the most commonly reported diagnoses among younger women. This study aimed to investigate the effect of age on recurrence in hormone receptor-positive breast cancer patients, and to identify its significant related factors.

Methods: Operable hormone receptor-positive breast cancer patients who underwent surgery at the Division of Head, Neck, and Breast Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 2008-2013 were retrospectively recruited. Age at diagnosis, follow-up time, staging, tumor characteristics, treatment, and date of recurrence were collected, recorded, and analyzed.

Results: Of the 431 patients that were included, 145 patients were aged 40 years or younger, and 286 patients were aged older than 40 years. The median follow-up time was 4.1 years. In multivariate analysis, the unadjusted recurrence rate was higher in T3-4, node positive, high pathological grade, and lymphovascular invasion. After adjusting for age, only N stage N1 remained statistically significant (hazard ratio [HR]: 2.75, 95% confidence interval [CI]: 1.18-6.40; p=0.19). The recurrence rate was found to be non-significantly higher in younger patients than in older patients (11% vs. 5.6%, p=0.21).

Conclusion: The results of this study revealed no significant difference between age groups for recurrence-free survival in women with hormone receptor-positive breast cancer; however, younger women did demonstrate a higher rate of recurrence. N stage N1 is an independent predictor of cancer recurrence.

Keywords: Age; hormone receptor-positive breast cancer; recurrence (Siriraj Med J 2019; 71: 438-445)

INTRODUCTION

Breast cancer is the most common cancer among women in Thailand. Even though breast cancer more often occurs in women over age 50, it also affects younger aged women. In 2018, there were 12,770 cases of breast cancer diagnosed in women under the age of 40 in the US.[1] Age is an important factor for predicting survival, with worse prognosis among young women compared to middle-aged women.[2] Some studies reported that breast cancer among younger-aged women is usually found at a later stage and that it has more aggressive subtypes, such as triple negative and HER2 overexpression.[3,4] However

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luminal subtype or hormone receptor positive breast cancer has been and continues to be the most common diagnosis in this younger age group.

Hormone receptor-positive breast cancer has better prognosis relative to survival and recurrence when compared to other types of breast cancer.[5,6] Thus, the hypothesis that the observed poor survival among young women depends solely on cancer subtype is questionable. Previous studies reported that hormone receptor status affects survival outcome in early-onset breast cancer, but their results are controversial. One large cohort study found that younger aged patients (≤40 years) with luminal A subtype had poorer disease-free survival and poorer distant metastasis-free survival than patients in the middle-aged group (41-60 years).[7] In contrast, Fallahpour, *et al*. found mortality rate increase with increasing age regardless of molecular subtype.[6]

The aim of this study was to investigate the effect of age on recurrence in hormone receptor-positive breast cancer patients, and to identify factors significantly associated with cancer recurrence.

MATERIALS AND METHODS

Study design and population

This retrospective study included operable hormone receptor-positive breast cancer patients who underwent surgery at the Division of Head, Neck, and Breast Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the 2008-2013 study period. All included patients had histologically-proven hormone receptor-positive breast cancer. Patients with metastatic disease, with history of neoadjuvant treatment, and/or with less than 2 years of follow-up were excluded. The protocol for this study was approved by the Siriraj Institutional Review Board (Si 658/2016), and the requirement to obtain written informed consent was waived due to the retrospective design of this study.

Data collection

Age at diagnosis, date of last follow-up, pathological staging, tumor characteristics, surgical treatment, adjuvant treatment, and date of recurrence diagnosis were collected, recorded, and analyzed.

Statistical analysis

Bivariate analysis of age, stage, tumor characteristics, surgical treatment, adjuvant treatment, and recurrence was performed. Statistical analyses were performed using SPSS for Windows version 22.0 (SPSS, Inc.; IBM Corp., Armonk, New York, USA). Categorical variables were compared using chi-square test or Fisher's exact test. Hazard ratios were used to compare recurrence between groups. Multivariate analysis by Cox proportional hazards model was performed to identify independent predictors of disease recurrence. Survival analysis was performed using the Kaplan-Meier method, with comparisons between groups performed using log-rank analysis. A result was considered statistically significant it its *p*value was less than 0.05.

RESULTS

Demographics

Of the 431 patients that were included, 145 patients were aged 40 years or younger, and 286 patients were aged older than 40 years. The median follow-up time was 4.1 years. There was no significant difference between age groups for T stage, N stage, lymphovascular invasion, or hormone receptor status. The recurrence rate was found to be non-significantly higher in younger patients than in older patients. Pathological grade was significantly higher in the younger age group than in the older age group ($p<0.001$) (Table 1).

Recurrence-free survival

Recurrence-free survival at 5 years in patients aged ≤40 years was 87.3% compared with 93.1% among patients aged >40 years ($p=0.21$) (Fig 1). Recurrence-free survival was significantly higher in both lower T stage ($p=0.07$) and lower N stage ($p=0.003$) (Fig 2 and 3).

Univariate analysis

Univariate analysis revealed T3-4, node positive, high pathological grade, and lymphovascular invasion to be statistically significantly associated with breast cancer recurrence. The recurrence rate was found to be higher among younger patients (11.0%) than among older (5.6%) patients; however, the difference between groups failed to achieve statistical significance (hazard ratio [HR]: 1.59, 95% confidence interval [CI]: 0.76-3.30; $p=0.21$) (Table 2).

Multivariate analysis

After adjusting for age, N stage N1 was identified as the only independent predictor of cancer recurrence (HR: 2.75, 95% CI: 1.18-6.40; $p=0.19$) (Table 3).

DISCUSSION

Age at diagnosis has long been established as an important prognostic factor in terms of predicting survival and recurrence. Many studies reported the survival of young breast cancer (YBC) patients to be significantly

TABLE 1. Staging, tumor characteristics, and treatments compared between age groups.

Variables	Age ≤40 (n=145)		Age >40 (n=286)		*p*-value
	Number	Percentage	Number	Percentage	
Follow-up time (yrs), mean±SD	4.53±1.27		4.03±0.46		***<0.001***
T stage					
T1	67	46.2%	152	53.1%	0.54
T2	72	49.7%	126	44.1%	
T3	5	3.4%	7	2.4%	
T4	1	7.0%	1	3.0%	
N stage					
N0	85	58.6%	192	67.1%	
N1	34	23.4%	59	20.6%	***0.05***
N2	19	13.1%	17	5.9%	
N3	7	4.8%	18	6.3%	
Pathological grade					
Low	21	14.5%	56	19.6%	
Intermediate	80	55.2%	190	66.4%	***<0.001***
High	44	30.3%	40	14.0%	
Lymphovascular invasion					
Negative	84	69.4%	174	74.7%	0.31
Positive	37	30.6%	59	25.3%	
HER-2					
Negative	91	77.1%	203	86.4%	***0.03***
Positive	27	22.9%	32	13.6%	
%ER, mean±SD	69.7±19.7		71.3±17.4		0.41
%PR, mean±SD	54.0±30.8		53.8±28.9		0.95
Breast surgery					
Wide excision	62	42.8%	92	32.2%	***0.03***
Mastectomy	83	57.2%	194	67.8%	
Axillary surgery					
SLNB	78	53.8%	188	65.7%	***0.02***
ALND	67	46.2%	98	34.3%	
Radiation					
No	129	89.0%	270	94.4%	***0.017***
Yes	16	11.0%	16	5.6%	
Chemotherapy					
No	20	13.8%	121()	42.3%	***<0.001***
Yes	125	86.2%	165()	57.7%	
Recurrence					
No	129	89.0%	270	94.4%	***0.05***
Yes	16	11.0%	16	5.6%	

A *p*-value<0.05 indicates statistical significance

Abbreviations: SD, standard deviation; T stage, tumor stage; N stage, lymph node stage; HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

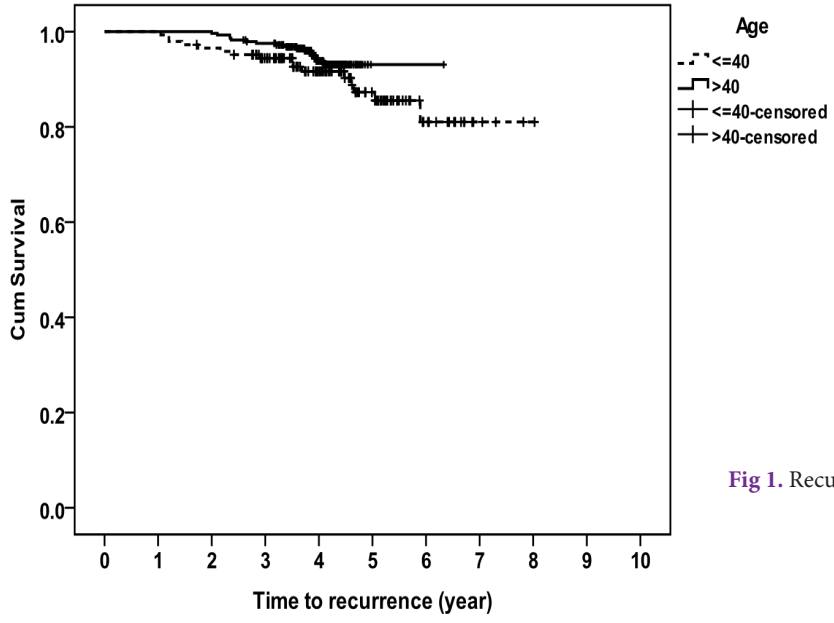

Fig 1. Recurrence-free survival stratified by age.

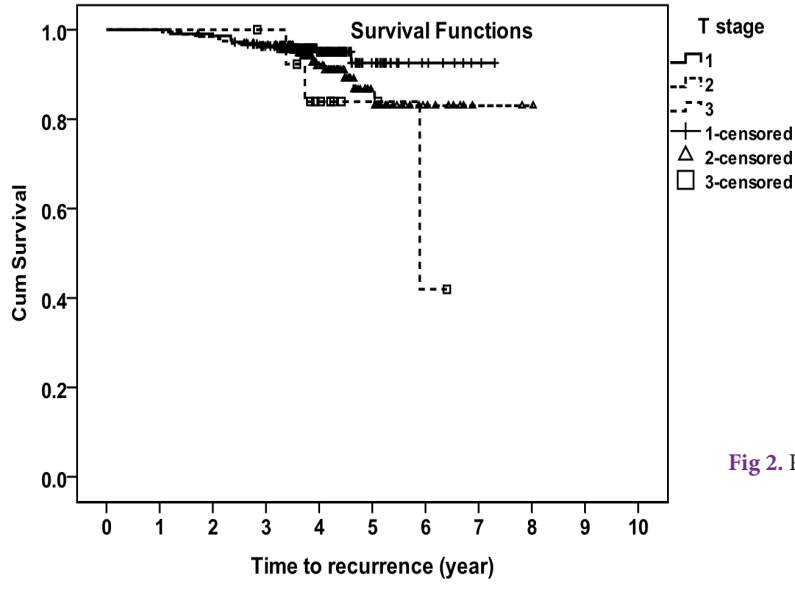

Fig 2. Recurrence-free survival stratified by T-stage.

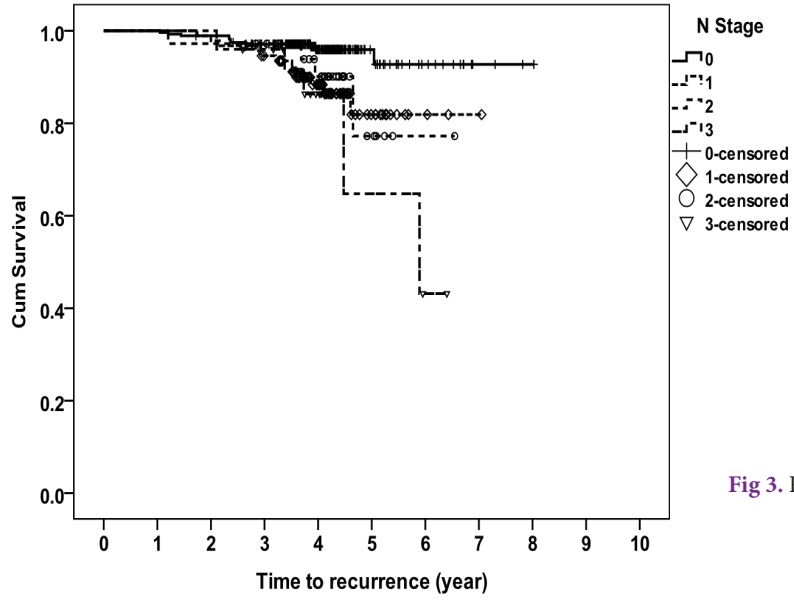

Fig 3. Recurrence-free survival stratified by N-stage.

TABLE 2. Univariate analysis for factors significantly associated with cancer recurrence.

Factors	No recurrence		Recurrence		Crude HR	95% CI	*p*-value
	Number	Percentage	Number	Percentage			
Age							
≤40	129	89.0%	16	11.0%	1.59	0.76-3.30	0.22
>40	270	94.4%	16	5.6%	1		
T stage							
T1	208	95.0%	11	5.0%	1		
T2	180	90.9%	18	9.1%	1.76	0.83-3.73	0.14
T3-4	11	78.6%	3	21.4%	3.79	1.05-13.68	***0.04***
N stage							
N0	266	96.0%	11	4.0%	1		
N1	81	87.1%	12	12.9%	3.20	1.41-7.27	***0.005***
N2	32	88.9%	4	11.1%	2.68	0.85-8.43	0.09
N3	20	80.0%	5	20.0%	4.98	1.72-14.41	***0.003***
Pathological grade							
Low	74	96.1%	3	3.9%	1		
Intermediate	254	94.1%	16	5.9%	1.46	0.42-5.03	0.54
High	71	84.5%	13	15.5%	4.00	1.14-14.06	***0.03***
Lymphovascular invasion							
Negative	246	95.3%	12	4.7%	1		
Positive	83	86.5%	13	13.5%	3.03	1.38-6.65	***0.006***
HER-2							
Negative	272	92.5%	22	7.5%	1		
Positive	53	89.8%	6	10.2%	1.26	0.51-3.12	0.61
Breast surgery							
Wide excision	146	94.8%	8	5.2%	1		
Mastectomy	253	91.3%	24	8.7%	1.77	0.79-3.96	0.16
Axillary surgery							
SLNB	256	96.2%	10	3.8%	1		
ALND	143	86.7%	22	13.3%	3.42	1.62-7.24	***0.001***
Radiation							
No	180	95.2%	9	4.8%	1		
Yes	219	90.5%	23	9.5%	1.94	0.89-4.20	0.092
Chemotherapy							
No	139	98.6%	2	1.4%	1		
Yes	260	89.7%	30	10.3%	6.48	1.54-27.2	***0.011***

A *p*-value<0.05 indicates statistical significance

Abbreviations: HR, hazard ratio; CI, confidence interval; T stage, tumor stage; N stage, lymph node stage; HER-2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

TABLE 3. Multivariate analysis for factors that independently predict cancer recurrence.

	No recurrence		Recurrence		Crude	95% CI	*p*-value	Adjusted	95% CI	*p*-value
	Number	Percentage	Number	Percentage	HR			HR		
Age										
≤40	129	89.0%	16	11.0%	1.59	0.76-3.30	0.22	0.81	0.37-1.73	0.59
>40	270	94.4%	16	5.6%	1			1		
T stage										
T1	208	95.0%	11	5.0%	1			1		
T2	180	90.9%	18	9.1%	1.76	0.83-3.73	0.14	1.23	0.55-2.74	0.61
T3-4	11	78.6%	3	21.4%	3.79	1.05-13.68	***0.04***	1.77	0.40-7.89	0.45
N stage										
N0	266	96.0%	11	4.0%	1			1		
N1	81	87.1%	12	12.9%	3.20	1.41-7.27	***0.005***	2.75	1.18-6.40	***0.02***
N2	32	88.9%	4	11.1%	2.68	0.85-8.43	0.09	2.16	0.65-7.16	0.21
N3	20	80.0%	5	20.0%	4.98	1.72-14.41	***0.003***	2.87	0.82-9.94	0.09
Pathological grade										
Low	74	96.1%	3	3.9%	1			1		
Intermediate	254	94.1%	16	5.9%	1.46	0.42-5.03	0.54	1.05	0.30-3.73	0.93
High	71	84.5%	13	15.5%	4.00	1.14-14.06	***0.03***	2.16	0.56-8.28	0.26

A *p*-value<0.05 indicates statistical significance

Abbreviations: HR, hazard ratio; CI, confidence interval; T stage, tumor stage; N stage, lymph node stage

lower than that of older breast cancer patients.[8-10] Even though the definition of YBC varies, 40 years of age is a generally accepted cutoff value that is used in most studies.[10,11] Brandt, *et al.* compared breast cancer-specific mortality between women aged <40 and women aged 40-49, and they found that younger women had a significantly worse 10-year-mortality rate (risk ratio [RR]: 1.40, 95% CI: 1.04-1.88).[10]

A recent meta-analysis reported 5- and 10-year local recurrence risk, and both were higher in YBC than in older-onset patients (5-year – RR: 2.64, 95% CI: 1.94-3.60; and, 10-year – RR: 2.37, 95% CI: 1.57-3.58).[12] In contrast, the present study, which focused on disease recurrence, found no significant difference in RFS between the younger-onset and older-onset groups (11.0% *vs.* 5.6%, respectively; *p*=0.22). This finding may be explained by the fact that a significantly greater number of young women received chemotherapy (CMT) than the number older women who received CMT (86.2% *vs.* 57.7%, respectively; *p*<0.001). Receiving CMT could imply more aggressive phenotypes and higher recurrence risk among younger aged patients. On the other hand, CMT may lower the risk of recurrence in this group. One study found significant improvement in the local recurrence rate among YBC who underwent breast conserving surgery and that were treated systemically (HR: 0.42, 95% CI: 0.28-0.60; *p*<0.0001).[13] The largest retrospective study analyzed the risk of local and distant recurrence compared between YBC and older-onset patients, and they found no significant difference between groups for either parameter (5-year LR: 3.9% *vs.* 4.5%; and, 5year DFS: 75.3% *vs.* 77.7%).[14]

The unfavorable prognosis of YBC patients may be explained by the fact that they had more aggressive biological subtypes and/or clinicopathological baselines. Typically, YBC is associated with poor prognostic factors, such as large tumor size, nodal involvement, high-grade tumor, absence of hormone receptor, and HER2

overexpression.[8,15,16] In our experience, the hormone receptor-positive subtype has better prognosis compared to the others; especially luminal A, which has the best survival. A large population-based study in Surveillance, Epidemiology, and End Results (SEER) data assessed the survival of operable breast cancer according to molecular subtypes, and they found the greatest 5-year breast cancer-specific survival in the hormone receptor positive and HER2 negative group (HR+/HER2-) (95.5%) compared to the triple-negative group (83.1%).[17] The present study also found superior overall survival in the HR+/HER2- subtype. Although hormone receptor positive breast cancer has a more favorable prognosis, many clinicians remain concerned that the age of diagnosis may adversely affect survival. Several publications reported disparate survival and recurrence results when age was used to assess the outcomes. Liu, *et al.* reported poor 5-year disease-free survival (DFS) and poor distant metastasis-free survival (DMFS) in luminal A young women (age ≤40 years) compared to age 41-60 (5-year DFS: 80% *vs.* 91.6%; $p<0.001$; and, 5-year DMFS: 83.8% *vs.* 93.8%; $p<0.001$). These differences between groups may be due to more aggressive clinicopathological characteristics in younger-onset patients. In our study, young women had significantly higher in tumor size (T3-4), more nodal metastasis, more lymphovascular invasion, and high nuclear grade; however, the difference in survival between groups was not significant. Worse outcome among younger women may also be explained by the fact that younger women continue to menstruate after chemotherapy. SOFT and TEXT trial could clarify in this case with their results showed that breast cancer patients whom still premenopausal status take the benefit of adding ovarian suppression to tamoxifen or exemestane, in order to increase disease free survival and freedom from distant recurrence, in patients who previously received chemotherapy.[18]

Limitations

This study has several limitations. First, the retrospective design of our study confers inherent weaknesses that include missing or incomplete data. Second, our relatively small sample size and short follow-up time (median: 4.1 years) may have limited the power of our survival analysis, and our ability to identify all significant associations and differences. Third, trastuzumab was not a standard treatment for breast cancer patients who had HER2 overexpression during the study period, so the observed high recurrence rate may have been due to inadequate treatment. Fourth, our data was from a single center that is Thailand's largest national tertiary referral center. As such, we are often referred cases that are judged to be difficult to manage in other care settings. This may limit the generalizability of our data to other care settings. Fifth and last, we did not have genetic profile data that can be used to predict the benefit of chemotherapy in high-risk groups.

CONCLUSION

The results of this study revealed no significant difference between age groups for recurrence-free survival in women with hormone receptor-positive breast cancer; however, younger women did demonstrate a higher rate of recurrence. N stage N1 is an independent predictor of cancer recurrence.

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