RESEARCH COMMUNICATION

Prognostic Factors for Elderly Breast Cancer Patients in University Malaya Medical Centre, Malaysia

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Abstract

Background: Information about elderly breast cancer patients' outcome is limited. This study aimed to evaluate the treatment outcomes in women aged 70 and above with specific analysis on prognostic clinicopathological features and treatment modalities. Materials and Methods: This retrospective study examined breast cancer patients between 1st January 1994 and 31st December 2004 in UMMC. Survival analysis was performed using the Kaplan-Meier method and comparisons between groups using the log-rank test. Univariate and multivariate analysis on prognostic factors were carried out using the Cox's proportionate hazard model for patient demographics, and tumour and treatment factors. Results: One hundred and thirty six patients were identified, with a median age at diagnosis of 75 years. Most had at least one co-morbidity (61.8%). Only 75.0% had a good performance status (ECOG 0-1). Mean tumour size was 4.4cm. Primary tumour stages (T stages) 3 and 4 were present in 8.1% and 30.1% of patients respectively, and 30.9% had stage III and 8.8% had stage IV disease based on overall AJCC staging. ER positivity was 58.1%. PR status was positive in 30.1%. Surgery was performed in 69.1% of the patients and mastectomy and axillary clearance were the commonest surgical procedures (50.7%). Some 79.4% of patients received hormonal therapy, 30.1% radiotherapy and only 3.6% chemotherapy. Non-standard treatment was given to 39.0% of patients due to a variety of reasons. The cumulative 5 years overall, relapse free and cause specific survivals were 51.9%, 79.7% and 73.3% respectively. Performance status, T3-4 tumour, presence of metastasis, tumour grade and ER status were independent prognostic factors for overall survival. For cause specific survival they were T4 tumour, presence of metastasis and ER status. Conclusion: The 5 years overall survival rate was 51.9% and 41.8% of deaths were non-breast cancer related deaths. Low survival rate was related to low life expectancy in this population. Locally advanced disease, metastatic disease and high ER negative rates play a major role in the survival of elderly breast cancer patients in Malaysia.

Keywords: Elderly patients - breast cancer - survival

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Introduction

Breast cancer is one of the most commonly diagnosed cancers in women in Malaysia. Female breast cancer accounted for 29.9% of all cancer incidences in Peninsular Malaysia in 2006. Elderly patients aged 70 & above had an incidence of 85.5 per 100,000 population (Malaysian Cancer Statistics, 2006). Knowledge on clinicopathological features, treatment and outcome in the elderly remains limited compared to their younger counterparts despite increasing incidence of breast cancer in this population. The relative under enrolment of elderly patients in clinical trials is an important factor contributing to this lack of knowledge. For example, a study of participants enrolled in 164 SWOG trials in the United States found that people aged 65 years and over were under-represented in cancer clinical trials. This was especially apparent in breast cancer trials; despite 49% of women with breast cancer being aged 65 years or over, only 9% of women enrolled in breast cancer trials were 65 years or older (Hutchins et al., 1999).

Clinicians are often wary of aggressive treatment in older patients due to perceived presence of increasing co-morbidities with age, worsening performance status, lower tolerability to these treatments due to decrease response of immune defense system and often times' patient refusal due to their own beliefs and values. These assumptions might lead to the policy of treating the elderly with a less intensive treatment schedule. This policy is often reinforced by the fatalistic attitude that these patients are at high risk of dying from diseases other than breast cancer before they can benefit from a possibly longer disease free survival (Bergman et al., 1991). This inadvertently lead to reluctance of clinicians to enroll elderly patients into clinical trials leading to no clear consensus about the most appropriate treatment approach for elderly breast cancer patients.

There are numerous study reports describing the

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clinico-pathological features in developing countries; however reports on outcome of treatment remain rare especially so with regards to elderly patients (Fakhro et al., 1999; Maalej et al., 1999; Ipkatt et al., 2002; Malik, 2002).The paucity of treatment outcome data for elderly breast cancer patients makes it even more important for more studies to focus on this group of patients. This study aims to evaluate the treatment outcomes of breast cancer in elderly women aged 70 and above with specific analysis on the prognostication of clinico-pathological features and treatment modalities.

Materials and Methods

All women treated for breast cancer aged 70 and above at UMMC between 1st January 1994 and 31st December 2004 were identified. These included patients who presented at any stage of the disease and whether the patients were treated with curative or palliative intent. Those excluded were due to missing case notes. A total of one hundred and thirty six patients were identified for analysis. Patients lost to follow up were contacted to determine their current status. Those not contactable were censored at the last date of follow up.

Relapse free survival was defined as the time interval from the date of diagnosis to the date of relapse. Patients who did not relapse were censored at the end of the study period. This endpoint included only patients who were treated with a curative intent.

Progression free survival was defined as the time interval from the date of diagnosis to the date of disease progression. This endpoint included patients who were treated with a palliative intent and patients with stage IV disease.

Overall survival was defined as the time interval from the date of diagnosis to the date of death from any cause. Patients who were alive were censored at the end of the study period. Cause specific survival was defined as the time interval from the date of diagnosis to the date of death from breast cancer. Patients who died from other causes and not breast cancer were censored at the time of death.

For early stage operable breast cancer, the standard treatment at UMMC at the time of the study period included mastectomy and axillary clearance or wide local excision and axillary clearance. No axillary surgery was required for carcinoma in situ. Chemotherapy was not indicated as adjuvant treatment as a routine practise in this group of patients. However, patients felt to be at high risk of recurrence provided they had no significant co-morbidity and good performance status could be treated with adjuvant chemotherapy. Indications for adjuvant radiotherapy included patients who underwent BCS (breast conserving surgery) and high risk post-mastectomy patients with tumour size 5 cm or more, tumour with 4 or more metastatic lymph nodes or positive surgical margins. Adjuvant hormonal therapy was indicated for patients with ER or PR positive tumours or unknown ER status.

Patients with locally advanced disease could undergo neoadjuvant chemotherapy or hormonal therapy to be followed by surgery. Surgery was not indicated in the presence of extensive local disease or metastatic disease. Palliative chemotherapy, hormone therapy or radiotherapy was given in the metastatic setting.

Statistical analysis was performed using the SPSS version 15.0 software. Survival probabilities were estimated using the Kaplan-Meier method and differences in survival compared using the log-rank test. Important prognostic factors were identified by multivariate analysis using the Cox proportional hazard model.

Results

Clinicopathological and Treatment characteristics

Between 1st January 1994 and 31st December 2004, 150 patients with breast cancer aged 70 and above were treated at UMMC. Case notes for these patients were available for 136 patients giving a retrieval rate of 91%. Clinicopathological characteristics of the 136 patients are listed in (Table 1).

Treatment received by these patients and whether they received standard or non-standard treatment with the attending reasons are listed in (Table 2).

Relapse Free Survival and Prognostic Factors

Analysis for relapse free survival was done for the 92 patients who were treated with a curative intent. Eighteen patients (19.6%) had recurrent disease after a median follow-up of 46.5 months. The overall 5 years relapse free survival was 79.7%. The cumulative 5 years relapse free survival rates for stage 0, I, II and III were 100%, 84.9%, 89.4% and 58.4% respectively (Figure 1).

In univariate analysis, performance status, primary tumour stage(T stage), nodal status, ER status, and treatment received (standard versus non-standard) were significant prognostic factors for relapse free survival. Parameters which had independent prognostic significance on multivariate Cox's regression analysis were T4 tumour (p=0.013), ER positivity (p=0.014) and unknown LVI status (p=0.012) (Table 3).

Progression Free Survival

The remaining 44 patients who were not analyzed for relapse free survival included 12 patients with metastatic disease and 32 patients with no metastatic disease who were treated with a palliative intent due to a variety of reasons discussed earlier. These patients were analyzed separately for progression free survival. The overall median progression free survival was 28 months with the non-metastatic group 36 months while the metastatic group 5 months (Figure 2).

Overall Survival and Prognostic Factors

The 5 years overall survival was 51.9%. There were 55 deaths with a median follow-up of 42.5 months. There were 32 deaths (58.2%) attributable to breast cancer. Twenty-three deaths (41.8%) were due to other causes. Other causes of death included heart failure (5 patients), old age (5 patients), acute myocardial infarction (4 patients), cerebrovascular accident (2 patients), renal failure (2 patients), dementia (1 patient), hypertension (1 patient), liver failure (1 patient), septicaemia (1 patient) and multiple myeloma (1 patient). The 5 years cumulative

Table 1. Characteristics of Patients and Tumours

	N =136 (%)
Age Range	
70-74	66 (48.6)
75-79	41 (30.1)
80 and above	29 (21.3)
Ethnic Group	
Malay	81 (59.6)
Chinese	28 (20.6)
Indian	23 (16.9)
Others	4 (2.9)
ECOG Performance	
0-1	102 (75.0)
2	21 (15.4)
3	13 (9.6)
No of Co-morbidity	
0	52 (38.2)
1-2	62 (45.6)
3 or more	22 (16.2)
Primary Tumour Stage	
Tis (carcinoma in situ)	5 (3.7)
1 (2.0cm or less)	30 (22.1)
2 (2.1cm-5.0cm)	49 (36.0)
3 (5.1cm and above)	11 (8.1)
4 (any size)	41 (30.1)
Nodal Status	
Negative	52 (38.2)
Positive	34 (25.0)
Unknown	50 (36.8)
Positive Nodes	
1-3	19 (55.9)
4-9	11 (32.4)
10 or more	4 (11.7)
Presence of Metastasis	
No	124 (91.1)
Yes	12 (8.9)
Overall AJCC Stage	
0	5 (3.6)
I	22 (16.2)
II	55 (40.4)
III	42 (30.9)
IV	12 (8.9)
Histological Type	
Ductal	113 (83.1)
Lobular	6 (4.4)
Others	17 (12.5)
Tumour Grade	
1	21 (15.4)
2	47 (34.6)
3	26 (19.1)
Unknown	42 (30.9)
ER Status	
Negative	35 (25.7)
Positive	79 (58.1)
Unknown	22 (16.2)
PR Status	
Negative	29 (21.3)
Positive	41 (30.1)
Unknown	66 (48.6)
Her-2 Status	
Negative	43 (31.6)
Positive	23 (16.9)
Unknown	70 (51.5)
LVI Status	
Negative	38 (27.9)
Positive	20 (14.7)
Unknown	78 (57.4)

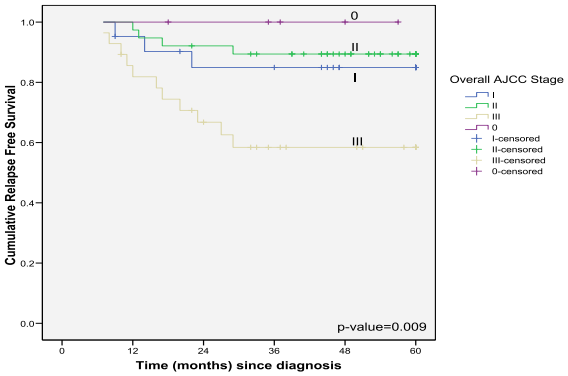

Figure 1. Kaplan-Meier Estimates of Relapse Free Survival According to overall AJCC Stage

overall survival for stages 0, I, II, III, IV were 66.7%, 78.9%, 63.3%, 34.8% and 0% respectively (Figure 3). The median overall survival for stage IV disease was 7 months.

In univariate analysis, age group, performance status, primary tumour stage, nodal status, presence of metastasis, overall AJCC stage, tumour grade, ER status, HER-2 status, LVI status and treatment received (standard versus non-standard) were significant prognostic factors for overall survival. Parameters which retained independent prognostic significance on Cox's multivariate analysis were performance status, primary tumour stage, presence of metastasis, tumour grade and ER status (Table 4).

Cause Specific Survival and Prognostic Factors

The 5 years cause specific survival for this group of 136 patients was 73.3%. There were 32 events at the end of the study period. The 5 years cumulative cause specific survival according to AJCC stage 0, I, II, III and IV were 100%, 90.2%, 92.0%, 53.2% and 0% respectively (Figure 4). The median cause specific survival for stage IV disease was 7 months.

Table 2. Treatment Characteristics

Therapy	No=136 (%)
Surgery	
Nil	42 (30.9)
Mastectomy alone	3 (2.2)
Mastectomy & AC	69 (50.7)
WLE	8 (5.9)
WLE & AC	14 (10.3)
Adjuvant Radiotherapy	
Yes	41 (30.1)
No	95 (69.9)
Neoadjuvant/Adjuvant Chemotherapy	
Yes	5 (3.6)
No	131 (96.4)
Adjuvant Hormonal Therapy	
Yes	108 (79.4)
No	28 (20.6)
Treatment Received	
Standard	83 (61.0)
Non-Standard	53 (39.0)
Reasons for Non-Standard Treatment	Total=53
Patient refusal	17 (32.0)
Patient defaulted	5 (9.5)
Poor performance status	14 (26.4)
Co-morbidities	5 (9.5)
Not Stated	12 (22.6)

Table 3. Cox's Multivariate Analysis of Prognostic Factors for Relapse Free Survival

Variable	Number Of Patients	Hazard Ratio	95% Confidence Interval	P-value
Primary Tumour Stage				
1	29	1.0	-	-
2	35	0.86	0.17-3.72	0.774
3	6	3.13	0.46-21.38	0.245
4	17	6.51	1.49-17.72	0.013*
Tis	5	NR	NR	0.983
ER Status				
Negative	31	1.0	-	-
Positive	54	0.21	0.06-0.73	0.014*
Unknown	7	0.29	0.06-1.11	0.068
LVI Status				
Negative	36	1.0	-	-
Positive	18	1.22	0.27-5.55	0.797
Unknown	38	5.03	1.43-17.72	0.012*

Note: The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared; against, * p-value < 0.05, NR: not relevant

Table 4. Cox's Multivariate Analysis of Prognostic Factors for overall Survival

Variable	Number Of Patients	Hazard Ratio	95% Confidence Interval	P-value
Performance Status				
0-1	102	1.0	-	-
2	21	2.19	1.05-4.55	0.036*
3	13	3.53	1.51-8.24	0.004*
Tumour Stage				
1	30	1.0	-	-
2	49	0.91	0.37-2.70	0.864
3	11	4.24	1.15-15.60	0.030*
4	41	3.45	1.19-10.04	0.023*
Tis	5	0.90	0.09-8.89	0.931
Presence of Metastasis				
No	124	1.0	-	-
Yes	12	3.87	1.70-8.81	0.001*
Tumour Grade				
1	21	1.0	-	-
2	47	4.70	1.04-21.17	0.044*
3	26	3.95	0.86-18.23	0.078
Unknown	42	5.67	1.14-28.27	0.034*
ER Status				
Negative	35	1.0	-	-
Positive	79	0.41	0.19-0.90	0.026*
Unknown	22	0.48	0.18-1.28	0.143

Note: The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared against, * p-value < 0.05.

Table 5. Cox's Multivariate Analysis of Prognostic Factors for Cause Specific Survival

Variable	Number Of Patients	Hazard Ratio	95% Confidenc Interval	P-value
Primary Tumour Stage				
1	30	1.0	-	-
2	49	0.71	0.12-4.31	0.711
3	11	4.29	0.75-24.44	0.101
4	41	6.95	1.57-30.78	0.011*
Tis	5	NR	NR	0.983
Presence of Metastasis				
No	124	1.0	-	-
Yes	12	7.62	3.03-19.16	0.000*
ER Status				
Negative	35	1.0	-	-
Positive	79	0.25	0.10-0.63	0.003*
Unknown	22	0.50	0.19-1.35	0.174

Note: The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared; against, * p-value < 0.05, NR: not relevant

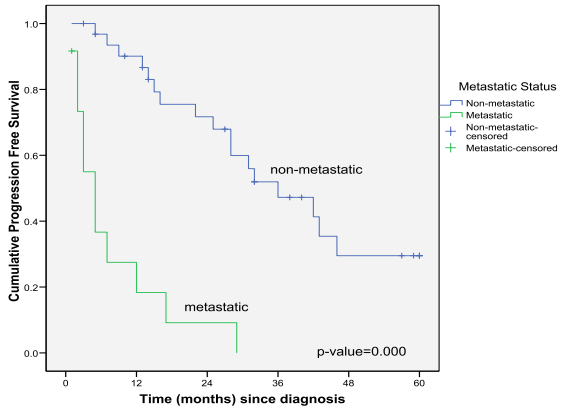

Figure 2. Kaplan-Meier Estimates of Progression Free Survival according to Presence of Metastatic Disease

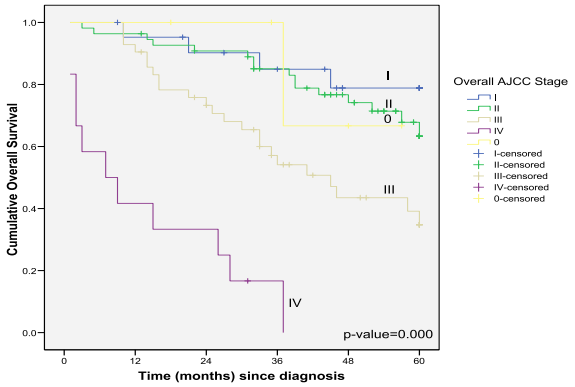

Figure 3. Kaplan-Meier Estimates of overall Survival according to overall AJCC Stage

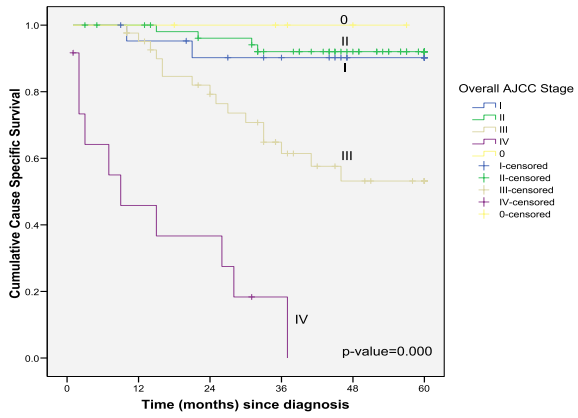

Figure 4. Kaplan-Meier Estimates of Cause Specific Survival according to overall AJCC Stage

In univariate analysis, age group, performance status, tumour stage, nodal status, presence of metastasis, overall AJCC stage, tumour grade, ER status, HER-2 status and LVI status were significant prognostic factors for cause specific survival. Parameters which retained independent prognostic significance on Cox's multivariate analysis were primary tumour stage, presence of metastasis and ER status (Table 5).

Discussion

The growing number of elderly breast cancer patients accentuates the need for more definite data relevant to the management of breast cancer in the elderly. Scarcity of this information in the literature especially in developing countries, where patient characteristics, tumour characteristics, treatment employed and treatment outcome may be different from those of developed countries present an urgent challenge for clinicians to embark on clinical research on elderly breast cancer patients.

The main finding of this series shows the 5 years overall survival rate was 51.9%. This figure is relatively low when compared to the rates quoted for elderly breast cancer patients in western countries, which ranged from 58% to 83% (Vercelli et al., 2006; National Cancer Statistics Clearing House and the National Death Index, AIHW, Australia). Independent prognostic factors for overall survival on multivariate analysis for patients in this series were performance status, primary tumour stage, presence of metastasis, tumour grade and ER status. This relatively low survival rate is partly due to a significant proportion of our patients presenting with advanced disease, with 38.2% of patients in this series presenting with T3 or T4 disease. T3 stage was associated with a hazard ratio of 4.24 (p value=0.030) while T4 stage was associated with a hazard ratio of 3.45 (p value=0.023) when compared to T1 stage as the reference group. In a French retrospective study involving 1755 elderly breast cancer patients over 70 years of age, only 24% of patients had T3 or T4 disease (Pierga et al., 2004).

Based on overall AJCC staging, 39.8% of patients in this series presented with advanced disease, with 30.9% having AJCC stage III disease and 8.9% having AJCC stage IV disease. Important factors such as awareness, socioeconomic status and access to medical care are closely linked to advanced stage of presentation (Chu et al., 2003). Traditional remedies/treatment is an important facet of life in this part of the world that cannot be taken lightly by clinicians because patients often opt for this approach first and after failure of this form of treatment only do they present to the clinicians. This problem is compounded by the widespread belief that cancer-related treatment is fraught with complications especially so with elderly patients.

Karnofsky performance scale and ECOG performance status have been shown to be an independent predictor of survival in oncology patients (Albain et al., 1991; Ishii et al., 1996; Bajorin et al., 1999; Motzer et al., 2004). Performance status was indeed found to be highly significant as an independent prognostic factor on multivariate analysis in predicting overall survival in this series. ECOG performance status 2 was associated with a hazard ratio of 2.19 (p-value=0.036) while performance status 3 was associated with a hazard ratio of 3.53 (p-value=0.004) when compared to performance status 0-1 as the reference group. In this series a high percentage of patients (25%) presented with poor performance status (2 or above) which could be another factor leading to the low overall survival rate.

With regards to tumour biology, this series found that grade was an independent prognostic factor for overall survival on multivariate analysis. Grade 2 disease had 4.70(95% CI 1.04-21.17) times hazard of mortality compared to grade 1 while unknown grade had a hazard

ratio of 5.67 (95% CI 1.14-28.27). Interestingly, only 15.4% of patients in this series had grade 1 disease which could be a factor contributing to the low overall survival rate. The French retrospective study discussed earlier, showed 25% of their patients presented with grade 1 disease (Pierga et al., 2004). It remains to be seen if our elderly patients do indeed present with higher grade disease as a large proportion of patients (30.9%) in this series had unknown tumour grade, which was related to patients who did not have histopathological grade assessment as they did not receive any surgical intervention and was diagnosed on fine needle aspiration cytology.

ER status was also found to be a significant prognostic factor in this series on multivariate analysis. Positive ER status was associated with a hazard ratio of 0.41 (p-value=0.026) while the hazard ratio for unknown ER status was 0.48 though this was statistically not significant (p value=0.143). Only 58.1% of patients in this series had positive ER status which is slightly low for elderly patients. A large case series performed in Italy involving more than three thousand elderly breast cancer patients showed ER positivity in 81% of patients aged 65-74 years, 82% of patients aged 75-84 years and 83% of patients aged above 84 years (Daidone et al., 2003). Similarly, the large French retrospective study referred to above showed 78.5% of their elderly patients above 70 years of age had ER positive tumours (Pierga et al., 2004). However, this series had 16.2% of patients with unknown ER status making it difficult to draw a firm conclusion as to whether the lower rate of ER positivity seen here had a contributory effect on the low overall survival rate.

Treatment modality is another possible determinant of survival outcome. As many as 39% of patients in this series did not receive standard treatment, mostly with regards to surgery and radiotherapy. However, when non-standard treatment was compared to standard treatment, it was found to have no influence on overall survival or cause specific survival on multivariate analysis. As many of the elderly patients (41.8%) in this series who died, died of other competing causes other than breast cancer, treatment (standard vs. non-standard) might only have a marginal effect on overall survival and thus require more events and larger number of patients to assess its prognostic importance.

Life expectancy is another possible factor that might contribute to the lower overall survival seen in this series especially so as 41.8% of deaths in this series were of other causes other than breast cancer deaths. A shorter life expectancy in Malaysia compared to those of developed countries could account partly for the survival difference. A recent estimate of life expectancy at birth for a Malaysian female is 76.7 years compared to 81.6 years for United Kingdom, 83.6 for Australia and 84.2 for Switzerland (United Nations World Population Prospects, 2006). Life expectancy in turn is closely related to lifestyle risk factors, environmental factors, human biology and medical care (Hinkle and Loring, 1977). Further improvement of overall survival for elderly breast cancer in our setting needs to take into account not just the cancer specific aspect of treatment but also the public health initiatives that can enhance the health of our society and ultimately improve our population's life expectancy.

The overall 5 years cause specific survival was 73.3% while the 5 years cause specific survival according to AJCC stage was 100%, 90.2%, 92.0%, 53.2% and 0% for stage 0, I, II, III and IV respectively. Significant independent predictors of cause specific survival on multivariate analysis included only tumour characteristics namely primary tumour stage, presence of metastasis and ER status. The cause specific survival especially for early stage disease is highly respectable. This does lend credence to the fact that the main area of focus should be concentrated on steps that can be taken to ensure more patients present in earlier stages of the disease when it is highly treatable.

The results of this series also show the over-riding importance of reporting on overall survival which relies on all cause mortality compared to cause specific survival which relies only on breast cancer mortality in elderly patients. The significant disparity between these endpoints is well illustrated here with a 5 years overall survival of 51.9% compared to a 5 years cause specific survival of 73.3%. We would not expect a difference this large in the younger patients because the likelihood of dying of other causes of death is much lower and if they do die they are more likely to die of breast cancer itself. As such the overall survival in younger patients often closely mirrors that of the cause specific survival. However, there can be a significant difference in the elderly patients as they often die of other causes and in this series 41.8% of deaths were due to non-breast cancer deaths. This is of great importance especially when considering the usage of any new treatment for elderly breast cancer patients when the available evidence for these treatment stems from clinical trials involving only younger patients often with a cut-off point of below 70 years of age. Extrapolation from these data involving younger patients to the elderly patients might not lead to the same survival benefit seen in the younger patients as these new treatment will have no effect on other conditions that the elderly patients might succumb to and in some situations might actually be detrimental as the elderly patients are often more susceptible to negative effects of treatment. Ideally high quality clinical trials involving elderly patients should be conducted for any new forms of treatment if these treatments were to be used as standard practice for the elderly patients.

Regarding limitations, this study is retrospective in nature and thus subjected to biases inherent to studies of this kind. Nevertheless, the results of this study reflect the status of breast cancer presentation, management and outcome in the elderly in a middle income developing nation.

The 5 years overall survival rate of 51.9% and cause specific survival rate of 73.3% serve as a template for future prospective studies on elderly breast cancer patients. Important areas to address to improve the overall survival rate in elderly breast cancer patients in this population include: Initiatives to raise breast cancer awareness and educating the public regarding treatability of this disease especially in its early stages can help assuage the fatalistic attitude towards this disease especially when the inflicted

individual is an elderly.

Further research on the social and cultural influences on late presentation in our setting is another area that can help determine the necessary actions to be taken to ensure more patients present in earlier stages. The other important aspect to consider is the complex issue concerning the general health of the elderly population which has a significant bearing on the overall survival of cancer patients, as shown in this study where 41.8% of deaths were of non-breast cancer deaths.

Public health initiatives that can be taken to improve the general health of our population will eventually lead to further improvement of this country's life expectancy thus also impacting on the survival rate of elderly breast cancer patients. As the elderly rapidly grow to form a significant proportion of patient demographics in Asia, more effort and emphasis on them have to be given to address these issues.

In conclusion, the 5 years overall survival rate was 51.9% and 41.8% of deaths were non-breast cancer related deaths. Low survival rate was related to low life expectancy in this population. Locally advanced disease, metastatic disease and high ER negative rates play a major role in survival of elderly breast cancer patients in Malaysia.

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