

Prevalence of Breast Cancer and its Associated Factors for Recurrence in Hospital Tengku Ampuan Afzan from 2008 to 2012

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ABSTRACT

INTRODUCTION: Breast cancer is the commonest malignancy in Malaysian women. Cancer recurrence commonly seen in the first 2 years can be detrimental. Thus, identifying its prognostic factors is important. **MATERIALS AND METHODS:** We have retrospectively analyzed 179 women with breast cancer based on 5 years single center database with minimum follow up of 2 years. The demographic and clinico-pathological characteristics were determined using descriptive statistics. Survival was calculated based on Kaplan-Meier method. Multivariate analysis by Cox proportional hazards was performed to evaluate the potential factors affecting breast cancer recurrence. **RESULTS:** Mean follow up was 42 months, with mean age 52 years and 60.9% presented in Stage II disease. Overall recurrence was 41.9% with local recurrence 2.1%, regional recurrence 12.3% and distant recurrence 27.4%. 50% of our patients developed recurrence at 25 months. On univariate analysis, time to first presentation was significantly correlated with recurrence. In multivariate analysis, the tumor size, lymph node positivity and lympho-vascular invasion were independently associated with recurrence. **Discussion:** To date, local studies on prognostic factors in breast cancer recurrence remained sparse. Based on this study, factors associated with breast cancer recurrence identified and coincides with the previous evidence. Furthermore, this would provide evidence to improve the survival for patients with breast cancer in local settings. **CONCLUSION:** Further studies also need to be done on the non-compliant patients with advanced disease at presentation to determine factors towards their perception of surgical care in breast oncology.

Keywords

breast cancer, recurrence, prognostic factor

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INTRODUCTION

Breast cancer is the commonest malignancy in Malaysian women. In Pahang, east coast state of Malaysia, breast cancer represents 27.8% of all cancer diagnosed in 2007.¹ In 2005, the Early Breast Cancer Trialist Collaborative group has conducted a meta-analysis and found that with every 4 local recurrences prevented, one fewer breast cancer death will occur at year 15.² Thus, by knowing prognostic factors to recurrence, overall survival could be expected to increase in breast cancer.

The previous study has identified several associated factors with breast cancer recurrence, which include age, mode of detection, and tumor characteristics such as size,

histological grade, nodal status, and hormonal status^{3,4} Cancer recurrence has been a detrimental factor towards survival with a peak of recurrence recorded in first 2 years of diagnoses.^{5,12,16} Thus, identifying its prognostic factors is important.

The purpose of this study is to determine the recurrence pattern in breast cancer, mean time of recurrence, and prognostic factors that are associated with a higher rate of recurrence in a small population of patients attending Hospital Tengku Ampuan Afzan (HTAA), which served as a government-based referral centre in the East Pahang.

MATERIALS AND METHODS

This study was a cross-sectional study in the populations derived from women diagnosed with breast cancer from January 2008 until December 2012 who attended a tertiary hospital in Kuantan, Malaysia. Cross-reference made with Pahang Cancer Registry and Pathology database. We included all patients with stage I- III breast cancer who complied with the treatment given and completed follow-up during the study duration or until death. Demographic data, clinicopathological characteristics, and breast cancer subtypes were collected. The primary endpoint measured was recurrence and divided into local, regional, and distant recurrences. Time to the first recurrence was also identified. Follow-up of at least 2 years from surgery was decided based on literature support of peak recurrence occurred in the first 2 years.

RESULT

A total number of 377 patients with breast cancer diagnosed from 2008 until 2012; of these 130 patients were excluded based on the exclusion criteria. 68 further records were not retrievable or have incomplete data. Consequently, 179 patients' data were analyzed. From this, 16% of our reference population was diagnosed with metastatic disease at presentation. In addition, a further 15.9% of the population did not adhere to protocol.

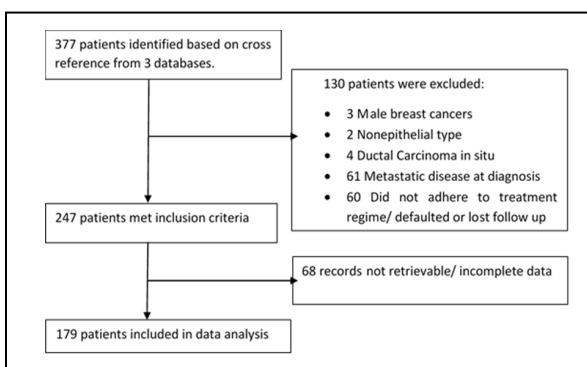


Figure 1 Sample recruitment process

The mean age of patients in the analysis was 52 years (SD 10.7), with only 11.7% in the young age group. The majority of patients were Malay ethnic (61.5%) followed by Chinese (29.3%). Only 10.1% of the subjects were screen-detected, while the mean time to presentation for all patients were 6.4 months (SD 7.2).

Table 1: Demographic data of the study sample

Variables	Mean (SD)	Frequency, N (%)
Age (years)	52.0 (10.7)	
< 40 Years old		21 (11.7)
> 40 Years old		158 (88.3)
Race		
Malay		110 (61.5)
Chinese		53 (29.6)
Indian		13 (7.3)
Others		3 (1.7)
Family history		
Yes		34 (19.0)
No		145 (81.0)
Menopause status		
Pre-menopause		49 (27.4)
Perimenopause		43 (24.0)
Postmenopause		87 (48.6)
Mode of detection		
Screen detection		18 (10.1)
Symptoms detection		161 (89.9)
Interval time to presentation (months)		6.4 (7.2)

SD= Standard deviation

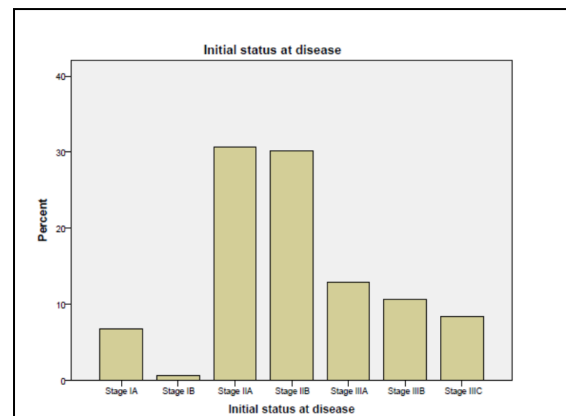


Figure 2 Distribution of stage at diagnosis.

Most of the women came in Stage II breast cancer (60.95) at initial diagnosis. Although node positivity comprised more than half of the sample, lympho-vascular invasion was seen only in 34.6% of cases. Almost 60% of cases were in Luminal group with Luminal B subtype more predominant.

After a mean follow up of 42.7 months, 41.9% patients developed recurrence and mean time to recurrence was 28.5 months (SD 15.5). Local recurrence comprised a minority with just over 2%, regional recurrence 12.3% and most had distant recurrence 27.4% as first site of recurrence.

Table 2: Clinicopathological characteristics of the study sample

Variables	Frequency, N (%)
Tumor size	
pT1(<2cm)	25 (14.0)
pT2(2-5cm)	99 (55.3)
pT3(>5cm)	30 (16.8)
pT4(Any size with skin/chest wall involvement)	25 (14.0)
Node status	
Node positive (N+)	107 (59.8)
Node negative (N-)	72 (40.2)
Initial stage at diagnosis	
IA	12 (6.7)
IB	1 (0.6)
IIA	55 (30.7)
IIB	54 (30.2)
IIIA	23 (12.8)
IIIB	19 (10.6)
IIIC	15 (8.4)
Histological grade	
Grade 1	49 (27.4)
Grade 2	84 (46.9)
Grade 3	46 (25.7)
Lymphovascular invasion (LVI)	
LVI positive	62 (34.6)
LVI negative/ not seen	117 (65.4)
Deep margin involvement	
No	35 (19.6)
Yes	144 (80.4)
Breast cancer subtypes	
Luminal group	106 (59.2)
Luminal A	23 (12.8)
Luminal B	83 (46.4)
HER 2 group	17 (9.5)
Triple negative group	56 (31.3)

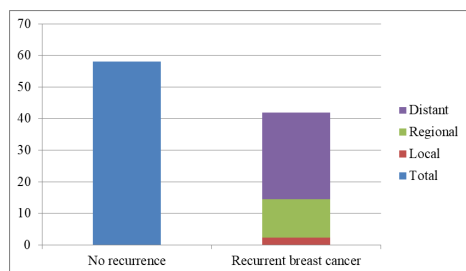


Figure 3 Distribution of recurrences.

In univariate analysis (Table 3), the only significant factor was time interval to presentation to hospital. There was no significant difference in other prognostic factors.

The survival analysis of recurrence suggests that at 25 months, almost 50% of patients develop recurrence. No recurrence occurred within the first 5 months and almost all patients developed recurrence within 60 months.

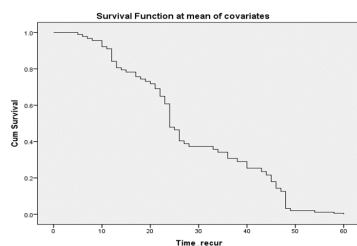


Figure 4 Kaplan Meier survival curve for recurrence with time to recur.

Table 3 Univariate Kaplan Meier analysis of recurrence

Variables	Frequency, N (%)	Recurrence, N (%) / Month, Mean (SD)	p value
Age (years)			
< 40 Years old	21 (11.7)	57.1	0.372
≥ 40 Years old	158 (88.3)	39.9	
Race			
Malay	110 (61.5)	42.7	0.531
Chinese	53 (29.6)	39.6	
Indian	13 (7.3)	46.2	
Others	3 (1.7)	33.3	
Family history			
Yes	34 (19.0)	44.1	0.736
No	145 (81.0)	41.4	
Menopause status			
Premenopause	49 (27.4)	46.9	0.431
Perimenopause	43 (24.0)	37.2	
Postmenopause	87 (48.6)	41.3	
Mode of detection			
Screen detection	18 (10.1)	16.7	0.683
Symptoms detection	161 (89.9)	44.7	
Time to first presentation			
With recurrence	75 (41.9)	7.85 (SD 8.924)	0.039
No recurrence	104 (58.1)	5.42 (SD 5.478)	
Tumour size			
T1	25 (14.0)	36.0	0.290
T2	99 (55.3)	34.3	
T3	30 (16.8)	43.3	
T4	25 (14.0)	76.0	
Node status			
Node positive	107 (59.8)	48.6	0.977
Node negative	72 (40.2)	31.9	
Initial stage at diagnosis			
IA	12 (6.7)	25.0	0.458
IB	1 (0.6)	0.0	
IIA	55 (30.7)	29.1	
IIB	54 (30.2)	38.9	
IIIA	23 (12.8)	65.2	
IIIB	19 (10.6)	63.1	
IIIC	15 (8.4)	53.3	
Histological grade			
Grade 1	49 (27.4)	26.5	0.179
Grade 2	84 (46.9)	41.7	
Grade 3	46 (25.7)	58.7	
Lymphovascular invasion (LVI)			
LVI positive	62 (34.6)	54.8	0.097
LVI negative	117 (65.4)	35.0	
Deep margin involve			
Yes	35 (19.6)	57.1	0.109
No	144 (80.4)	38.2	
Breast cancer subtypes			
Luminal group	106 (59.2)	38.7	0.245
Luminal A	23 (12.8)	47.8	
Luminal B	83 (46.4)	36.1	
HER 2 group	17 (9.5)	52.9	
Triple negative	56 (31.3)	44.6	

In multivariate analysis (Table 4), further independent associations were proven to be associated with breast cancer recurrence. Breast cancer patients with positive nodes are at a higher risk of recurrence (HR 2.14, 95% CI 1.032-4.418, p=0.041). Tumor size was also an independent prognostic indicator to recurrence (HR 0.335, 95% CI 0.126-0.886, p=0.028), while lympho-vascular invasion gave a negative prognostic indicator to breast cancer recurrence. (HR 2.039, 95% CI 1.078-3.857, p=0.029).

Table 4: Multivariable Cox Proportional Hazards models by factors of recurrence

Factors	Hazard ratio	95% Confidence Interval	p value
Age group <40 vs ≥40	1.36	0.499-3.707	0.548
Race	0.663	0.371-1.185	0.166
Family history	1.096	0.514- 2.337	0.813
Menopausal status	1.078	0.426-2.725	0.874
Method of detection	0.714	0.130-3.937	0.699
Time to presentation	0.977	0.944-1.011	0.175
Tumor size			
≤2cm vs T4 tumor	0.730	0.186-2.859	0.651
2-5cm vs T4 tumor	0.335	0.126-0.886	0.028
5cm vs T4 tumor	0.445	0.186-1.063	0.069
Nodes positive	2.136	1.032-4.418	0.041
Stage at diagnosis	1.031	0.783-1.357	0.827
Grading			
Grade 1 vs Grade 2	0.857	0.399-1.842	0.692
Grade 1 vs Grade 3	1.125	0.469-2.698	
Lymphovascular invasion	2.039	1.078-3.857	0.029
Deep margin	1.262	0.618-2.576	0.523
Breast cancer subtype			
Luminal vs Triple negative	0.843	0.333-2.133	0.718
Luminal vs HER2	1.442	0.764- 2.721	0.258

DISCUSSION

Breast cancer has been described as the most common malignancy in the female population not just in Malaysia but globally. In Pahang, the east coast state of Malaysia, breast cancer represents 27.8% of all cancer diagnosed in 2007¹. The demographic distributions in this study were in keeping with the National Cancer Registry Report with the mean of age in patients was 52 (SD 10.7) and stage of diagnosis predominantly in Stage II disease.

Breast cancer recurrences posed a challenge in managing patients, as it correlated with overall survival. The overall recurrence in this study was 41.9% after a mean of 42 months follow-up, which was higher than the western data, 13%⁶. Our local recurrence rate was in keeping with western data in their 10 years data base⁷. The advancement of adjuvant hormonal therapy has been postulated to these result.⁴

Distant recurrence in this study was observed in 27.4% of the samples and based on the Kaplan Meier survival curve; we extrapolated that at 25 months, 50% of the patients developed recurrences. This is relatively higher than other Asian countries, e.g Filipino.⁸ However, this coincides with our early Malaysian data of 40.5% locoregional recurrence rate.^{9,10} This results in further disease progression and overall low survival rate coincides with early Malaysian study in 2005 of 49.4% overall 5-year survival.¹¹ Higher incidence of distant metastases and overall recurrence in Malaysian women was a result of the late stage of presentation with heavy nodal burden, longer interval time to presentation, and higher younger age women.^{10,12,13}

Although our results for univariate analysis were only significant for a time interval to the first presentation, subsequent multivariate analysis of Cox regression showed tumor size, lymph node positivity, and lymphovascular invasion were independently associated with recurrence. This could be due to univariate analysis alone might not be sufficient to determine the association, attributed to the influence of large within-group variation. The multivariate analysis became significant due to the accumulation of evidence from the individual variable in the overall test.

In patients with recurrence, our study has shown a significant correlation with time to the first presentation, in which the mean time was 7.85 (SD 8.92) as compared to 5.42 (SD 5.48) without recurrence. Patients with earlier presentation generally have smaller tumor sizes or impalpable lumps detected via radiological screening. Screen-detected cancer has a more favourable outcome and less tumor recurrence.⁴ However the detection of the symptoms less than 1 month has been significantly correlated with higher survival as compared to increasing duration of symptoms with 12% decrease in survival if presented after 1 year.¹⁰

Tumor size was found to be a significant factor of recurrence as proven by previous studies.^{14,15} As for the role of nodal positivity and lympho-vascular invasion in shorter survival and a higher rate of breast cancer recurrence is also supported by other studies.^{14,15,16}

The lympho-vascular invasion has been identified as the independent prognostic factor for higher locoregional recurrence with a strong correlation of breast cancer-specific survival and distant metastasis-free survival.^{16,17,18}

Despite that, we still need to acknowledge the late presentation of breast cancer among Malaysian women with mostly were diagnosed in Stage III and IV (50-60%) and non-compliant group (15.9% in our study) probably refusal to modern medical treatment due to social factors and perception towards diagnosis.¹⁹

Although multiple large cohort studies have previously addressed the correlation of several prognostic factors with recurrence, local studies have remained sparse. Thus, we present 5-year data on breast cancer outcome in the East Pahang population with a mean follow up of 42 months and identified the significant prognostic factors towards recurrence, in which we hope to optimize our care thus increasing survival for patients with breast cancer in our local settings.

CONCLUSION

Understanding the significant prognostic factor in breast cancer recurrence improved overall survival of the breast cancer population.

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