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RESEARCH ARTICLE

Relapse profile and recurrence free survival of breast cancer patients – bridging the gap in Sri Lanka

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Abstract: Breast cancer (BC) is the commonest cancer among females in Sri Lanka since 2000. This study was designed to determine the profile of recurrences, recurrence free survival (RFS) and the impact of the clinico-pathological features on the RFS of BC patients in the Southern Sri Lanka. This retro-prospective study included BC patients who sought the services from the Immunohistochemistry laboratory at the Department of Pathology, Faculty of Medicine, University of Ruhuna from May 2006 to December 2012. Tumour grading and scoring for estrogen receptor (ER), progesterone receptor (PR) and Her2 were done by principle investigator. The Chi-square test, Kaplan-Meier model and the Cox-regression model were used for data analysis using SPSS. A total of 923 BC patients were included. Of the total 923 patients, 188 had at least one recurrence (local-34, distant-154) during a mean follow up period of 45 months. Five year RFS was 74% (local- 94%, distance-78%). The RFS decreased with the increasing tumour size (p=0.002), Nottingham grade (p=0.002), lymph-node stage (p<0.001), pathological stage (p<0.001), NPI (p=<0.001) and with the presence of lympho-vascular invasion (p=0.011). ER positive (p=0.032), PR positive (p=0.008) and Her2 negative (p=0.025) tumours had an increased RFS. In the multivariate analysis, lymph node stage1-3 (p<0.001), Nottingham grade 3 (p=0.006) and expression of PR (p=0.024) became significant. Lymph node stage, Nottingham Grade and expression of PR have an independent effect on the RFS of BC patients in Southern Sri Lanka. Lymph node stage is the best predictor of recurrent breast cancer.

Keywords: Breast cancer, Relapse profile, Recurrence free survival, Sothern Sri Lanka

Introduction

Breast cancer was the second commonest cancer among Sri Lankan females and has become the commonest cancer since year 2000 (National Cancer Control Programme, 1995, 2000, 2014). It is the commonest cancer in Sri Lanka, when all age groups and both females and males are taken into account (National Cancer Control Programme, 2014). The age standardized incidence of breast cancer in females in Sri Lanka has increased from 17.3 per 100,000 in 2001 to 24.7 per 100,000 in 2010 with an estimated annual percentage change of 4.4 (Fernando et al., 2020). Out of all females diagnosed of cancers, breast cancer has affected 25.4% patients in the year 2014 (National Cancer Control Programme, 2014).

There are no published data on mortality rates for breast cancer by districts in Sri Lanka. It has been previously reported that breast cancers in Sri Lankan females are mostly high grade on par with the rest of the Asian population, contrary to the western scenario (Mudduwa & Thalagala, 2010; Peiris et al., 2017). Breast cancer stage at presentation is still

higher in Sri Lanka compared to resource high countries as only 9.6% of the reported breast cancer patients had stage I tumours at presentation according to the latest Cancer registry data given for 2010 (National Cancer Control Programme, 2010). The difference in the clinico-pathological profile of breast cancer patients in Sri Lanka may have an effect on their survival in terms of breast cancer specific survival and recurrence free survival (RFS). In a previous publication we stated that the breast cancer specific survival is 78.8% (Peiris et al., 2015). Absence of a national level mammographic breast cancer screening programme may have contributed to the relatively late presentation of patients and to the survival.

Challenges of managing breast cancer are many. Patients treated for early invasive breast cancer are at risk of developing a relapse and/or new primary breast cancer (National Institute of Health and Care Excellence (NICE) guidelines, 2009). There are three main types of recurrences; local recurrence, regional recurrence and distant metastasis. Most of the previous studies have considered both local and regional recurrences together as loco-regional recurrences (Dominici et al., 2012; Rudra et al., 2015; Yildirim & Berberoglu, 2008). Loco-regional recurrences can occur in different tissue sites which include the ipsilateral breast, chest wall, mastectomy scar and regional lymph nodes. The type of relapse that occurs most frequently is distant metastasis and the most frequent sites of metastasis are bone, liver and lung (Mansell et al., 2009; Ursaru et al., 2015). Distant metastasis is the primary cause of breast cancer specific mortality even in early stage cancer (Park et al., 2014).

The recurrence free interval (RFI) of patients reflects the benefit of primary treatment which has been received. RFI is expressed in different terms; relapse free interval, disease free survival, breast cancer free interval and loco-regional relapse free survival, especially for clinical trials (Gourgou-Bourgade et al., 2015; Hudis et al., 2007; Rakha, 2013). The two most common treatment options available for patients presenting with early stage breast cancer are breast conserving surgery followed by radiation therapy or mastectomy. The European Society for Medical Oncology (ESMO) 2011 guidelines recommend post-mastectomy radiotherapy for high risk patients presented with involved resection margin, involved axillary lymph nodes/with 1-3 positive lymph nodes and T3-T4 tumours (Cardoso et al., 2019). The next treatment option to reduce the possibility of developing a relapse is adjuvant systemic therapy for those who have a risk of recurrence. Status of the oestrogen receptor (ER) and human epidermal growth factor receptor 2 (Her2) are the most relevant predictive factors used to select the high-risk patients for adjuvant systemic treatment (Cardoso et al., 2019).

In Sri Lanka too, accepted guidelines (ESMO guidelines, St Gallen guidelines) are used in managing breast cancer patients. However, these guidelines have not been scientifically validated in our setting. Further, there are no published data on breast cancer recurrence among the breast cancer patients in Sri Lanka in order to measure the magnitude of treatment failure. Therefore, this study was designed to determine the profile of recurrences, RFS and the impact of the clinico-pathological features on the RFS of a cohort of female breast cancer patients in Southern Sri Lanka. The recurrence profile and the influence of clinico-pathological factors on RFS of BC patients in the Southern Sri Lanka, has been studied extensively for the first time.

Methodology

This retro-prospective cohort study included all breast cancer patients who had sought the imunohistochemistry (IHC) laboratory services of the Diagnostic Immunohistochemistry Laboratory in the Department of Pathology, Faculty of Medicine, University of Ruhuna from May 2006 to December 2012. This unit was the only IHC laboratory that was available to cater to the cancer patients of Southern Sri Lanka from 2006 to the completion of the study. Therefore, the study sample represents the breast cancer patients in the geographic area mentioned. This study was approved by the Ethical Review Committee of the Faculty of Medicine, University of Ruhuna and informed written consent was obtained from all individual participants included in this study.

The histopathological features of breast cancers were retrieved from the laboratory records available in the

department. Nottingham grading of all breast cancers were done by a single investigator using the haematoxylin and eosin (H&E) stained slides to eliminate inter-observer variation. Nottingham Prognostic Index (NPI) was calculated for all breast cancers using the formula; NPI = 0.2 × tumour size (cm) + lymph node stage (1, 2 or 3) + histological grade (1, 2 or 3) (National Health Services Breast Screening Programme, 2005).

Clinical details of the patients were retrieved from the clinic records.

Laboratory methods

Slides with sections immunohistochemically stained for ER, progesterone receptor (PR) and Her2 expression were retrieved from the archives of the department for evaluation. Primary monoclonal mouse antihuman estrogen receptor α clone 1D5 (Dako-M7047), monoclonal mouse antihuman progesterone receptor (Dako- M3569) and polyclonal rabbit antihuman c-erbB-2 oncoprotein (Dako-A0485) have been used with the secondary antibody (Dako Real EnVisionTM) for IHC staining of all breast cancers to assess ER, PR and Her2 expression. Scoring of ER and PR expressions were done using Allred Score and Her2 expression was assessed using the UK recommendations for all breast cancers (Ellis et al., 2004). IHC assessment too was done by a single investigator eliminating inter-observer variation. Her2 +2 cases have been referred for FISH assessment and when it became positive the tumour was considered positive for Her2. The complete absence of staining for ER, PR and a score of 0 or +1 for Her2 were considered the criterion for categorizing as triple negative breast cancer (TNBC) for this analysis.

Tumours were categorized as ER/PR positive if the total score for ER/PR was >2 and negative if the total score was 0 or 2 (Hammond et al., 2010). The four breast cancer IHC subtypes were identified according to the immunohistochemical expression of ER, PR and Her2 as follows; luminal A: ER and/or PR positive, Her2 negative; luminal B: ER and/or PR positive and Her2 positive; Her2 positive subtype: ER and PR negative, Her2 positive and TNBC: ER, PR and Her2 negative.

Follow up and outcomes

The study subjects were followed up for recurrence or death at six months intervals. The study ended on 31st December 2013. The median follow-up time was 41.5months (range: 12-138months). One third of the total population was followed up beyond four years from the date of diagnosis (81% for 24 months, 55.6% for 36 months, 40.4% for 48 months and 31% for five or more years).

The RFS was calculated from the date of surgery/date of commencement of neoadjuvant chemotherapy to the date of diagnosis of the recurrence (local/distant metastasis) (Rakha, 2013). Radiological and histopathological data were used to confirm the recurrence. The date on which the said investigation done was considered the date of recurrence. The patients not experiencing the relevant end point were censored at the last follow-up. Death was not considered as an event (Rakha, 2013). The RFI was measured from the date of first therapeutic intervention to the date of confirmation of the first recurrence in months (Rakha, 2013).

Statistical Analysis

The Pearson chi-square test was used to determine the association between clinico-pathological features and the development of recurrence and RFI. The Kaplan-Meier model was used to estimate the RFS and the log-rank test was used to compare the survival of different groups. Univariate analysis was performed with the Kaplan-Meier model and multivariate analysis was done with the Cox proportional hazards model using the backward stepwise factor retention method to estimate the predictors of survival. All the factors which had a p <0.100 in the univariate analysis was considered for the multivariate analysis. A p value < 0.05 was considered significant in all analyses.

Results

A total of 944 breast cancer patients had sought the IHC service during the stated period of study. Patients who had no details on recurrence were excluded from the study (n=11). Patients who had contra-lateral breast cancers (n=6) and primary cancers other than breast (n=4) were categorized as secondary cancer and not considered as an event for the estimation of RFS.

A total of 923 patients were included in this study. Out of the total, 188 breast cancer patients developed recurrences (loco-regional recurrence -34, distant metastasis -153 and both -1) during the follow up period. A significant majority (79.6%, 735/923) of the patients did not develop recurrences. More than 50% (99/188) of them developed a recurrence within the first 24 months of the initial treatment. Loco-regional recurrences developed in 18 patients and distant metastasis were diagnosed in 81 patients. The median RFI of the patients who had recurrence in the current study was 22 months (range: 12-102 months).

Out of all patients with recurrent breast cancer, 114 patients died during the follow up period. This included 109 deaths due to breast cancer and five deaths due to causes other than breast cancer. Out of all who had a loco-regional recurrence, 56% (19/34) died during the follow up period. Sixty two percent (95/154) of patients, who had distant metastasis also died during the follow up period.

One fourth; 26.6% (41/154) of all who had metastatic disease developed metastasis in multiple organs. The commonest site of the distant metastasis in this cohort was bone (32.4%, 50/154) and other sites of metastasis were brain, lung and liver.

Treatment prior to recurrence

Multiple treatment modalities had been used to treat these patients before they developed a recurrence. The majority of the patients had undergone mastectomy (98%, 907/923) and axillary node clearance up to level I – III (97%, 897/923). Chemotherapy has been given to 90.7% (838/923) of patients (only neoadjuvant: 7.4%, neoadjuvant and adjuvant chemotherapy: 9.7%, only adjuvant:

73.5%). Only 14 out of 923 (1.5%) patients had refused to receive chemotherapy and only 7.6% (70/923) of patients had not been recommended for chemotherapy.

Radiotherapy had been given to 73% (671/923) of the study subjects. Out of the patients who had hormone receptor positive breast cancers, 92% (350/380) had received hormone therapy. Only 5.8% (9/155) patients had received the complete course of trastuzumab. Comparatively effective number of trastuzumab cycles (≥9 cycles) had been given only to14.8% (23/155) of patients with Her2 positive tumours (Joensuu, et al., 2009). Seven of these 23 (30%) patients developed recurrences while 27% of those who had <9 cycles or no trastuzumab also developed recurrences.

Out of the 188 patients with recurrent breast cancer, 50% (94/188) had received a combination of chemotherapy, radiotherapy and targeted therapy (hormone therapy or anti-Her2 therapy), 22% (42/188) had chemotherapy and radiotherapy; 12% (22/188) had chemotherapy and hormone therapy; 1% (18/188) had received only chemotherapy; three patients had received chemotherapy and anti-Her2 therapy and only two patients had refused taking any form of adjuvant therapy. The majority of the patients (69%, 129/188) were on adjuvant therapy (chemotherapy/hormone therapy) when they had a recurrence. Only 30% (56/188) of patients developed recurrences following completion of the recommended treatment.

Association between clinico-pathological features and development of recurrence

The prevalence of aggressive clinico-pathological features was high within this cohort of breast cancer patients (Table 1). Most breast cancers were >2cm in size and of Nottingham grade 2/3, TNM stage II or higher with an NPI >3.4. All the considered clinico-pathological features were significantly associated with the development of recurrences except the presence of associated DCIS and the distance to the closest resection margin (Table 1).

Table 1: Association between clinico-pathological features and development of recurrence

Clinico-pathological feature		Total (%)	Recurrence (n=188)	No recurrence (n=735)	*P* value
Age at presentation					<0.001
	≤35 years	63 (7%)	25 (40%)	38 (60%)	
	36-60 years	650 (70%)	129 (20%)	521 (80%)	
	>60 years	210 (23%)	34 (16%)	176 (84%)	
Presence of associated DCIS					0.959
	Yes	318 (35%)	64 (20%)	254 (80%)	
	No	592 (64%)	120 (20%)	472 (80%)	
	Unknown data	13 (1%)	4	9	
Tumour size					0.003
	T1 (≤20 mm)	288 (31%)	41 (14%)	247 (86%)	
	T2 (>20-50 mm)	515 (56%)	120 (23%)	395 (77%)	
	T3 (>50 mm)	64 (7%)	18 (28%)	46 (72%)	
	Unknown data	56 (6%)	9	47	
Nottingham grade					0.001
	Grade 1	94 (10%)	11 (12%)	83 (88%)	
	Grade 2	350 (38%)	66 (19%)	284 (81%)	
	Grade 3	328 (36%)	92 (28%)	236 (72%)	
	Unknown data	151 (16%)	19	132	
Presence of LVI					0.010
	Yes	257 (28%)	66 (26%)	191 (74%)	
	No	652 (71%)	118 (18%)	534 (82%)	
	Unknown data	14 (1%)	4	10	
Lymph-node stage					<0.001
	0	396 (43%)	48 (12%)	348 (88%)	
	1	222 (24%)	44 (20%)	178 (80%)	
	2	170 (18%)	54 (32%)	116 (68%)	
	3	96 (10%)	35 (36%)	61 (64%)	
	Unknown data	39 (4%)	7	32	
Pathological stage					<0.001
	I	161 (18%)	18 (11%)	143 (89%)	

	II	411 (45%)	66 (16%)	345 (84%)	
	III	279 (30%)	90 (32%)	189 (68%)	
	IV	13 (1%)	5 (38%)	8 (62%)	
	Unknown data	59 (6%)	09	50	
Nottingham prognostic index					<0.001
	≤3.4	108 (12%)	14 (13%)	94 (87%)	
	3.4-5.4	387 (42%)	59 (15%)	328 (85%)	
	>5.4	239 (26%)	87 (36%)	152 (64%)	
	Unknown data	189 (20%)	28	161	
Distance to resection margin					0.617
Reaches margin		51 (6%)	12 (23%)	39 (77%)	
Closest margin is ≤2 mm from the tumour		151 (16%)	32 (21%)	119 (79%)	
Negative margin (>2 mm clearance)		600 (65%)	113 (19%)	487 (81%)	
Unknown data		121 (13%)	31	90	

n, number; p, significance; DCIS, ductal carcinoma in situ; LVI, lympho-vascular invasion; unknown data, details were not available.

The Her2 over expression and absence of ER and PR were significantly associated with the development of recurrences (Table 2). There was a significant difference between the patients who had recurrence and no recurrence in terms of IHC tumour subtypes.

Her2 positive subtype had the highest prevalence of recurrences while luminal A had the lowest (Table 2). There was no significant difference in prevalence of recurrence between the TNBC and non-TNBC groups (Table 2).

Table 2: Association between IHC markers and development of recurrence

IHC markers		Total (%)	Recurrence (n=188)	No recurrence (n=735)	*P* value
ER					0.008
	Positive	315 (34%)	53 (17%)	262 (83%)	
	Negative	472 (51%)	117 (25%)	355 (75%)	
	Unknown data	136(15%)	18	118	
PR					0.007
	Positive	329 (36%)	55 (17%)	274 (83%)	
	Negative	450 (49%)	111 (25%)	339 (75%)	
	Unknown data	144(15%)	22	122	
Her2					0.033

Positive	155 (17%)	43 (28%)	112 (72%)	
Negative	585 (63%)	116 (20%)	469 (80%)	
Unknown data	183(20%)	29	154	
Triple negative breast cancer				0.329
Yes	262 (28%)	61 (23%)	201 (77%)	
No	504 (55%)	102 (20%)	402 (80%)	
Unknown data	157(17%)	25	132	
IHC subtypes				0.028
Luminal A	304 (33%)	51 (17%)	253 (83%)	
Luminal B	45 (5%)	11 (24%)	34 (76%)	
Her2 positive	108 (12%)	32 (30%)	76 (70%)	
Basal like	275 (30%)	65 (24%)	210 (76%)	
Unknown data	191 (20%)	29	162	

IHC, immunohistochemical; n, number; p, significance; ER, oestrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor 2; unknown data, information was not available.

Association between clinico-pathological features and RFI

There was a significant upward trend of developing recurrences with time, in ER/PR positive tumours while a downward trend was noted for ER/PR negative breast cancers (ER: p=0.005 and PR: p=0.002; χ2 trend<0.001) (Figure 1 and 2). The mean RFI for ER/PR positive breast cancers was 33 months (SD±21) and it was 22 months (SD±16) for ER/PR negative breast cancers. The other clinico-pathological features considered for this study were not associated with the RFI of the recurrent breast cancer.
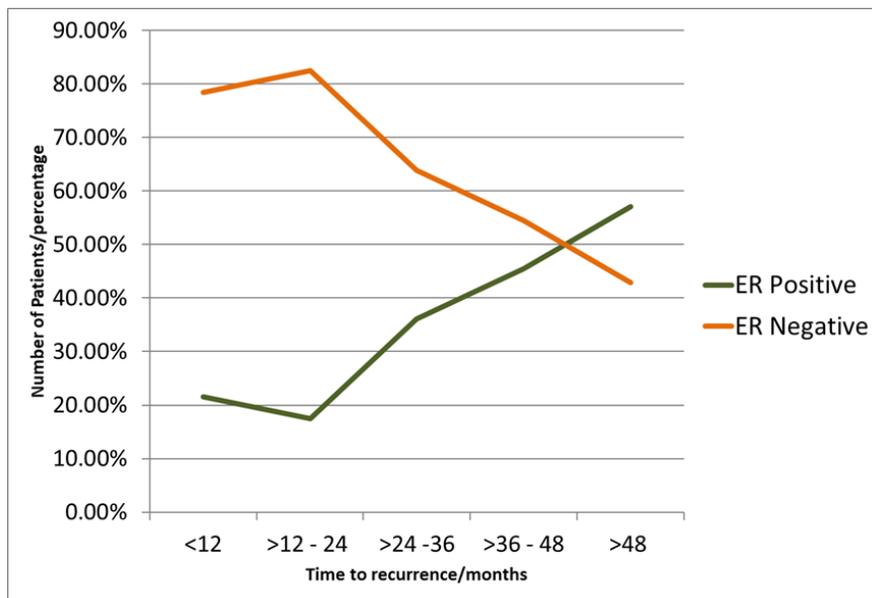

Figure 1: Comparison of RFI of ER positive and negative breast cancers (p=0.005 and χ2 trend<0.001).

Note: RFI was calculated in months. A total of 170 breast cancer patients who had recurrences were included (ER positive = 53, ER negative =117). ER status of 18 patients who had recurrence could not be assessed as the tissues in the blocks were not in a suitable state.
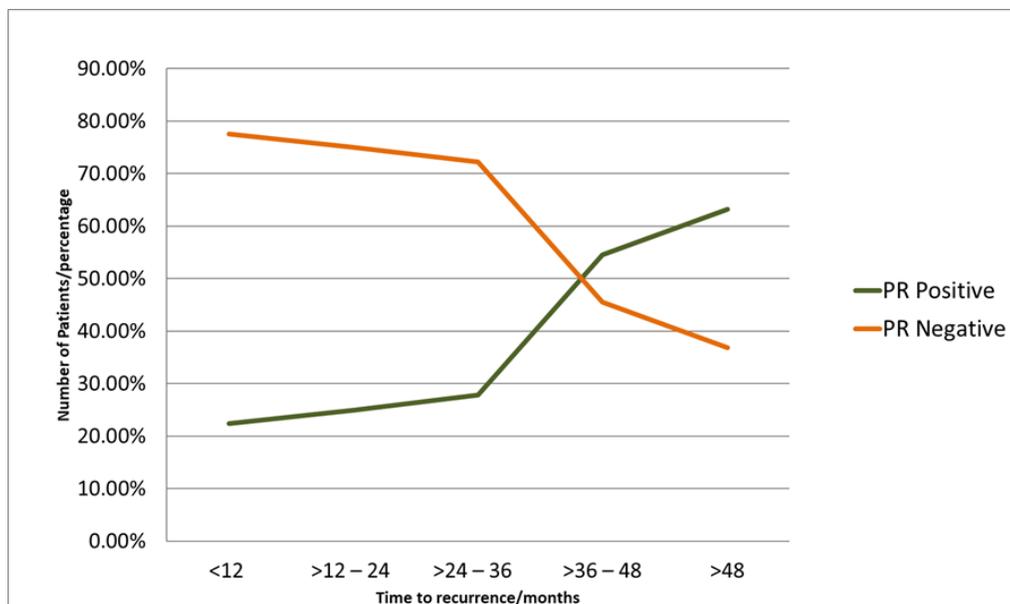

Figure 2: Comparison of RFI of PR positive and negative breast cancers (p=0.002 and χ2 trend<0.001).

Note: RFI was calculated in months. A total of 166 breast cancer patients who had recurrences were included (PR positive = 55, ER negative =111).ER status of 22 patients who had recurrence could not be assessed as the tissues in the blocks were not in a suitable state.

Recurrence free survival

Both loco-regional recurrence and distant metastasis were included as events. Patients who had died before the recurrence were censored at the date of death. Five year RFS of this study population was 74.7%. The mean RFS time was 93.15 months (SE 8.58; 95% CI 76.34-109.96) and median RFS time was 102.00 months (SE 11.34; 95% CI 79.77-124.22).

Effect of the tumour characteristics on the RFS

Univariate analysis was done using the Kaplan-Meier model and Cox proportional hazards model. The p values for a particular feature that were obtained from the two methods were equal.

According to the univariate analysis, RFS decreased with the increase in tumour size, Nottingham grade, lymph node stage, pathological stage, NPI and in the presence of lympho-vascular invasion with a statistical significance (log-rank p<0.01). (Table 3) Presence of associated DCIS and positive margin did not significantly associate with the RFS. The youngest age group had the worst RFS compared to the others. The differences between the RFS curves of the different age groups were statistically significant (p <0.001).

Breast cancer patients with ER/PR positive tumours and negative Her2 over expression had better RFS compared to the tumours with ER/PR negative and Her2 over expressing tumours. However, triple negative status did not influence the RFS. Luminal A had the best RFS while Her2 positive subtype had the worst RFS. (Table 3)

All categories of tumour size (T2<T3) and lymph node stage (stage1,2,3) had a significant negative effect on the RFS against their references (T1 and stage 0).

Table 3: Univariate analysis of the effect of clinico-pathological features on the RFS by Cox proportional hazards model

Factor	HR	95% CI	p value	Factor	HR	95% CI	p value
Age at presentation			<0.001	Nottingham prognostic index			<0.001
≤35 years	Reference			≤3.4	Reference		
36-60 years	0.421	0.275 - 0.647		3.4-5.4	1.282	0.716 - 2.297	
>60 years	0.357	0.213 – 0.599		>5.4	3.675	2.087 - 6.470	
Presence of associated DCIS			0.424	Lympho-vascular invasion			0.006
Presence/Absence	1.132	0.835 - 1.535		Presence/Absence	1.517	1.222 - 2.052	
Tumour size			0.005	Margin clearance			0.483
T1 (≤20 mm)	Reference			Reaches margin	1.490	0.776 – 2.859	
T2 (>20-50 mm)	1.638	1.149 - 2.336		Closest margin (≤2 mm)	1.049	0.684 – 1.607	
T3 (>50 mm)	2.180	1.252 - 3.795		Negative margin (>2 mm)	Reference		
Nottingham grade			0.002				
Grade 1	Reference			ER expression			0.016
Grade 2	1.651	0.872 - 3.128		Presence /Absence	1.487	1.075 - 2.075	
Grade 3	2.532	1.354 - 4.735		PR expression			0.004
				Presence/Absence	1.594	1.154 - 2.203	
Lymph-node stage			<0.001	Her2 expression			0.002
0	Reference			Presence/Absence	1.753	1.233 -2.494	
1	1.717	1.141 - 2.586		Triple negative breast cancer			0.477
2	3.185	2.156 - 4.705		Presence/Absence	1.122	0.817 - 1.542	
3	4.470	2.881 - 6.936					
Pathological stage			<0.001	IHC subtypes			0.002
I	Reference			Luminal A	Reference		
II	1.417	0.841 - 2.386		Luminal B	1.849	0.963 – 3.552	
III	3.627	2.185 - 6.022		Her2 + subtype	2.268	1.455 – 3.536	
IV	8.260	3.048 - 22.386		Basal like	1.468	1.017 – 2.118	

HR, hazard ratio; CI, confidence interval; p, significance; DCIS, ductal carcinoma in situ; ER, oestrogen receptor; PR, progesterone receptor; Her 2, human epidermal growth factor receptor 2; IHC, immunohistochemical

Table 4: Multivariate analysis of tumour features predicting the RFS

Factor	HR	95% CI	*P* value
Age at presentation			
≤35 years	Reference		0.007
36-60 years	0.448	0.282 – 0.710	
>60 years	0.466	0.269 – 0.810	
Nottingham grade			0.015
Grade 1	Reference		
Grade 2	1.509	0.792 – 2.875	
Grade 3	2.139	1.133 – 4.039	
Lymph node stage			
0 (No positive LNs)	Reference		0.001
1 (1-3 positive LNs)	1.667	1.087 – 2.558	
2 (4-9 positive LNs)	2.718	1.781 – 4.148	
3 (>10 positive LNs)	4.123	2.585 – 6.577	
Tumour size	a		0.188
Lympho-vascular invasion	a		0.441
IHC markers			
PR			0.049
Positive	Reference		
Negative	1.400	1.002 - 1.957	
Her 2			0.006
Positive	1.652	1.154 - 2.366	
Negative	Reference		
ER	a		0.724

HR, hazard ratio; CI, confidence interval; p, significance; LNs, lymph nodes; a, removed from the final model; IHC, immunohistochemical; PR, progesterone receptor; Her 2, human epidermal growth factor receptor 2; ER, estrogen receptor

However only the worst categories of Nottingham grade (grade 3), pathological stages (stage III and IV), NPI (>5.4) and IHC categories (Her2 + and TNBC) had an influence on the RFS which was again a negative effect (Table 3).

All the covariates which had a p<0.100 in the univariate analysis were taken to the multivariate analysis. Multivariate analysis revealed that age at presentation, Nottingham grade, lymph node stage, absence of PR and Her2 over expression independently affected the RFS (Table 4). However, the grade 2 did not have an independent effect on the RFS, it was the tumour being grade 3 that influenced the RFS. Lymph node stage 1 to 3 individually had a

significant independent effect on RFS compared to those who did not have positive lymph nodes. Presence of lympho-vascular invasion, tumour size and expression of ER had no independent effect on the RFS.

Discussion

Cancer incidence and mortality rates have increased in Sri Lanka since year 2000 (National Cancer Control Programme, 2010, 2014). Crude incidence rate for all cancers was 111.2 /100,000 population in 2014. One in every 40 Sri Lankan females has a risk of developing a breast cancer during their lifetime. These cancer data have been calculated for the country and there is no data available district or province wise (National Cancer Control Programme, 2000, 2010, 2014). Survival data on breast cancer in Sri Lankan patients are also not available in the published literature except for our previous publications on breast cancer specific survival and one on triple negative breast cancer (Peiris et al., 2015, 2017; Wijesinghe et al., 2020). Therefore, this study was designed to determine one other aspect of the survival of breast cancer in a Sri Lankan cohort of patients; that is RFS. The five-year RFS of our cohort was 74.7% which is lower compared to other Asian countries; eg: India (94%) and China (80.7%) (Dong et al., 2014; Yadav, Sharma, Singh, & Singh, 2007). Therefore, it is important to study the profile of recurrence and impact of clinico-pathological features on the RFS of female breast cancer patients in Sri Lanka and we have selected a cohort of patients from the tertiary care center in the Southern Province.

The current cohort of patients has high prevalence of many aggressive features increasing the risk of recurrent breast cancer (Table 2, 3). In the present study, younger age at presentation, large tumour size, high grade tumours, presence of lympho-vascular invasion, lymph node stage 1-3, advanced pathological stage, absence of ER, PR expression and Her2 over expression had a significant positive effect on the development of recurrences. Younger age (<35 years) at presentation, presence of lympho-vascular invasion, multi-centricity have been identified in previous studies as major predictors of loco-regional recurrence (Buchanan et al., 2006).

Similarly higher tumour stage, higher nodal stage and locally advanced stage are also found to be associated with high rates of loco-regional recurrence and distant metastasis (Yadav, Sharma, Singh, Singh, et al., 2007). Further, classification of breast cancer by biological subtypes has proven to be a strong predictor of distant relapse. Females with TNBC tumours, who have either positive nodes or lympho-vascular invasion are at markedly increased risk of loco-regional recurrence (Dominici et al., 2012).

Majority in the current study had received systemic adjuvant therapy (chemotherapy and endocrine therapy based on the hormone receptor status) and post-mastectomy radiotherapy to reduce the subsequent risk of loco-regional relapse (Goldhirsch et al., 2006). As a result, only a 20% of the total had recurrences; either loco-regional recurrence or distant metastasis in the current study.

Local recurrences are more frequent in patients treated with breast conservative surgery and radiotherapy than in patients with radical mastectomy (Ursaru et al., 2015). The prevalence of loco-regional recurrence after mastectomy for invasive breast cancer varies from 4% to 9% due to inadequate axillary sampling, incomplete surgical technique and suboptimal systemic therapy (Bakar et al., 2015; Buchanan et al., 2006; Lee et al., 2011; Yildirim & Berberoglu, 2008). In the present study, the most common surgical management was mastectomy with axillary clearance which gives a better local control of the cancer. More than 70% of the patients had received radiotherapy following mastectomy. Post-mastectomy radiotherapy reduces the risk of loco-regional recurrence in breast cancer patients who are at high risk (He et al., 2015; Kim et al., 2010; Li et al., 2014). A 78% of the study subjects who had a margin clearance ≤2 mm and had no recurrence. It is well known that minimal margin clearance is not a significant risk factor of loco-regional recurrence where all patients had received complete course of radiotherapy (Feigenberg et al., 2003). Therefore, a lower prevalence of loco-regional recurrence as a primary site treatment failure is observed in the present study compared to the others (Chairat et al., 2013).

In the current study, 16.6% (154/923) of patients had distant metastasis probably due to the prevalence of poor prognostic features which are known to impart a significant risk of distant metastasis (Goldhirsch et al., 2006; Park et al., 2014; Yildirim & Berberoglu, 2008). Especially, lymph node positive breast cancers are at high risk of developing distant metastasis (Chairat et al., 2013; Li et al., 2014). In the present study, 54% of patients had lymph node metastasis. Many previous studies have reported that chemotherapy, radiotherapy and endocrine therapy reduce the risk of recurrence; which explains why the majority in the current study did not develop recurrences (EBCTCG, 2005; Overgaard et al., 2007; Thürlimann, 2007; Yadav, Sharma, Singh, Singh, et al., 2007).

Her2 over expression is well known to carry a greater risk of distant metastasis (Park et al., 2014; Verma et al., 2010). In the present cohort too the prevalence of recurrence was highest among the Her2 positive IHC subgroup (Table 2). To reduce the risk of relapse intensive adjuvant treatment with trastuzumab is recommended for Her2 positive breast cancers (Verma et al., 2010). Even though 59% of the Her2 positive patients in the current study had not received even a single dose of trastuzuamb, they had received advanced adjuvant chemotherapy. That may be the reason why the majority of the Her2 positive patients (72%) had no recurrences during the follow up period.

The expression of either ER or PR has reduced the risk of recurrence; yet only PR showed an independent effect on the RFS in this study. This has been proved previously by some authors highlighting the importance assessment of PR expression (Purdie et al., 2014). However there is no difference in risk of recurrence between TNBC and Non-TNBC in our cohort. A recent cohort study done in a different institution in Sri Lanka supports this finding. (Wijesinghe et al., 2020). This may probably be due to the inclusion of Her2 negative breast cancer with low risk in the TNBC group with ER/PR negative high-risk patients and vice versa nullifying the good and bad effects.

In the present study, first distant metastasis of one third of the patients was diagnosed in the bone. Other common sites were the brain, lungs and multiple organs. The natural history of distant metastasis is women with ER positive tumours more often develop metastasis to the bone, and ER negative tumours more often develop early liver and brain (Kennecke et al., 2010). However, due to the smaller sample size of the patients with distant metastasis, the association of IHC subtypes with the site of metastasis was not assessed.

Recurrence free interval

ER/PR positive breast cancers had a significant upward trend in developing recurrences over time while the ER/PR negative patients had a downward trend in this study cohort. This is in keeping with the previous studies done in other countries which have demonstrated that the survival advantage of hormone receptor expressing tumours is time dependent and hormone receptor positive breast cancers are associated with favourable short term prognosis (Brewster et al., 2008; Hess et al., 2003).

Recurrence free survival

Most of the publications on recurrent breast cancer in the literature have addressed either loco-regional recurrence or distant metastasis and publications on RFS combining both types are limited. A study done on early stage Her2 positive breast cancers has shown that patients with >9 lymph nodes and PR negative tumours had worse RFS (Tonyali et al., 2013). Positive lymph nodes affect the loco-regional recurrence free survival and distant metastasis free survival (Li et al., 2014; Park et al., 2014).

In addition to lymph node stage, younger age at presentation, Nottingham grade3, absence of PR and over expression of Her2 had an independent negative effect on the RFS of the current study population. All these are well known risk factors for development of recurrences (Chairat et al., 2013; Lee et al., 2011; Li et al., 2014; Park et al., 2014; Yildirim & Berberoglu, 2008). Our study too highlights this effect and further demonstrates that each stage of lymph node metastasis independently affects the recurrence free survival compared to those without positive lymph nodes.

One of the strengths of the present study is that we have eliminated the inter-observer variation in the assessment of four parameters by re-evaluating the slides for ER, PR, Her2 and Nottingham grade by a single rater. The total sample was recruited from a single oncology unit which minimized the effects of differences in treatment. However, this study had a retrospective component and it carried some of the inherent limitations of retrospective studies; some of the data were not available for a proportion of patients eg.: Her2 expression was not available for 20%. The Her2 stained slides of 20% were faded and not suitable for re-evaluation by the investigators. Re-doing immunostaining for the faded slides was impossible as the tissue in the wax blocks have already perished. Unsuitability of archival material for re-processing for assessment is one of the limitations of retrospective studies for survival analysis. Missing data was handled by pairwise deletion maximizing the use of available data. A large sample was recruited expecting some amount of missing data because of this inherent drawback in retrospective studies.

The effects of time related changes in the treatment due to the unavailability of certain drugs and alterations in treatment protocols accordingly may have affected the results limiting the usage of the data in the current context. Yet, the result of this study fills a longstanding gap in the scientific data related to prognosis of breast cancer patients in Sri Lanka. There are no reports of studies done on breast cancer survival in Sri Lankan patients comparable to the length of follow up and the larger size of the sample like this study report. The couple of studies available are limited to less than 200 patients with a mean follow up of around two years.

In conclusion, the five-year RFS of the current cohort was 74.7%. The prevalence of breast cancer recurrence in the present study is less than what would be expected for a population of patients with aggressive clinico-pathological features. This may be attributed to the aggressive treatment; both surgical and adjuvant, they had received. Therefore, primary treatment failure rate has been low even though patients presented with many poor prognostic features. The upward trend in the development of recurrence over time of hormone receptor expressing

breast cancers and downward trend of the same in non hormone expressing tumours too were recognized in the current study sample.

Almost all clinico-pathological features assessed were associated with breast cancer recurrences conforming to the findings of the previous publications and confirming their applicability as risk factors and predictors of recurrences in our study setting too. This study proved that the lymph node stage remains the best predictor of recurrent breast disease in our setting too.

Acknowledgement

Conflicts of interest

The authors declare that they have no conflicts of interests.

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