RESEARCH COMMUNICATION

High Tumour Stage and Margin Clearance are Still Important Prognostic Factors for Post-Mastectomy Locoregional Recurrence in Malaysia

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Abstract

Background: Locoregional recurrence after mastectomy for breast cancer may predict distant recurrence and mortality. This study examined the pattern and rates of post-mastectomy locoregional recurrence (PMLRR), survival outcome and prognostic factors for isolated PMLRR (ILR) in a breast cancer cohort in University of Malaya Medical Center (UMMC). Methods: We studied 522 patients who underwent mastectomy between 1998 and 2002 and followed them up until 2008. We defined PMLRR as recurrence to the axilla, supraclavicular nodes and or chest wall. ILR was defined as PMLRR occurring as an isolated event. Prognostic factors for locoregional recurrence were determined using the Cox proportional hazards regression model. Results: The overall PMLRR rate was 16.4%. ILR developed in 42 of 522 patients (8.0%). Within this subgroup, 25 (59.5%) remained disease free after treatment while 17 (40.5%) suffered disease progression. Univariate analyses identified race, age, size, stage, margin involvement, lymph node involvement, grade, lymphovascular invasion and ER status as probable prognostic factors for ILR. Cox regression resulted in only Stage III disease and margin involvement as independent prognostic factors. The hazard of ILR was 2.5 times higher when the margins were involved compared to when they were clear (aHRR 2.5; 95% CI 1.3 to 5.0). Similarly, compared with stage I those with Stage II (aHRR 2.1; 95%CI 0.6 to 6.8) and stage III (aHRR 4.6; 95%CI 1.4 to 15.9) had worse prognosis for ILR. Conclusion: Margin involvement and Stage III disease were identified to be independent prognostic factors for ILR. Close follow-up of high risk patients and prompt treatment of locoregional recurrence were recommended.

Keywords: Breast cancer - post-mastectomy locoregional recurrence - risk factors - margin involvement - stage

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Introduction

Breast conserving surgery is becoming an important modality for treatment of early breast cancer. However, mastectomy with axillary clearance is still the mainstay treatment for breast cancer in the Asia Pacific region especially for those patients who present with late staged operable disease. Most women in Malaysia present late due to several reasons including cultural beliefs and ethnic diversity, strong beliefs in traditional medicine, negative perception of the disease, poverty, poor education, fear, denial and unavailability of population-based screening programmes. Therefore mastectomy is still very widely practised (Hisham and Yip, 2003; 2004; Leong et al., 2007; Taib et al., 2007).

PMLRR is important as it may predict distant recurrence and outcome. Worldwide incidence for PMLRR ranges widely from 5% to more than 40%(Overgaard et al., 1997; Overgaard et al., 1999; Katz et al., 2000; Farid and Rasool, 2005; Jagsi et al., 2005; Buchanan et al., 2006). This wide range may be explained by suboptimal treatment in some patients and the non-uniform definitions of LRR used in various studies.

Present data shows that following PMLRR, one third of these patients will remain disease free following treatment, one third will develop distant metastasis and the remaining one third presents with simultaneous distant recurrence (Clemons et al., 2001; Buchanan CL et al., 2006). A few studies have identified a favourable subgroup of patient who survived more than 5 years after treatment of LRR (Halverson et al., 1992; Willner et al., 1997).

Patients with solitary chest wall or axillary nodule, aged above 50 years with a disease free interval of 1 year and had node negative pT1-2 primary tumours were found to have better prognosis (Willner et al., 1997), (Halverson et al., 1992).

Treatment strategies for LRR are not so well defined. Surgical resection of the recurrent nodule can be curative or palliative for local control. Simple excision alone can control local disease in 25-40% of the patients (Shah

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and Urban, 1975; Zoetmulder and van Dongen, 1988; Salvadori et al., 1999). For isolated chest wall recurrence only, complete resection of all recurrent disease has been shown to improve survival (Beck et al., 1983; Aberizk et al., 1986; Andry et al., 1989), with the greatest benefit seen in patients with a longer disease-free interval (Zoetmulder and van Dongen, 1988; Touboul et al., 1999).

Radiotherapy has been used for local control of PMLRR. Retrospective series have shown response rates of 60-70% and 5 year survival rates of 20-40% for this modality of treatment (Chu et al., 1976; Bedwinek et al., 1981; Chen et al., 1985; Aberizk et al., 1986; Schwaibold et al., 1991). However, more than 50% of these tumours recur locally despite adequate radiotherapy fields (Aberizk et al., 1986; Schwaibold et al., 1991).

The role of systemic treatment for LRR is unclear. In retrospective studies, chemotherapy at the time of LRR has either resulted in some (Beck et al., 1983; Haylock, Coppin, Jackson, Basco, & Wilson, 2000)or no survival benefit (Bedwinek et al., 1981; Schwaibold et al., 1991). However, these are retrospective studies and there is no prospective data available.

Breast cancer outcome information in Malaysia is scarce with few information on survival (Mohd Taib et al., 2008; Leong et al., 2009). We aimed to determine prognostic factors of postmastectomy locoregional recurrence in Asian breast cancer patients who underwent mastectomy; and to determine the pattern and rates of post- mastectomy locoregional and systemic recurrence; ultimately leading to better post-mastectomy surveillance in this population of patients.

Materials and Methods

This is a cohort study of breast cancer patients who underwent mastectomy in UMMC between 1 January 1998 and 31 December 2002. Data was obtained from the Institutional Breast Cancer Registry in UMMC, and was supplemented by patients' medical records. A total of 571 patients underwent mastectomy during 1998 to 2002. 49 patients were excluded because of Stage IV disease (at presentation or documentation of distant metastasis within 3 months post mastectomy) and histology other than carcinoma: eg, sarcoma, angiosarcoma and malignant phylloides. An institutional protocol on adjuvant chemotherapy and radiotherapy was used. All patients that were included for the study were followed up until 15 June 2008. The primary end point of the study was development of PMLRR, defined as recurrence to the axilla, supraclavicular nodes and / or chest wall including skin and muscle. Contralateral breast cancer was not considered as PMLRR. All recurrences were histologically confirmed . All patients with operable isolated locoregional recurrence received surgical intervention followed by radiotherapy if they had not had it. Radiotherapy and chemotherapy were only used in cases of distant recurrences (DR) occurring within 3 months after detection of PMLRR (defined as synchronous local and distant recurrence). ILR was defined as PMLRR occurring as an isolated event. Time to recurrence was calculated as the time from operation to time of first recurrence. The mortality status until 4th April 2006 was ascertained from the National Registry of Births and Deaths.

In UMMC, the criteria for adjuvant chemotherapy include node positive disease or node negative patients with high risk prognostic factor such as young age (< 50 years), tumour size above 2cm, and high grade. Adjuvant chemotherapy 5-fluorouracil 500mg/m^2 Day 1(D1), epirubicin 75 mg/m^2 D1, cyclophosphamide 500mg/m^2 D1 (FEC) every 3 weeks for 6 cycles (340/386, 88.1%) or Doxorubicin 60mg/m^2 D1, Cyclophosphamide 600mg/m^2 D1(AC) every 3 weeks for 4 cycles followed by Paclitaxel 175mg/m^2 D1 every 3 weeks for 4 cycles (24/386,6.2%) for low risk patients. Cyclophosphamide 600 mg/m^2 D1, Methotrexate 40 mg/m^2 D1,5-fluorouracil 600mg/m^2 D1 (CMF) every 3 weeks for 6 cycles (22/386, 5.7%) were used for poor cardiac risk patients. Indications for adjuvant radiotherapy include node positive disease, tumour size more than 5 cm, T4 disease and microscopically involved margins. Patients with positive nodes had radiotherapy to the chest wall with or without supraclavicular fossa. Axillary radiotherapy were given to patients with residual non-operable axillary node involvement

The data was entered and analysed using SPSS version 16.0. Descriptive statistics was used to summarize the distribution of the covariates. Time to event analysis was used and censoring events were defined as: no LRR at follow-up, diagnosis of distant metastasis and death without recurrence. Kaplan-Meier survival estimates were calculated and survival curves compared using the log rank test. All prognostic factors for PMLRR, OS and DFS were further investigated using Cox proportional hazards model. Regression estimates were summarised as Hazard Rate Ratio (HRR) with a 95% Confidence Interval. A two-tailed p-value of less than 0.05 was considered to

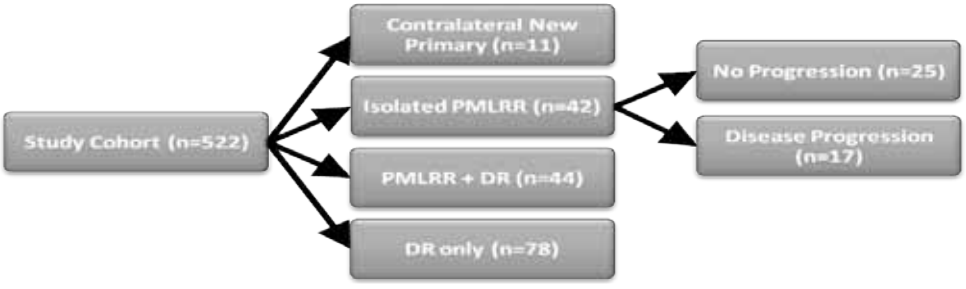

Figure 1. Outcome of 522 Post-Mastectomy Patients in the UMMC Breast Cancer Cohort. DR, Distant recurrence; PMLRR, Post-mastectomy locoregional recurrence

Table 1. Sites of Locoregional Recurrence in the UMMC Breast Cancer Cohort n=522

Site	n (%)
Chest Wall	43 (50)
Chest Wall + Regional Lymph Node*	14 (16.2)
Axillary Lymph Node Alone	13 (15.1)
Supraclavicular Lymph Node	15 (17.4)
Supraclavicular + Axillary Lymph Node	1 (0.1)

*include ipsilateral axillary and/or supclavicular lymph nodes.

be significant.

Results

A total of 522 patients were eligible for this study. The age distribution of the cohort ranged from 26 to 81 years old. The median age for the entire cohort was 50.0 years and the mean was 51.2 years (SD 10.3). Majority of patients presented in the 40-49 age groups. The patterns of locoregional recurrence are illustrated in Figure 1 and Table 1. PMLRR occurred in 86 patients during the period of study from 1 January 1998 to 15 June 2008 with a median follow up time of 67 months (SD 32.3 months). Overall PMLRR rate was 16.4% (crude rate). ILR occurred in 42 patients or 8.0% (crude rate). The cumulative incidence for ILR at 10 years was 11.1%. Most of the ILR developed in the first 3 years post mastectomy, with 28 patients (66.7%) having an ILR within 36 months and 36 (85.7%) within 60 months.

The 5 year and 10 year ILR free survival were 91.8% and 88.9% respectively. The 5 year and 8 year overall survival for this study population were 76.1% and 66.4% respectively. The median follow up was 57 months. Disease free survival in this study was defined as the length of time for which a patient survives with no sign of LRR or DR after mastectomy. The 5 year and 10 year disease free survival in this study cohort were 69.5% and 57.9% respectively. The second recurrence free survival in this study was defined as the length of time for which a patient survives with no further recurrence (local or distant) after developing an initial PMLRR. The 3 year and 5 year survival rate for second recurrence free were 61.9% and 54.2% respectively.

Prognostic factors for ILR

Univariate analyses identified race, age, size, stage, margin involvement, lymph node involvement, grade, lymphovascular invasion and ER status as probable prognostic factors for ILR (Table 2).

Our study also found that while neoadjuvant chemotherapy and chest wall radiotherapy were associated with a higher risk of ILR on univariate analysis, treatment with tamoxifen was not found to be a significant factor (refer to Table 4). These co-variates were included in the

Table 2. Prognostic Factors of ILR in the UMMC Breast Cancer Cohort

		n (%)	10 year Cumulative survival (%)	p value	Crude Hazard Rate Ratio (95% CI)	Adjusted Hazard Rate Ratio (95% CI)
Race	Chinese	348(66.7)	90.3		1.0	-
	Malay	93(17.8)	81.1	0.01	2.4 (1.2 – 4.7)	-
	Indian	74(14.2)	90.3	0.70	1.2 (0.5 – 2.9)	-
	*Not Available	7 (1.3)				
Age	>55 years	172(33.0)	90.9		1.0	-
	36-55 years	324(62.1)	90.8	0.42	1.3 (0.7 – 2.7)	-
	<35 years	26 (5.0)	84.4	0.21	2.7 (0.96– 8.1)	-
Size (cm)	≤2.0	117(22.4)	94.1		1.0	-
	2.1-5.0	279(53.4)	89.2	0.29	1.6 (1.0 – 3.6)	-
	>5.1	113(21.6)	79.8	0.006	3.7 (1.6 – 6.4)	-
	*Not Available	13 (2.5)				
Stage	I	74(14.2)	95.3		1.0	1.0
	II	313(59.9)	90.1	0.27	2.0 (0.6 – 6.6)	2.1 (0.6 – 6.8)
	III	122(23.4)	78.8	0.009	5.1 (1.4 – 17.5)	4.6 (1.4 – 15.9)
	*Not Available	13 (2.5)				
Margins	Clear	354(67.8)	90.1		1.0	1.0
	Involved	77(14.8)	79.2	0.02	2.9 (1.5 – 5.7)	2.5 (1.3 – 5.0)
	Not Available	91(17.4)	92.7	0.51	0.7 (0.2 – 2.0)	0.6 (0.2 – 2.0)
Involved Lymph	0	241(45.9)	92.1		1.0	-
Nodes	1-3	154(29.3)	84.5	0.03	2.2 (1.1 – 4.4)	-
	4 or more	122(23.3)	87.9	0.18	1.7 (0.7 – 3.9)	-
	*Not available	5 (0.9)				
Grade	3	171(32.8)	84.9		1.0	-
	2	231(44.3)	92.3	0.02	0.5(0.2 – 0.9)	-
	1	32 (6.1)	79.4	0.79	0.8(0.3 – 2.5)	-
	Not Available	88(16.9)	92.4	0.10	0.4(0.2 – 1.1)	-
Lymphovascular	No	193 (37)	88.1		1.0	-
Invasion	Yes	167 (32)	90.3	0.92	0.9 (0.5 - 2.0)	-
	Not Available	162 (31)	89.0	0.90	1.0 (0.5 – 2.1)	-
ER Status	Negative	230(44.0)	87.7		1.0	-
	Positive	263(50.4)	89.5	0.28	0.7 (0.4 – 1.3)	-
	Not Available	29 (5.6)	92.1	0.56	0.4 (0.1 – 2.7)	-

*Excluded from analysis

Table 3. Adjuvant Treatment Modalities of Mastectomy Patients in the UMMC Breast Cancer Cohort

	N (%)	10 year Cumulative survival (%)	p value	Crude Hazard Rate Ratio
Chemotherapy				
No	136(26.1)	87.1		1.0
Adjuvant	331(63.4)	91.5	0.51	0.7 (0.3 – 1.6)
Neoadjuvant	55(10.5)	75.6	0.03	2.7 (1.1 – 6.6)
Chest Wall RT				
No	175(33.5)	90.9		1.0
Yes	345(66.2)	87.8	0.005	2.1 (1.2 – 3.6)
*Not available	2 (0.3)			
Hormonal Treatment				
No	198(37.9)	88.2		1.0
Tamoxifen	317(60.7)	89.5	0.297	0.7 (0.3 – 1.3)
*Not available	7 (1.4)			

*Excluded from analysis

Table 4. Post Mastectomy Radiotherapy (RT) in Node Positive Patients

Lymph Node Involvement	n	Received RT n (%)		No RT n (%)	No information
1-3 Lymph Nodes	153	134 (87.6%)		19(12.4%)	1[#]
*Site of RT		CW	104(77.6%)		
		CW + Boost	15(11.2%)		
		CW + SCF	8 (6.0%)		
		CW + SCF +Boost	1 (0.7%)		
		Site not known	6 (4.5%)		
≥ 4 Lymph Nodes	121	113(93.4%)		8(6.6%)	1[#]
*Site of RT					
		CW + SCF	70(61.2%)		
		CW	26(23.0%)		
		CW + Boost	11 (9.7%)		
		CW + SCF +Axilla	2 (1.8%)		
		CW+Boost+SCF	1 (0.9%)		
		CW+Boost+SCF+Axilla	1 (0.9%)		
		Site not known	2 (1.8%)		

*CW = Chest Wall; Boost= Boost to tumour bed; SCF= Supraclavicular Fossa; [#]Excluded from analysis

multivariate model and were found not to be statistically significant.There were unavailable data that were removed from the analyses as shown in Tables 3 and 4.

87.5% of patients with tumour greater than 5cm received chest wall radiotherapy. In our cohort, 75.7% of node positive patients received adjuvant chemotherapy while 13.8% received neoadjuvant chemotherapy. However, only 77.8% of ER negative patients received chemotherapy. This might be due to patient refusal or unfit medical conditions.

Post-Mastectomy Radiotherapy And Pattern 0f Recurrence

Sixty six point two percent or 345 out of 520 (2 radiotherapy data were missing) received radiotherapy. 20% or 69 out of 345 of those who received radiotherapy developed recurrences, of which only 9.3 %(32 patients) were ILR.

Of these 32 patients; 16(50%) recurred in the chest wall (CW), 7 (21.9%) recurred both in CW and regional nodes, 5 (15.6%) were in the axilla alone and 4 (12.5%) were in the SCF only. Only 24 of these patients out of 345 who received radiotherapy (6.96%) were in-field recurrences.

Post-Mastectomy Radiotherapy and Lymph Node Involvement

Table 4 illustrates the radiotherapy trends in node positive patients. In this study, 87.6%(134/ 153) of patients with 1 to 3 positive nodes received radiotherapy (RT). 93.4% of patients with 4 or more positive nodes received radiotherapy.

Definition of Clear margins and Risk of Recurrence

As this study cohort was from a retrospective database, we could not categorise into distance from margins due to the inconsistent documentation of close margins. Therefore, clear surgical margins were taken as microscopically uninvolved margins. 76.6 % (59/77) of those with microscopically involved margins and 64.7%(229/354) of those with clear margins were given radiotherapy. Information on margins were not available in 17.4% of the cases. This was included in the multivariate analysis and was found not to be an important factor. However involved margins (p=0.02) was found to be 2.9 times at risk of locoregional failure compared to uninvolved margins (Table 2).

Multivariate Analysis

The most parsimonious model for ILR using Cox proportional hazard regression only included margin involvement and Stage 3 tumours. The hazard of ILR was 2.5 times higher when the margins were involved compared to when it was clear (aHRR 2.5; 95% CI 1.3 to 5.0). Similarly, compared with stage I those with Stage

II (aHRR 2.1; 95%CI 0.6 to 6.8) and stage III (aHRR 4.6; 95%CI 1.4 to 15.9) had a worse prognosis of ILR.

Discussion

Loco-regional control remains an important goal in the management of breast cancer because of its impact on survival and quality of life for the patient. Our 10 year loco-regional recurrence rate of 8.0% (crude) and 11.1% (actuarial) for ILR in patients without metastatic disease was in agreement with results in other recent studies (Jager et al., 1999; Kamby and Sengelov, 1999; Cheng et al., 2000; Taghian et al., 2004; Jagsi R et al., 2005; Buchanan CL et al., 2006; Taghian et al., 2006). These figures were comparable with western data and are acceptable for a tertiary center with a dedicated breast unit. The M.D. Anderson Cancer Centre had a local failure rate of 4-22%(Katz et al., 2000; Jagsi R et al., 2005). Similarly, the overall PMLRR rate which includes LRR with and without DR at 16.2% (crude) and 22.8% (actuarial) at 10 years was also comparable to the earlier published series(Jager et al., 1999; Kamby and Sengelov, 1999; Cheng et al., 2000; Taghian et al., 2004; Jagsi R et al., 2005; Buchanan CL et al., 2006; Taghian et al., 2006). These earlier published series had LRR rates that ranged from 2% to 19%. The methods and patient selection in these various study vary differently but generally, Stage 4 cancers were excluded. The limitation of our study was its retrospective nature. Several records were incomplete and certain data were unavailable. Tables 3 and 4 highlight the unavailable values for each co-variate. We chose to study patients who were treated at this time because 1998 was the time where in-house radiotherapy services became available at UMMC and it also provided an optimal time frame (10 years) to study the incidence of PMLRR.

We found that 66.7% of those who had an ILR developed it by 36 months. Similar trend was noted with the overall PMLRR group where 62.8% of them had PMLRR with or without simultaneous distant metastasis at 36 months. Previous studies had also found similar findings where majority of the LRR were isolated and occurred within the first 3 years (Cheng et al., 2000; Jagsi R et al., 2005). Our study indicates that during the 10 year follow up period, about half of the patients with PMLRR will have synchronous distant disease while in the remaining half, PMLRR occurred as an isolated event. From the ILR group, around 60% did not progress after treatment while the remaining 40% developed distant disease later on. Buchanan et al., (2006) (Buchanan CL et al., 2006) in their series with a 6 year follow up period, also found that about a third who present with PMLRR will have synchronous distant disease; distant disease will develop in one-third and the remaining one third would remain disease free.

Our study obtained a 10 year ILR free survival rate of 88.9% and the overall PMLRR free survival was 77.2%. These figures are comparable with current available data mainly from the western population (Katz et al., 2000; Clemons et al., 2001; Katz et al., 2001; Beenken et al., 2003). The 5 year survival rates are given on Table 2. The commonest site of recurrence in this study was the chest wall. This is in agreement with current published data (Willner et al., 1997; Clemons et al., 2001) .

The 3 year and 5 year survival rate for second recurrence free survival was 61.9% and 54.2% respectively. However, due to the low sample size (17 from 42 who had disease progression) and shorter follow-up period for second recurrence, this might not be a true representation. The commonest site of second recurrence was distant recurrence, 15 of 17 patients occurred during the first 24 months after detection of initial LRR. Other studies have also demonstrated that more than half of the patients experience a second recurrence within 5 years after initial treatment of the first LRR (Kamby and Sengelov, 1999).

There were reports of better survival in patients with chest wall recurrences compared to other sites of recurrences (Toonkel et al., 1983). Recurrences in the supraclavicular fossa tend to have a poorer prognosis (Toonkel et al., 1983; Halverson et al., 1993). Those with concomitant chest wall and regional node involvement were also associated with a poor outcome (Halverson et al., 1993; Clemons et al., 2001). Multiple sites of recurrence and the size of the largest recurrence had also been reported to adversely affect the prognosis (Bedwinek et al., 1981). This data suggests that close follow up is warranted after initial treatment for LRR, even though development of a second recurrence would generally mean a poor prognosis for the patient.

In our study, Malay race, regional lymph node involvement, higher stage tumour, size > 5.0cm, margin involvement, and grade 3 tumours were identified on univariate analysis as significant prognostic factors for ILR. Neoadjuvant chemotherapy and chest wall radiotherapy were also found to be significant prognostic factors due to the fact that they involve higher staged patients. Thus, multivariate analysis by a Cox proportional-hazards model revealed that only Stage and Margins were the independent factors for ILR.

While surgical margin status has been generally assumed by many clinicians to be associated with higher risk for PMLRR, there has been no firm data to support this hypothesis. This is due to the inconsistent definition of a close or positive margin and inconsistent results from current available studies (Katz et al., 2000; Truong et al., 2004).

An earlier report by Mentzer et al., (1986) failed to correlate local recurrence with distance from deep surgical margins (Mentzer et al., 1986). Another study by Ahlborn et al., (1988) demonstrated a local recurrence rate of 6% for patients with tumour present within 5mm of the resection margin post mastectomy (Ahlborn et al., 1988). However, these earlier studies were limited by relatively short follow up time. A more recent report Freedman et al in 1998 reported a higher incidence of LRR in women aged 50 or younger with close or positive margins (≤ 5mm) (Freedman et al., 1998). Similarly, Truong at al in 2004 observed a higher rate of LRR was seen in younger patients with positive surgical margins (Truong et al., 2004).

Although our data support the importance of the status of surgical margins following mastectomy, our finding of positive margin as an adverse prognostic factor for PMLRR

is independent of patient age. Therefore, the presence of a positive margin of resection should be considered as an independent indicator for post mastectomy adjuvant radiotherapy. Planning of mastectomy incision and use of local flaps in the context of locally advanced breast cancer and neoadjuvant chemotherapy to improve status of surgical margins should be considered carefully when planning management of such patients. Consideration for re-excision may be made in selected cases, however not when deep surgical margins are involved. In this study none of the patients received surgical re-excision. Patients with involved margins (15.6%) (12/77) received boost of 10 Gy/5 fractions.

Previous published studies have found pathological T stage and number of involved lymph nodes were independent predictors of PMLRR. However, due to differing criteria in patient selection and treatment protocol, results have been varied. This occurred because the studies on LRR were retrospective single institution studies.

Our study demonstrated that larger tumour size and higher number of involved lymph nodes were associated with PMLRR as in previous studies but were not independent factors.

In this study, 4 or more positive lymph nodes were not found to be a significant prognostic factor on univariate analysis and multivariate analysis. Neither was it significant when stratified according to the 4-9, and 10 or more lymph nodes involved.

Extracapsular spread of axillary lymph nodes data were not routinely collected thus was not included in the analysis. Though it remains an important feature in the indications for axillary radiotherapy (Huang et al., 2005).

Stage of disease was identified as an independent prognostic factor for ILR on multivariate analysis. Katz et al reported that tumour of greater than 5 cm was an independent predictor of LRR (Katz et al., 2001). Another study by Jager et al found similar results to our current study (Jager et al., 1999). Their study demonstrated that T-stage and nodal status were independent factor associated with LRR. The study by Recht et al., (1999) in the Eastern Cooperative Oncology Group on 2016 patients also found tumour size as a prognostic factor for LRR. In a review of locoregionally recurrence breast cancer, Clemons et al., (2001) reported that only primary tumour size, stage and axillary node involvement have been consistently associated with PMLRR risk while other factors such as histology, grade, age, ER status, menopausal status and margins have only been variably associated with the risk of LRR. A higher disease stage at presentation should therefore be given more attention and comprehensive adjuvant therapy should be given to this group of high risk patients.

Grade 3 tumours were also associated with a higher risk of isolated PMLRR on univariate analysis. However, data from previous studies have been inconsistent. Wallgren et al reported that in pre- and postmenopausal women with node positive disease a higher tumour grade was associated with a significantly higher risk of LRR (Wallgren et al., 2003). This was not observed in node negative women. However, another study by Buchanan et al did not demonstrate any association between higher tumour grade and the risk of PMLRR (Buchanan CL et al., 2006).

Univariate analysis of treatment modalities (Table 4) showed a negative correlation with regional recurrence. This finding is most likely due to selection bias where 98.2% of the patients who were given neoadjuvant chemotherapy presented with Stage 3 which itself is an independent prognostic factor for ILR. While recent advancements in adjuvant chemotherapy have prolonged survival and quality of life, its role in preventing PMLRR is less clear.

Only 55 out of 122 Stage III patients received neoadjuvant chemotherapy, the rest received primary mastectomy. The reasons for low rates of neoadjuvant chemotherapy in this setting include effective palliation of fungating, bleeding and foul smelling breast lesions, patient choice and to prevent high default rates after neoadjuvant chemotherapy (Jager et al., 1999; Chong et al., 2009)

In-field radiotherapy recurrences occurred in 24/345 patients (6.96%) of those receiving radiotherapy in this study. Postmastectomy in-field recurrence ranged from 2.2% (Jager et al., 1999) to 4.2% (Killander et al., 2009). These patient populations were 58% and 67% node positive respectively, but these patient populations were not locally advanced breast cancer. In locally advanced breast cancer the ILR were 9% in irradiated patients (Huang et al., 2005). Thus the 7% in-field recurrence rate in our study was related to the severity of disease. Although randomised trials did not show superiority of neoadjuvant treatment in survival (Mamounas & Fisher, 2001), in the setting of locally advanced disease the benefit of clear margins is paramount. Other behavioural and aspects of treatment unique in our setting ie. high defaulter rates need to be addressed by other means besides surgery, hence neoadjuvant chemotherapy should be recommended in locally advanced cancer.

A major limitation of this study was its retrospective nature. A prospective complete data collection is warranted to enable us to understand better the natural course of this disease. Standardised pathological reporting especially with regards to margins and other pathological markers should be advocated. The clinical assessment of surgical incisions to ensure clear margins should be done, the use of local flaps and neoadjuvant therapy should be done judiciously. Clinical assessment and documentation of LRR should be standardised to enable future studies to be carried out with more accuracy. Standardised chemotherapy and radiotherapy may improve outcome, standardised institutional protocols can be drafted and patients' treatment can be tailored to an agreed consensus after taking into consideration the individual risks and benefits.

In conclusion, margin involvement and higher disease stage were identified to be independent prognostic factors for ILR. The ILR rate in this cohort of patients was 8.0% over a median follow up of 67 months. The overall PMLRR was 16.4%. The 10 year ILR free survival was 88.9%. PMLRR commonly occurred within the first 3 years post mastectomy. PMLRR is not always a sign of

heralding systemic disease. More than half of the patients with ILR did not develop subsequent distant recurrence. Close follow up of patients at higher risk of PMLRR and prompt treatment are recommended.

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