RESEARCH ARTICLE

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Overall Survival and Local Recurrence Among Breast Cancer Patients in Hospital Sultanah Nora Ismail Batu Pahat, 2007-2013

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Abstract

Objective: To gauge surgical outcome in breast cancer patients with particular reference to overall survival and recurrence free survival among breast cancer patients in Hospital Sultanah Nora Ismail Batu Pahat, Johor, Malaysia. **Methods:** Patients undergoing ablative breast cancer surgery were identified and clinical records were assessed. Inclusion criteria for enrolment were stage I-IV breast malignancy necessitating resection with or without radiotherapy/ chemotherapy from 2007 to 2013. All individuals had a pre-operative assessment. The post operative assessment period ranged from 1 year to 5 years. Survival distributions were analyzed using Kaplan-Meier curves. **Results:** A total of 121 patients were included in this study, with an age range of 28-78 years. Some 98% had undergone local excision/ lumpectomy/ mastectomy with axillary clearance. While 81% of patients underwent chemotherapy, only 69% had radiotherapy. Tumours were oestrogen receptor positive in 58% of cases and progesterone receptor positive in 62%. Local recurrence was detected in 10%. The mean age at diagnosis was 51.3 + 10.4 years. The overall survival analysis was based on 22 deaths among the 121 patients (18.2%). Three-year and five-year survival rates were 87.6% and 78.4%, respectively. Analysis of recurrence-free-survival (RFS) was based on 12 events among 121 patients. The Kaplan-Meier RFS analysis revealed that in 90% of the patients with recurrence, it occurred within 45 months. The five year RFS rate was 84.5%. The median time taken from diagnosis to ablative surgery was 51 days (upper limit of 791 days). Only distant metastasis was a significant factor that impacted on both overall survival and recurrence-free survival ($p<0.001$). **Conclusion:** Overall survival among our breast cancer patients in our facility is comparable to other in other tertiary centres in the country. A trend for earlier detection was noted.

Keywords: Breast cancer- surgery- recurrence- survival- Malaysia

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Introduction

Cancer is a leading cause of morbidity and mortality worldwide, accounting for approximately 14 million new cases and 8.2 million deaths in 2012 (Bray et al., 2013; Ferlay et al., 2013). After lung cancer, breast cancer is the second most common cancer in the world (Yip et al., 2006; World Health Organization, 2014), and is the most frequently occurring cancer in women globally, comprising 25% of all cancer cases diagnosed in 2012 (World Health Organization, 2012). Breast cancer affects women both in more and less developed regions, although the incidence is higher in less developed regions (Yip et al., 2006; World Health Organization, 2014). Indeed, there is a significant geographical variation in the incidence of the disease, with rates ranging from 27 per 100,000 people in Middle Africa and Eastern Asia to 96 per 100,000 in Western Europe (Ferlay et al., 2013). In terms of mortality, breast cancer is the fifth leading cause of overall cancer related deaths (522,000 deaths) (Yip et al., 2006; World Health Organization, 2014). Survival has probably improved because of a mixture of earlier detection of the disease (both through screening and earlier symptomatic presentation), and biological changes that have made the disease more susceptible to hormonal therapy and improved treatment (Eileen, 2012).

The American Cancer Society estimates that 231 840 women will be diagnosed with breast carcinoma and 40290 women will die from it in 2015. While the surgical intervention has contributed to the improvement in survival rates, this has not been of similar rates in other developing countries.

In Peninsular Malaysia and East Malaysia, breast cancer is the most common cancer among females and also

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the leading cancer among population regardless of sex and ethnic groups (Khan et al., 2015). There were 3,242 female breast cancer cases registered in the National Cancer Registry for 2007, representing 18.1% of all cancer cases and 32.1% of all female cases registered. This presents an age-standardized ratio of breast cancer incidence of 29.1 per 100,000 women. This rate however differs between the three main races in Malaysia: the Malays, Chinese and Indians.

In terms of survival, Bhoo Pathy et al., (2015) reported the value of adjuvant radiotherapy that appeared to be independently associated with a survival gain in locally advanced as well as in very young triple negative breast cancer in a cohort of Asian patients in 5 centres. Saxena et al., (2012) revealed that Malaysian (middle-income country) patients were less often diagnosed with in situ breast cancer and more likely to be diagnosed with late stage disease as compared to Singaporean (high income country) patients and this translated into a 72% increased risk of death as compared to Singaporean patients. Taib et al., (2012) reported an improvement in breast cancer survival for 2 cohorts of patients compared between 1993 to 1997 and 1998 to 2002 among patients treated at the University Malaya Medical Centre, Malaysia. Stage of disease, lymph node (LN) involvement, size and grade were identified as independent prognostic factors in cohort one. For the second cohort; stage and LN involvement remained independent factors with the addition of oestrogen receptor (ER) status and ethnicity.

The Department of Surgery in Hospital Sultanah Nora Ismail, Batu Pahat was set up in 1994. It has since been offering many surgical services that include breast, endocrine and gastroenterology fields.

However, there has not been any clinical audits conducted to measure the survival rate among breast cancer patients (surgical) in this hospital. Thus, it is timely that a study in conducted to ascertain the surgical outcome of breast cancer patients as this would allow us to gauge the progress of the surgical services in this major district hospital as compared to other major hospitals in Malaysia.

Within Malaysia, the population based cancer registry has its limitation, particularly when the outcome and recurrence rate is scarcely reported. It is against this background that we aim to study overall survival, disease-free survival and local recurrence among breast cancer patients in Hospital Sultanah Nora Ismail Batu Pahat, Johor.

This study is conducted to ascertain the overall survival and local recurrence among breast cancer patients.

Specific aims of study

i) Primary Outcome: Overall survival, disease free survival among breast cancer patient who have undergone surgery (+ chemotherapy/ radiotherapy)

ii) To identify the types of surgical treatment options offered

Materials and Methods

We reviewed our institutional experience with patients who underwent ablative breast cancer surgery from 1st January 2007 to 31st December 2013. Inclusion criteria for enrolment were stage I-IV breast malignancy necessitating resections with or without radiotherapy/ chemotherapy. Staging of the disease was in accordance to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition (12). The late stage is defined as breast cancer at either stage III or IV of the disease.

All breast cancer patients who have been surgical treated (curative intention) within the period of 2007- 2013 had their records traced. The following data is captured:

a) Demographic details (age, race, occupation, family history of breast cancer, socioeconomic status)

b) Details of diagnosis and intervention: date of presentation, date of first surgical consult, date of diagnosis, date of treatment

c) Details of recurrence: local; regional; loco-regional; systemic/ distant metastasis

d) Operating notes details (lobectomy, breast conserving therapy, complete mastectomy, with/without axillary clearance).

e) Patients' follow-up details; follow up dates, last follow up date, staging, date/s of recurrence and death (if any) is identified. If needed, a crosscheck is done with the patient's next of kin or from the National Registry of Birth and Death on the patient's vital status (patients' who defaulted follow-up).

The post-operative assessment period ranged from 1 year to 5 years. Disease-free survival was defined as the interval between the date of ablative breast surgery and the date of the last consultation or recurrence. Only patients who underwent ablative cancer surgery were included in this audit. All the resection specimens are assessed by a single pathologist using a standard protocol. Data on mortality (all-causes) were obtained through record linkage with the National Registration Department in Malaysia from year 2007 to 2015, using the unique national identification number. Recurrence free survival (RFS) and overall survival (OS) were the end points in this study. RFS was measured from date of surgery to the first date of documented recurrence and was censored at the date of last follow-up. OS time was calculated from the date of surgery to the date of death and censored by the last date of follow-up. The method of Kaplan-Meier was used to evaluate OS and RFS, and the log-rank test was used for comparison analysis. The Cox proportional hazard model was used to estimate the hazard ratios for univariable analysis with the variables included gender, race, T-staging, neck dissection, site, radiotherapy and nodal metastasis. Hazard ratios indicating the effects of prognostic factors on the risk of event (death or recurrence) were calculated and presented with 95% confidence intervals (CI). The Cox model was then carried out for multivariable analysis including all the variables using the Enter method. The reported p-values were based on two-sided tests, and p-values less than 0.05 were considered statistically significant. All statistical analyses used PASW Statistics version 18

(SPSS Inc, Chicago, IL, USA).

Results

We identified 356 breast cancer patients within the period of 2007 to 2013. Upon exclusion, the current study reports on a group of 121 patients who were diagnosed with invasive ductal carcinoma, invasive lobular carcinoma, mucinous carcinoma of the breast, ductal carcinoma in situ, phyllodes tumour or dermatofibrosarcoma protuberans. Excluded patients included patients who were operated in other hospitals

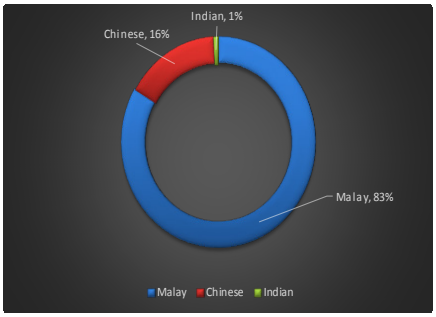

Figure 1. Racial Distribution (N=121)

Table 1. Distribution of Patients by Staging

Stage	n	%
I	14	11.6
II	55	45.4
III	44	36.4
IV	8	6.6
Total	121	100

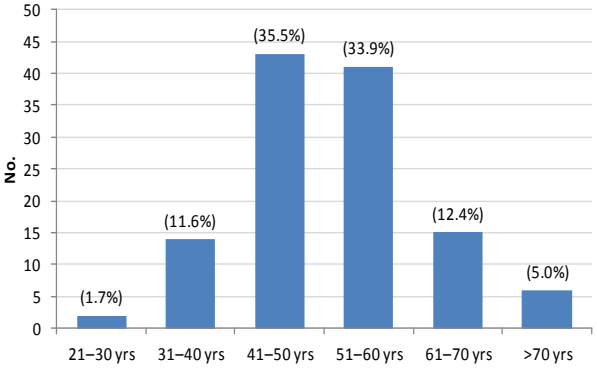

Figure 2. Age Distribution at Diagnosis (N=121)

Table 2. Comparison of Survival Experience by Factors

Variable	Overall survival				Recurrence-free survival			
	Death[a]		X^2 statistics (df)[b]	P-value[b]	Recurrence[a]		X^2 statistics (df)[b]	P-value[b]
	No, n (%) (n=99)	Yes, n (%) (n=22)			No, n (%) (n=109)	Yes, n (%) (n=12)		
Age at diagnosis:								
≤45 years	30 (30.3)	5 (22.7)	1.43 (1)	0.23	31 (28.4)	4 (33.3)	0.04 (1)	0.84
>45 years	69 (69.7)	17 (77.3)			78 (71.6)	8 (66.7)		
Duration from diagnosis to surgery:								
≤30 days	23 (23.2)	4 (18.2)	3.05 (2)	0.22	25 (22.9)	2 (16.7)	3.52 (2)	0.17
31–90 days	46 (46.5)	15 (68.2)			52 (47.7)	9 (75.0)		
>90 days	30 (30.3)	3 (13.6)			32 (29.4)	1 (8.3)		
Staging:								
I	14 (14.1)	0 (0.0)	8.01 (3)	0.05	14 (12.8)	0 (0.0)	4.92 (3)	0.18
II	47 (47.5)	8 (36.4)			50 (45.9)	5 (41.7)		
III	32 (32.3)	12 (54.5)			37 (33.9)	7 (58.3)		
IV	6 (6.1)	2 (9.1)			8 (7.3)	0 (0.0)		
Estrogen receptor status:								
Negative	33 (33.3)	10 (45.5)	1.50 (1)	0.22	39 (35.8)	4 (33.3)	0.00 (1)	0.98
Positive	59 (59.6)	11 (50.0)			63 (57.8)	7 (58.3)		
Progesterone receptor status:								
Negative	29 (29.3)	9 (40.9)	1.42 (1)	0.23	35 (32.1)	3 (25.0)	0.10 (1)	0.76
Positive	63 (63.6)	12 (54.5)			67 (61.5)	8 (66.7)		
Radiotherapy:								
Yes	68 (68.7)	16 (72.7)	0.36 (1)	0.55	77 (70.6)	7 (58.3)	1.08 (1)	0.3
No	27 (27.3)	5 (22.7)			27 (24.8)	5 (41.7)		
Chemotherapy:								
Yes	78 (78.8)	20 (90.9)	4.57 (1)	0.033	89 (81.7)	9 (75.0)	0.10 (1)	0.749
No	18 (18.2)	1 (4.5)			16 (14.7)	3 (25.0)		
Distant metastasis:								
Yes	15 (15.2)	11 (50.0)	12.28 (1)	<0.001	17 (15.6)	9 (75.0)	24.30 (1)	<0.001
No	84 (84.8)	11 (50.0)			92 (84.4)	3 (25.0)		

SE, Standard error; [a] Column percentage is presented, the remaining unreported percentage is the missing value; [b] Overall log rank test.

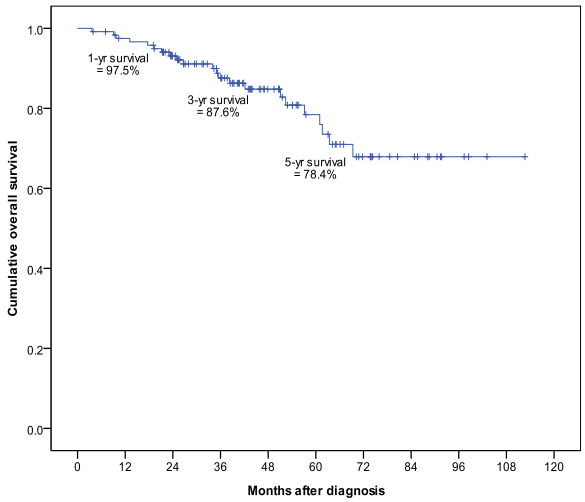

Figure 3. Cumulative Overall Survival in 121 Women with Breast Cancer; End Date, Date of Death (as of December 2015), or Date of Last Follow-up for Censored Cases

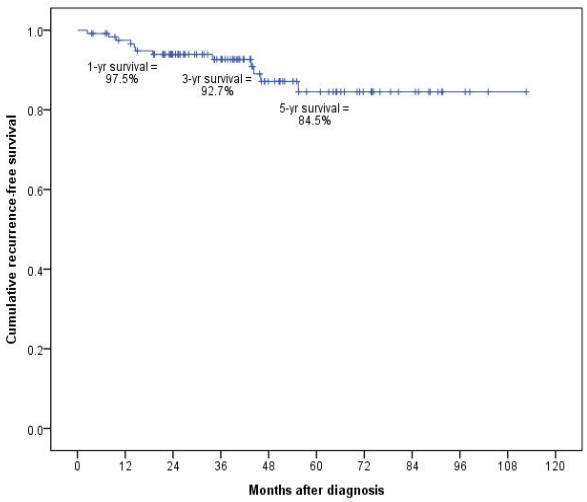

Figure 4. Cumulative Recurrence-free Survival in 121 Women with Breast Cancer; End Date, Date of Recurrence, or Date of Last Follow-up for Censored Cases

and referred in for chemotherapy and follow up, patients who were not operable, patients who declined surgical intervention and patients who were lost to follow up upon diagnosis.

The majority of these patients was Malay (Figure 1) and in the age range of 41-60 years (Figure 2). 98% of patients underwent local excision/ lumpectomy/ mastectomy with axillary clearance. Only 2 patients did not have axillary clearance (diagnosed with ductal carcinoma in situ). 81% of patients underwent chemotherapy while 69% patients had radiotherapy. 58% of patients were oestrogen receptor positive and 62% were progesterone

Table 3. Association between Factors and Overall Survival in the Study Population

Variable	Death[a]		Univariable analysis				Multivariable analysis[c]			
	No, n (%) (n=99)	Yes, n (%) (n=22)	Crude HR	(95% CI HR)	X^2 stat. (df)[b]	P value[b]	Adj. HR	(95% CI HR)	X^2 stat. (df)[b]	P value[b]
Age at diagnosis:										
≤45 years	30 (30.3)	5 (22.7)	0.55	(0.20, 1.49)	1.39 (1)	0.239	0.55	(0.18, 1.64)	1.17 (1)	0.28
>45 years	69 (69.7)	17 (77.3)	1.00	(ref)			1.00	(ref)		
Duration from diagnosis to surgery:										
≤30 days	23 (23.2)	4 (18.2)	1.48	(0.33, 6.64)	0.27 (1)	0.605	1.14	(0.19, 6.71)	0.02 (1)	0.89
31–90 days	46 (46.5)	15 (68.2)	2.63	(0.76, 9.07)	2.33 (1)	0.127	2.49	(0.53, 11.8)	1.32 (1)	0.25
>90 days	30 (30.3)	3 (13.6)	1.00	(ref)			1.00	(ref)		
Staging:										
I*	14 (14.1)	0 (0.0)	-	-	-	-	-	-	-	-
II	47 (47.5)	8 (36.4)	0.38	(0.08, 1.80)	1.48 (1)	0.22	0.42	(0.03, 6.01)	0.42 (1)	0.52
III	32 (32.3)	12 (54.5)	0.88	(0.20, 3.93)	0.03 (1)	0.87	0.58	(0.04, 7.94)	0.16 (1)	0.69
IV	6 (6.1)	2 (9.1)	1.00	(ref)			1.00	(ref)		
Estrogen receptor status:										
Negative	33 (33.3)	10 (45.5)	1.00	(ref)			1.00	(ref)		
Positive	59 (59.6)	11 (50.0)	0.59	(0.25, 1.39)	1.46 (1)	0.23	0.41	(0.12, 1.34)	2.19 (1)	0.14
Progesterone receptor status:										
Negative	29 (29.3)	9 (40.9)	1.00	(ref)			1.00	(ref)		
Positive	63 (63.6)	12 (54.5)	0.59	(0.25, 1.41)	1.38 (1)	0.24	0.63	(0.18, 2.13)	0.56 (1)	0.45
Radiotherapy:										
Yes	68 (68.7)	16 (72.7)	1.00	(ref)			1.00	(ref)		
No	27 (27.3)	5 (22.7)	0.73	(0.27, 2.02)	0.36 (1)	0.55	1.75	(0.59, 5.17)	1.01 (1)	0.31
Distant metastasis:										
Yes	15 (15.2)	11 (50.0)	1.00	(ref)			1.00	(ref)		
No	84 (84.8)	11 (50.0)	0.25	(0.11, 0.58)	10.5 (1)	0.001	0.21	(0.07, 0.63)	7.85 (1)	0.01

Adj. HR, Adjusted Hazard Ratio; [a] Column percentage is presented, the remaining unreported percentage is the missing value; [b] Wald test; [c] Multivariable analysis; total cases available = 107 (with 20 events); *Non-convergence in model (as the observation in the event is zero).

Table 4. Association between Factors and Recurrence-free Survival in the Study Population

Variable	Recurrence[a]		Univariable analysis				Multivariable analysis[c]			
	No, n (%) (n=109)	Yes, n (%) (n=12)	Crude HR	(95% CI HR)	X^2 stat. (df)[b]	P value[b]	Adj. HR	(95% CI HR)	X^2 stat. (df)[b]	P value[b]
Age at diagnosis:										
≤45 years	31 (28.4)	4 (33.3)	1.13	(0.34, 3.77)	0.04 (1)	0.84	3.19	(0.63, 16.17)	1.97 (1)	0.16
>45 years	78 (71.6)	8 (66.7)	1.00	(ref)			1.00	(ref)		
Duration from diagnosis to surgery:										
≤30 days	25 (22.9)	2 (16.7)	0.65	(0.14, 2.95)	0.32 (1)	0.57	0.23	(0.03, 1.77)	1.99 (1)	0.16
>30 days	84 (77.1)	10 (83.3)	1.00	(ref)			1.00	(ref)		
Staging:										
I*	14 (12.8)	0 (0.0)	-	-	-	-	-	-	-	-
II	50 (45.9)	5 (41.7)	0.46	(0.15, 1.48)	1.69 (1)	0.19	1.44	(0.23, 9.14)	0.15 (1)	0.70
III	37 (33.9)	7 (58.3)	1.00	(ref)			1.00	(ref)		
IV	8 (7.3)	0 (0.0)	-	-	-	-	-	-	-	-
Estrogen receptor status:										
Negative	39 (35.8)	4 (33.3)	1.00	(ref)			1.00	(ref)		
Positive	63 (57.8)	7 (58.3)	1.02	(0.30, 3.48)	0.00 (1)	0.98	0.37	(0.07, 2.00)	1.34 (1)	0.25
Progesterone receptor status:										
Negative	35 (32.1)	3 (25.0)	1.00	(ref)			1.00	(ref)		
Positive	67 (61.5)	8 (66.7)	1.23	(0.33, 4.66)	0.10 (1)	0.76	0.29	(0.03, 2.39)	1.33 (1)	0.25
Radiotherapy:										
Yes	77 (70.6)	7 (58.3)	1.00	(ref)			1.00	(ref)		
No	27 (24.8)	5 (41.7)	1.83	(0.58, 5.81)	1.05 (1)	0.31	4.05	(0.77, 21.41)	2.72 (1)	0.1
Chemotherapy:										
Yes	89 (81.7)	9 (75.0)	1.00	(ref)			1.00	(ref)		
No	16 (14.7)	3 (25.0)	1.24	(0.33, 4.67)	0.10 (1)	0.749	2.16	(0.26, 18.34)	0.50 (1)	0.48
Distant metastasis:										
Yes	17 (15.6)	9 (75.0)	1.00	(ref)			1.00	(ref)		
No	92 (84.4)	3 (25.0)	0.08	(0.02, 0.29)	14.6(1)	<0.001	0.01	(0.00, 0.12)	13.1(1)	<0.001

Adj. HR, Adjusted Hazard Ratio; [a] Column percentage is presented, the remaining unreported percentage is the missing value; [b] Wald test; [c] Multivariable analysis; total cases available, 106 (with 11 events); *Non-convergence in model (as the observation in the event is zero).

receptor positive. Local recurrence was detected in 10% of the patients. The mean age at diagnosis was 51.3 years old (standard deviation of 10.4 years).

The overall survival analysis was based on 22 deaths among the 121 patients (18.2%), as of December 2015. The overall survival time at 75% is 61.6 months (did not reach a median survival), and demonstrated a plateau at 68%, beginning at approximately 6 years (Figure 3). Three-year and five-year survival rates were 87.6% and 78.4%, respectively. The analysis of RFS was based on 12 events among 121 patients (Figure 4). The Kaplan-Meier RFS analysis revealed that 90% of

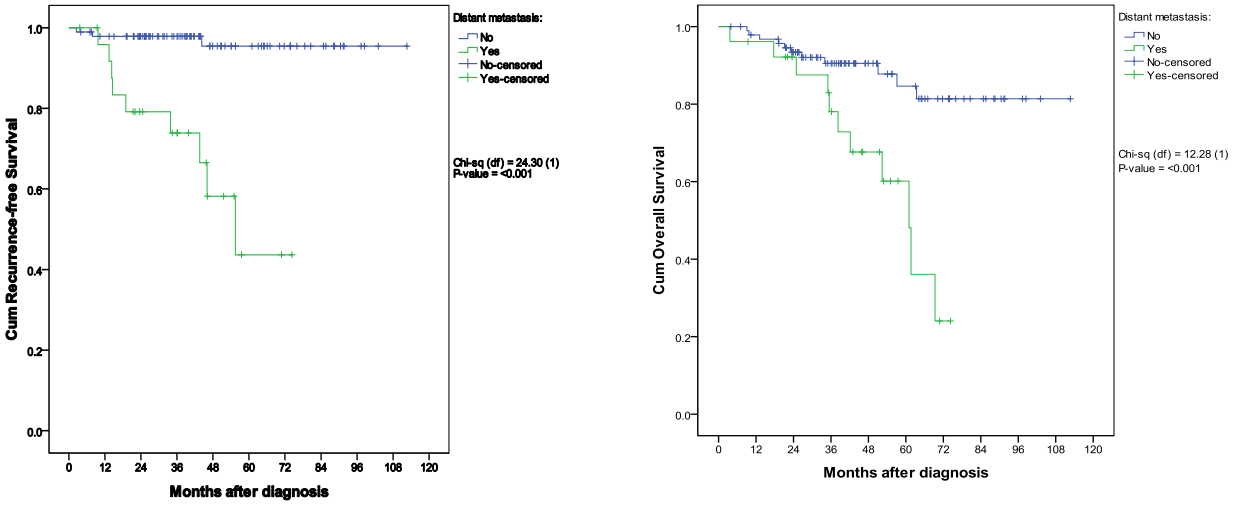

Figure 5. Overall Survival and Recurrence-free Survival by Distant Metastasis

the patients have reached the event of recurrence at 45 months. The median RFS has not yet been reached, with a plateau of the Kaplan–Meier curve at 84.4% after 4.5 years (longest follow-up 112 months). One year RFS rate was 97.5% and five years RFS rate was 84.5%. The median time taken from diagnosis to ablative surgery was 51 days (range of 791 days).

Only distant metastasis was the significant factors that impacted both overall survival and recurrence-free survival of the patients (Figure 5, Table 2, 3, 4)

Discussion

The survival of patients with breast cancer depends on prognostic variables that include staging of the disease during the first diagnosis, size of the tumour, the menstrual status and the histopathology. In addition to that, it is also influenced by other complex underlying factors; the population structures which include the population age structure and ethnicity; socio-economic status, and the availability of effective health care system which include the screening programmes which enhance the early detection of cases and also accessibility to high quality treatment (Hortobagyi et al., 2005; Tan et al., 2007).

There are general principles in cancer surgery: the performance of a maximum operation for minimal disease, and cure is more likely to occur if microscopic loci of the lesion are removed before gross extensive involvement takes place. The performance of a node clearing procedure, even when the axilla is clinically negative, has radically altered the incidence of recurrent disease (9.5 % in this series).

We found that a majority in this cohort of patients were diagnosed with breast cancer at stage II (45.4%). Within the same state, Mao et al., (2015) reported that majority of the patients in Segamat Hospital were diagnosed with breast cancer at a later stage: stage III (17.3%) and stage IV (42.3%). A cross-sectional study in three referral medical centres in the East Coast of Malaysia and two public hospitals in Kuala Lumpur demonstrated late stage at presentation to be 44.8% (Stage III) and 11.3% (Stage IV) respectively. Another prospective study done in Queen Elizabeth Hospital, Kota Kinabalu, Sabah, noted presentation at 36.6% (Stage III) and 15.6% (Stage IV) . This is in contrast with the presentation in this series as Stage IV presentation accounted for only 6.6% of the total number of patients. The increased availability of high quality imaging facilities in recent years may have enabled detection of cancer metastases before they became clinically evident, resulting in more patients who would have been previously classified as having non-metastatic breast cancer migrating to stage IV. This (Will Rogers) phenomenon may partly explain the (apparent) survival improvement of patients with metastatic breast cancer. However, this cohort only included patient who were operable and thus inoperable Stage IV cases have been excluded from this study. Notwithstanding this, it is worthwhile to note that a larger proportion of patients have presented in an earlier stage and this could be contributory to the improved survival among breast cancer patients.

This study reaffirms the prognostic role of staging and distant metastasis in the survival of breast cancer patients. The 5 year overall survival in this centre is relatively similar (78.4%) to other reported centres in Malaysia. Taib et al., (2011) reported a 5-year survival rate of 75.7%. Pathy et al,. (2011) studied on 2545 cohort patients from two hospital-based practices (Singapore and Malaysia) and reported a combined 5-year survival rate of 79%. The increasing 5-year survival rate of more than 80% has been reported in European countries (Berrino et al., 2007), United Stated (American Cancer Society, 2012) and developed Asian country like Japan (Tsukuma et al., 2006) and Hong Kong (Kwong et al., 2011) . Abdullah et al., (2013) conducted a retrospective cohort study by examining the data on breast cancer patient who were hospitalised in majority of the hospitals in Malaysia and reported an overall 5-year survival rate of 49% who were diagnosed within the years of 2000 to 2005. However, these reported figures may have included palliative care patients who were excluded in our study. There have been, and will continue to be, substantial changes in the use, or methods, of screening, surgery, pathology, radiotherapy, and systemic adjuvant therapy since many of these studies began. In particular, tumour sizes are generally smaller, systemic therapy is more effective, radiotherapy is less likely to be given to the internal mammary chain of lymph nodes or to a surgically-cleared axilla, and there has been increasing recognition of the late side-effects of radiotherapy and of the need when treating early breast cancer to limit doses to the heart and lungs. Moreover, advances in early diagnosis, surgery, and systemic therapy mean that the 5-year risks of local recurrence might well be much less than in these studies.

In conclusion and recommendation, the overall 5-year survival rate of breast cancer patients in this centre is comparable to survival rates in the country's tertiary centres and to developed nations. This may be a reflection of the impact of the effectiveness of prevention programmes that has been in place in the recent years. More similar clinical audits could help to continuously monitor the progress of the survival among breast cancer patients.

Conflict of interest

None declared.

Acknowledgements

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