RESEARCH COMMUNICATION

Improvement in Survival of Breast Cancer Patients - Trends in Survival over Two Time Periods in a Single Institution in an Asia Pacific Country, Malaysia

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Abstract

Background: There is improvement in breast cancer survival in the developed world, but information on breast cancer survival trends in the Asia Pacific region is limited. The aim of the study was to evaluate survival trends and factors that affect survival in Malaysia. Methods : Two prospective groups of 423 and 965 newly diagnosed breast cancer patients in University of Malaya Medical Centre, Kuala Lumpur, Malaysia diagnosed in two time periods ie. 1993 to 1997 and in 1998 to 2002 were studied. Vital status was obtained from the National Registry of Births and Deaths. The overall survival was calculated from the date of diagnosis to the date of death from any cause. The survival differences between the two groups were analysed using the log-rank or Peto-Wilcoxon method. Survival estimates and independent prognostic factors were estimated by the Kaplan-Meier method and multivariate analysis using Cox proportional hazard models. P values less than 0.05 were considered statistically significant. Analyses were performed using SPlus 2000 Professional Release 2. Results and Discussion : Median follow-up for the two groups were 55 months (SD 29.2 months) in the first group and 52 months(SD 24.43) in the second group. There was improvement in 5-year observed survival from 58.4% (CI 0.54-0.63) to 75.7% (CI 0.73-0.79). The improvement in survival was significantly seen in all co-variates ($p<0.05$) except for those aged 40 years and below($p= 0.27$), tumour size 2 to 5 cm ($p=0.11$), grade 3 ($p=0.32$) and patients with Stage IV disease($p= 0.80$). 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 ER status and ethnicity. Conclusions : There was improvement in 5-year observed survival. Besides known prognostic factors, Malay ethnicity was an independent prognostic factor.

Keywords: Breast cancer - Malaysia - survival - prognostic factors

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Introduction

Malaysia is a middle income country in the Asia Pacific region with a population of 28.1 million. Breast cancer is the commonest cancer in Malaysia with the age standardised rate for females of 47.4 per 100,000 women. The incidence was higher in Chinese women (ASR 59.9 per 100,000 women) compared to Indian (ASR 54.2) and Malay (ASR 34.9) (Lim et al., 2008). Malaysia has a multiracial composition with Malays being the majority followed by the Chinese and Indians. Population based screening had not been implemented in Malaysia. Breast cancer specific survival information in Malaysia is scarce, however due to mandatory reporting of deaths in Malaysia, observed survival can be obtained (Yip et al., 2006);(Mohd Taib et al, 2008).

University Malaya Medical Centre (UMMC) is a 900 bed tertiary public hospital located in urban Kuala Lumpur. This study is the first in Malaysia to show an improvement in survival in different time periods. This study also identified important prognostic factors to guide cancer control strategies in Malaysia.

Materials and Methods

Patient Selection

Pre-invasive cancers and patients that defaulted treatment were excluded from the study. We identified 423 patients from 1993-97 and 965 patients in 1998-2002. The time frames were chosen, because there were significant changes in the oncology practice in the institution. The development of oncology services had improved over the years with the incorporation of trained oncologists in 1998. In-house radiotherapy and daycare chemotherapy services were started in 1998 and 1999 respectively. Prior to this, patients received chemotherapy in the ward administered by surgeons and radiotherapy services were obtained in a different public institution. In 1993 to 1997 the Cyclophosphamide, Methotrexate and 5-Fluorouracil (CMF) regiment was used and in 1998 to

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2002, 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) was used as first line adjuvant treatment and CMF was given only to patients with cardiac problems.

Outcome Measures

Reporting of deaths to the National Registry of Births and Deaths in Malaysia is mandatory by law in Malaysia. The UMMC institutional breast cancer registry was reviewed for all newly diagnosed patients in 1993 to 1997 and 1998 to 2002. The patients were identified through the national identity card number. Vital status was obtained from the National Registry of Births and Deaths in December 2002 for those diagnosed in 1993-97 and March 2006 for those diagnosed in 1998-2002. Hence there was similar short term follow-up for both time periods. Breast cancer specific mortality was not used because 44.4 % of deaths in Malaysia were non-medically certified (Yusoff, 2005). Overall survival was calculated from the date of diagnosis to the date of death from any cause. Thus, those who were alive were censored at the end of the study date.

Statistical Analysis

Patients were divided into two groups according to their year of diagnosis, group 1 was diagnosed between 1993-97 and group 2 between 1998-2002. Survival outcomes comparing both time periods were estimated using the Kaplan-Meier method and compared between groups using the log-rank statistical test. The log-rank test was used if the proportional hazard assumptions were met. Otherwise, the Peto-Wilcoxon test was employed to compare the survival of the two groups. Only in five instances were the assumption not met, rendering the use of the Peto-Wilcoxon test (Refer Table 2).

Cox proportional hazard models were fit to determine survival outcomes after adjustment to patient characteristics. The proportion hazards assumption was assessed visually with plots of model residuals. In group 1, the Kaplan Meier plot showed the crossing of at least two of the curves for size, ER and age (results not shown) and when fit to the best fitted model, these variables gave insignificant values ($p>0.05$). Therefore, there was no doubt in the validity of the proportional hazards assumptions across the groups for stage, lymph node status, size and grade in group 1. In group 2, the curves separated in all the Kaplan-Meier plots, hence the proportion hazards assumptions were satisfied.

As for identifying important prognostic factors, we employed the forward selection approach in the multivariate Cox regression model. The selection was based on the log-likelihood ratio statistic. Models were adjusted for stage, ethnicity, age, size, lymph node involvement, Bloom-Richardson grade and oestrogen receptor (ER) . P values less than 0.05 were considered statistically significant. All analyses were performed using SPlus 2000 Professional Release 2.

The analyses had limitations in that relative survival was not used, to explain the background variability of ethnicity and age groups within the population. Unavailable data was inherent at that time of practice. ER testing was not routinely done in the first group, unavailable ER status improved from 64.8% in the first group to only 15.2% in the second group. As for Grade, it reduced from 43.7% to 29.0%. This is due to a maturing institutional breast cancer multidisciplinary team. Surgical dependant pathological co-variates may be also be unavailable due to the non-surgical nature of treatment of stage IV disease. Despite obtaining data from a prospective surgical database, data on adjuvant therapy was not readily available. There was a large proportion of missing data for lymph node status, grade and ER status, in group 1. These variables were mainly derived post surgery and from laboratory testing and were missing because the patients did not undergo surgery due to Stage IV disease.They were not removed from analysis but was labelled as "not available" because we wished to evaluate other available clinical variables such as age, ethnicity and stage.

Results

We identified 423 patients from group 1 and 965 patients in group 2. Median follow-up for the two groups were similar at 55 months (SD 29.2 months) in the first group and 52 months (SD 24.43) in the second group. Characteristics of the two groups of patients were shown in Table 1. More than 60% of the patients were of Chinese ethnicity. Similarly for both groups about 17% of patients were diagnosed below the age of 40 years. The median age for group 1993-97 was 49 years (range, 25 to 90 years) and for 1998-2002 was also 49 (range, 21-92 years). Majority (~49%) of the patients in both groups were Stage II and about 30% were stage III and IV in both groups. Although there was an increase in proportion of ≤ 2cm tumours in

Table 1. Clinico-pathological Characteristics of the Study Subjects by Period of Diagnosis

		Group 1 1993-1997		Group 2 1998-2002		Chi-square (p)
Ethnic group	Chinese	264	62.4	611	63.3	0.45
	Indian	69	26.4	120	12.4	
	Malay	90	34.1	234	24.3	
Age Median (range)		49(25-90)		49 (21-92)		
	≤ 40	72	17.0	170	17.6	0.58
	41-59	253	59.8	603	62.5	
	≥ 60	98	23.2	192	19.9	
Stage at diagnosis	Stage 1	73	17.3	207	21.5	0.76
	Stage 2	206	48.7	471	48.8	
	Stage 3	74	17.5	171	17.7	
	Stage 4	70	16.6	116	12.0	
Tumour	Mean(SD)	4.47(3.32)		4.35(3.8)		
	≤ 2	49	11.6	285	28.8	0.92
	>2 - 5	207	49.0	429	43.3	
	>5	167	39.5	251	25.3	
Lymph node status	0	165	39.0	395	40.9	0.93
	1-3	97	22.9	207	21.5	
	≥ 4	75	17.7	167	17.3	
	NA	86	20.3	196	20.3	
Grade	1 and 2	161	38.1	440	45.6	0.91
	3	77	18.2	245	25.5	
	NA	185	43.7	280	29.0	
Estrogen receptor	Positive	69	16.3	467	48.4	0.67
	Neg	80	18.9	351	36.4	
	NA	274	64.8	147	15.2	

Data are No and %; NA, Not Available

Table 2. Five-year Survival Probabilities By Various Clinico-Pathological Variables

Co-variate		1993-1997 SP	95% CI	1998-2002 SP	95% CI	p-value
Ethnic	Chinese	0.63	(0.58, 0.70)	0.81	(0.78, 0.85)	<0.01
group	Indian	0.57	(0.46, 0.70)	0.80	(0.74, 0.88)	<0.01
	Malay	0.46	(0.37, 0.58)	0.58	(0.52, 0.66)	<0.01
Age	≤ 40	0.59	(0.49, 0.70)	0.67	(0.60, 0.75)	0.27*
at	41-59	0.56	(0.50, 0.63)	0.76	(0.73, 0.80)	<0.01
diagnosis	≥ 60	0.65	(0.56, 0.75)	0.84	(0.79,-0.90)	<0.01
Stage	1	0.82	(0.73, 0.91)	0.95	(0.92, 0.99)	<0.01
at	2	0.72	(0.67, 0.79)	0.88	(0.84, 0.91)	<0.01
diagnosis	3	0.40	(0.30, 0.53)	0.56	(0.48, 0.64)	0.02
	4	0.13	(0.07, 0.24)	0.19	(0.12, 0.28)	0.80*
Tumour	≤ 2	0.80	(0.69, 0.92)	0.94	(0.79, 0.86)	<0.01
Size	>2 – 5	0.77	(0.71, 0.83)	0.82	(0.79, 0.86)	0.11*
(cm)	>5	0.30	(0.23, 0.38)	0.44	(0.37, 0.51)	<0.01
Lymph	0	0.79	(0.73, 0.85)	0.94	(0.91, 0.97)	<0.01
node	1-3	0.64	(0.55, 0.74)	0.82	(0.77, 0.88)	<0.01
status	≥ 4	0.46	(0.36 , 0.60)	0.63	(0.55, 0.71)	<0.01
	NA	0.23	(0.16, 0.34)	0.41	(0.34, 0.49)	<0.01
Grade	1- 2	0.73	(0.66, 0.81)	0.88	(0.85, 0.91)	<0.01
	3	0.55	(0.45, 0.68)	0.71	(0.65, 0.77)	<0.32*
	NA	0.47	(0.41, 0.55)	0.60	(0.54, 0.67)	<0.51*
Estrogen	Pos	0.62	(0.51, 0.76)	0.86	(0.83 , 0.90)	<0.01
receptor	Neg	0.51	(0.40, 0.64)	0.73	(0.68, 0.78)	<0.01
	NA	0.59	(0.54, 0.66)	0.49	(0.41, 0.58)	0.03

SP, 5-year survival probability; *Peto Wilcoxon Test

Table 3. Best Fitted Multivariate Models in Group 1 (n= 423) and 2 (n= 965) based on Cox Regression

Characteristic	1993-1997 HR	95% CI		1998-2002 HR	95% CI	p-value
Stage 1	1.00			1.00		
Stage 2	1.33	(0.70, 2.51)	0.38	1.81	(0.85,3.84)	<0.01
Stage 3	2.09	(1.00, 4.38)	0.05	5.08	(2.36,11.0)	<0.01
Stage 4	4.49	(2.16, 9.35)	<0.01	13.7	(6.26,29.8)	<0.01
LN 0	1.00			1.00		
LN 1-3	1.21	(0.76, 1.92)	0.42	5.36	(3.06,9.39)	<0.01
LN ≥4	1.64	(1.02, 2.65)	0.04	2.10	(1.21,3.67)	<0.01
NA	2.30	(1.42, 3.72)	<0.01	3.26	(1.91,5.58)	<0.01
≤ 2cm	1.00					
2-5cm	1.05	(0.53, 2.08)	0.88	-*	-*	-
≥5 cm	1.89	(0.92, 3.89)	0.08			
Grade 1-2	1.00					
Grade 3	1.84	(1.19, 2.85)	0.01	-*	-*	-
NA	1.28	(0.87, 1.87)	0.21			
ER positive				1.00		
ER negative	-*	-*	-	2.01	(1.46,2.77)	<0.01
NA				1.16	(0.78,1.73)	0.05
Chinese				1.00		
Indian	-*	-*	-	1.11	(0.72,1.71)	0.07
Malay				1.47	(1.11,1.94)	<0.01
Age	-*	-*	-	-*	-*	-

*Not identified as important factors; ** Interaction terms were not significant in all important factors

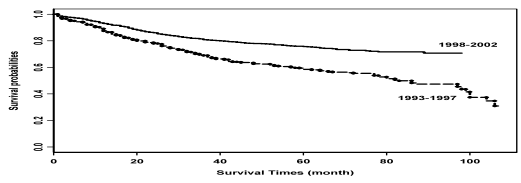

Figure 1. Five-Year Survival Probabilities for Patients diagnosed in 1993-97(n=423) and 1998-2002 (n=965)

the second group from 11.6% to 28.8%, the difference was not statistically significant (p=0.58). Axillary lymph node involvement was similar in both groups with 40.6% in the first group and 38.8% in the second group, data was not available for 20.3% in both groups where in Stage IV cancers, surgical axillary clearance was not performed. Grade was not available for 43.7% of cases in group 1 and only 29.0% in group 2. Similarly 64.8% of ER status was not reported in group one and only 15.2% were not reported in group two.

Table 2 illustrates the 5-year survival probabilities for each variable, and hypothesis testing results comparing the survival probabilities of both time periods. Although there were no statistical significant difference in the proportion of stage at presentation, age at diagnosis, tumour size, lymph node involvement, grade and ER status between the two groups as tabulated in Table 1, there was improvement in observed overall 5-year survival from 58.4% (CI 0.54-0.63) to 75.7% (CI 0.73-0.79) as given in Figure 1. The improvement in survival was significantly seen in all co-variates (p<0.05) except for those aged 40 years and below (p= 0.27), tumour size 2 to 5 cm (p=0.08), patients with Stage IV disease (p= 0.80) and Grade 3 (p= 0.32). The improvement in 5-year survival could be seen in all stages; stage I improved from 81.7% to 95.2%, stage II from 72.4% to 87.5%, stage III 39.9% to 55.6%. Although Stage IV improved from 12.8% to 18.7% (p=0.43) it was not statistically significant. Improvement in 5-year survival was statistically significant in all ethnicities; Chinese ethnicity was 63% to 81.4%, Indian ethnicity was 57% to 80.4%, and Malay ethnicity was 46% to 58.3%. Young women (≤ 40 years) was 59% to 66.9% but was not statistically significant. Women 60 years and above had statistically improved survival from 65% to 84%. Survival also improved for those categorised by lymph node involvement. The 5 year survival improved from 78.8% to 94% for node negative patients; for 1-3 involved nodes, from 63.7% to 82.4%; and those with 4 or more lymph node involvement was from 46.2% to 62.6%. Those with unavailable lymph node status, were those who did not undergo axillary dissection. Their 5-year survival also improved from 23.2% to 40.9%. Due to the large numbers of unavailable information, improvement in survival in relation to ER status and Grade of tumour was impossible to interpret.

Table 3 illustrates the results of the multivariate models for observed survival for group 1 and group 2 that were done separately. By employing the forward selection procedure, we obtained the 'best' fitted multivariate model for group 1 where: stage of disease, lymph node involvement, size and grade were identified as important prognostic factors. For group 2; stage and lymph node involvement were still independent factors with the addition of ER status and ethnicity. The interaction terms between the identified important variables for both groups were not significant. Size of tumour and grade was found to be an independent factor in the first but not the second group. Estrogen receptor status was an independent factor in the second group but not in the first group. It was found that 64.8% of cases in group 1 did not have an ER status. This may have confounded the findings of ER as

a prognostic factor in the first group. In the second group those with ER negative tumours had two times the hazards of mortality compared to ER positive cases. Only in the second group was ethnicity an independent prognostic factor with Malay patients having 1.5 times risk of death compared to Chinese women($p<0.01$).

Compared to Stage I, Stage IV patients had 4.5 times risk of death in the first group as compared to 13.7 times in the second group. Stage III patients had twice risk of death compared to Stage 1 in group 1 compared to 5 times risk of mortality in group 2. In the first group those with four or more involved nodes had 1.6 times hazards of mortality compared to a node negative (pN0) patient. In the second group, this group had 3.3 times risk compared to pN0 group. Age was found not to be an independent prognostic factor in both time periods.

Discussion

There is a global trend of reduced mortality in the developed world, and an expected increase in mortality in developing countries (Bray et al., 2004). This study is the only one in Malaysia to show an improvement in survival of breast cancer patients.

It was unexpected that improvement of survival was seen in this institution based upon the proportion of stage at presentation. This study showed that the two groups were similar by proportions of stage, age, ethnicity, tumour size, lymph node status, grade and ER status (Table 1). The median follow-up for both groups were similar and exceeded 52 months, thus enabling comparison of short term survival in both groups. The vital status of all the patients in the dataset was accurate due to the mandatory reporting of deaths in Malaysia. This study was not designed to obtain information from the last follow-up of the patient, thus disease free survival and breast cancer specific mortality were not sought.

Although this study did not include treatment data, there was indirect information with regards to improved oncology services. Availability of trained clinical oncologists, in-house radiotherapy and daycare chemotherapy services that began in 1998 and 1999 respectively may have contributed to the improvement in survival. Along with that, incorporation of anthracycline based chemotherapy in 1998 may have contributed to the improved survival. Anthracycline based chemotherapy had been shown to increase breast cancer survival (Levine et al., 2001).

The 5-year relative survival for women younger than 75 years with breast carcinoma was 43-63% in developing countries, the survival differences were due to both late stage at presentation and the availability and quality of adjuvant treatment (Sankaranarayanan et al., 1996). There was disparity in survival in different regions in the world, even between developed nations. The Surveillance Epidemiology and End Results (SEER) 5-year survival rates in United States for 1990 was 89% and in the European series (EUROCARE) 79%. The differences had been attributed to the later stage of diagnosis in elderly women in Europe as compared to those in the United States (Sant et al., 2004).

Although there was scarcity in stage specific survival information for both time periods in the literature, the first group in this study had lower survival within this era compared to those in Europe (Sant et al., 2003) and South East Asia (Lim et al.,2001), but were similar to those in Saudi Arabia (El-Saghir et al.,2006). The second group in this study had similar survival rates to Singapore, the 5 year survival were 97%, 83%, 56% and 17% for stage I, II, III and IV respectively (Lim et al., 2001). In Korea, a higher survival of more advanced disease where stage III and IV had survival of 65% and 29.3% respectively were reported (Son et al., 2006) compared to this study and the Singapore study.

Identified subgroups that had no improved survival from this study were Malay ethnicity, 40 years and younger, grade 3 and stage IV disease. Further studies are needed urgently to identify the underlying factors that brought about the survival disparity in these subgroups. Future directions in research would be differences in biology of the tumour, host response to the tumour, pharmacogenomic issues, socioeconomic issues and access and adherence to treatment. Although there was a high incidence of breast cancer in Chinese ethnicity which was also seen in the Malaysian National Cancer Registry (Lim et al., 2008), this group had better survival compared to the other ethnic groups. In this study the Malays in both groups presented with more advanced disease compared to the Chinese and Indians. Studies in other centres in Malaysia also confirm the late pattern of presentation in Malay women and other non-Chinese ethnic groups (Leong et al., 2007);(Leong et al., 2009). Strategic planning in overcoming associated problems like late stage at diagnosis, non-adherence to treatment and prescription of more efficacious agents and finding financial resources to treat these groups of patients will be important in finding solutions.

Studies have shown improvement in survival of stage IV breast cancer are due to the availability of multiple active drugs in breast cancer (O'Shaughnessy, 2005). Anthracycline containing regiments are freely available to patients in Malaysia. However, Taxanes, other chemotherapeutic agents and targeted therapies were mostly out of pocket expenditure for most of the population except for those with insurance and employment coverage. The unavailability of polychemotherapy for those with stage IV disease due to financial reasons as well as availability of more active agents in the era of the studied population may be factors that contributed to the lack of improved survival in stage IV breast cancer. The effect of surviving Stage IV breast cancer in Malaysia remains to be seen in the future with the availability of more active agents like the Taxanes and targeted therapies.

There was no statistical significant improvement in survival for Grade 3 tumour in the two time periods. Studies do show that Grade was an important prognostic factor (Bloom & Richardson, 1957);(Elson CW &, Ellis IO,1991);(O'Reilly et al.,1990). Although grade was found to be an independent prognostic factor in group 1, the numbers of unavailable data would caution further interpretation. This was also seen in group 2.

In this study, improvement in survival did not occur

in women 40 years and younger but age was not an independent prognostic factor with multivariate analysis. This was similar in other studies (Paluch-Shimon et al., 2010). However, some studies did show that breast cancer was more aggressive in younger women (Aryandono et al., 2006);(El Saghir, 2006);(Kim et. al, 2007).

In conclusion, there has been significant improvement in observed breast cancer survival in this institution even without improvement of stage at diagnosis. However young age (40 years and less), tumour size 2-5 cm, grade 3 and metastatic disease did not have improved outcomes. Traditional markers of poor prognosis like stage, lymph node status and ER status were confirmed amongst Malaysian patients. Other unique negative independent prognostic factors that was found was the Malay ethnicity. These findings need to be confirmed in other centres in Malaysia and future studies on tumour biology, pharmacogenomics, access to care, treatment adherence, health economics and psychosocial aspects should be carried out to guide cancer control strategies in Malaysia.

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