Original Research Article

Study of correlation of clinical outcome of with respect to various prognostic factors of loco-regional recurrences in breast cancer

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Abstract

Background: Management of primary breast cancer has changed considerably in the last decade, with establishment of new paradigms for Loco-Regional Therapy (LRT) as well as systemic treatment. **Objective:** To find correlation of clinical outcome with respect to various prognostic factors (hormone receptor status, Her2 status, grade of tumor, LVI). **Material and Methods:** The present prospective observational study was done at Tata Memorial Hospital, Mumbai and Advanced Center for Treatment and Education of Cancer, Navi Mumbai. A total of 100 consecutive patients of local/ regional/ Loco-regional recurrences and fulfilling the study inclusion criteria were invited to participate in this study. Statistical analysis was done using SPSS Statistics version 20.0. Survival period was defined as the period from the date of diagnosis to the development of recurrence or to the date of the last recorded clinical followup. **Results:** Disease free interval (DFI) before a LRR is a strong prognostic factor for overall survival and women with longer DFI have longer survival. Besides the DFI, age and surgical removal of the recurrence were significantly associated with survival after recurrence. **Conclusion:** The numerous prognostic factors affect survival after diagnosis of recurrence includes clinical stage at primary diagnosis, nodal positivity, presence of lymphovascular invasion and perinodal extension as well as site/s of recurrence.

Key Words: Correlation, prognostic, Loco-Regional Recurrences, Breast cancer.

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INTRODUCTION

The female breast has always been a symbol of beauty, fertility and feminity. In disease, however, it has challenged clinicians since antiquity. Story of breast cancer is told in the acts and artifacts of the human struggle against disease. Worldwide, breast cancer is the commonest type of cancer and the major cause of cancer-related mortality among women[1]. According to Global Cancer Statistics 1.15 million cases are diagnosed each year.[2] By 2020, 70% of the world's cancer cases will be in poor countries, with a fifth in India. The Indian Council of Medical Research(ICMR) released an analysis of cancer cases among women in 4 metro cities from 1982 to 2005, showing that until about 10 years ago,10 per 100 000 women got breast cancer, compared with 23 per 100 000 now. By 2020, breast cancer is said to overtake cervical cancer as the most common type of cancer among all women in India.[3] Management of primary breast cancer has changed considerably in the last decade,[4-7] with establishment of new paradigms for Loco-Regional Therapy (LRT) as well as systemic treatment. As a result, the breast cancer survival has improved considerably, thereby leading to a relative increase in the incidence of disease recurrence in the form of Loco-Regional Recurrence (LRR) especially in women with early breast cancer (EBC). Incidence of LRR after Breast Conservation Surgery (BCS) varies based on the receipt of adjuvant Loco-Regional as well as systemic therapy. For patients who had received Loco-Regional Radiotherapy (LRRT), incidence in EBC is in the range of 3%-5%[7]at 10 years

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after treatment and for those who did not receive LRRT incidence is approximately 35%[7-10]. For Locally Advanced Breast Cancer (LABC), the disease recurrence at distant sites is an equally important problem. The incidence of 5-year LRR for LABC has been reported in the range of 5%-8% post breast conservation and 7%-10% post mastectomy.[11]

OBJECTIVE: To find correlation of clinical outcome with respect to various prognostic factors (hormone receptor status, Her2 status, grade of tumor, LVI).

MATERIAL AND METHODS

The present prospective observational study was done during January 2015-January 2017 at Tata Memorial Hospital, Mumbai and Advanced Center for Treatment and Education of Cancer, Navi Mumbai. The Study has been registered for CTRI. (I.D.: REF/2015/12/010205) A total of 100 consecutive patients of local/ regional/ Loco-regional recurrences and fulfilling the study inclusion criteria were invited to participate in this study.

Inclusion Criteria: Age: ≥ 18 years. Known case of invasive breast carcinoma. Stage I – III (Operable breast cancer or Locally Advanced breast cancer) at initial presentation. All previous loco-regional treatment at Tata Memorial Center (TMC) with availability of full details of Loco-Regional treatment (Both Surgery and Radiotherapy). Presenting with untreated local or regional recurrence as the first event (with or without distant metastasis evident clinically or detected during work up).

Exclusion Criteria: Age < 18 years. At initial presentation, In situ carcinoma, phylloides, sarcoma or any histology other than invasive breast carcinoma. Male breast. Stage IV (distant metastasis) at initial presentation. Local or regional recurrence not confirmed or has been treated with any modality before enrolment in study. Not willing to give consent.

Women who agreed to participate and provided written consent were accrued in the study. For the consenting women, details of clinical, radiological and histopathological findings including ER, PR, HER2 status at initial diagnosis were recorded from the case file and available Electronic Medical Records (EMR). Details of surgery, radiotherapy and systemic therapy (for the re-treatment of LRR), its sequence and response were recorded. A local recurrence (LR) (defined as recurrence in residual breast tissue or thoracic wall), locoregional recurrence (RR) (defined as recurrence in the ipsilateral lymph drainage area or axillary/infraclavicular/supraclavicular area) and systemic recurrence (DR) (defined as all other forms of recurrence) along with the corresponding 18 months disease free survival and overall survival rates. Statistical analysis was done using SPSS Statistics version 20.0. Survival period was defined as the period from the date of diagnosis to the development of recurrence or to the date of the last recorded clinical follow up. All variables found on univariate analysis ($p < 0.05$) to affect survival were included in a multivariate model. Hazard ratios and 95 % confidence intervals (95 % CI) were calculated and validated using the Cox proportional hazards model. Statistical significance was defined as $p < 0.05$ test results. Survival analysis, using the Kaplan Meier method, was performed to evaluate the prognosis after local recurrence. End-points were overall survival, distant disease-free survival and survival without subsequent local recurrence, including local progression of disease. Survival curves were calculated from the date of salvage treatment of local recurrence or the date of the diagnosis of local recurrence when salvage treatment was not given. The following variables were analysed to assess their ability to predict distant recurrence-free survival: age at diagnosis of local recurrence; time interval from initial surgery to recurrence; mode of detection, location, size and histologic type of local recurrence; size, nodal status, histologic grade and microscopic margins of the original tumour; and presence of vascular invasion and extensive intraductal component (EIC) in the original tumour. Actuarial curves were compared by means of the two-tailed log-rank test. A multivariate analysis using the Cox proportional hazards model was performed to evaluate the independent predictive effect of the covariates. Hazard ratios (with 95% confidence intervals (95% CI) and P values) were estimated for each covariate in relation to the reference.

RESULTS

Table 1: Patient characteristics of primary disease at presentation

CHARACTERISTICS		Frequency	Percent
Menstrual status	Premenopausal	47	47
	Peri-menopausal	10	10
	Post menopausal	43	43
Laterality	Right	39	39
	Left	59	59
	Bilateral	2	2
Diagnosis	OBC	39	39
	LOBC	6	6
	LABC	55	55

Primaryquadrant	UOQ	25	25
	UIQ	6	6
	LIQ	4	4
	LOQ	3	3
	CQ	1	1
	More Than One Quadrant	61	61
Clinical T_size	cT1	10	10
	cT2	44	44
	cT3	30	30
	cT4	16	16
Clinical N_stage	N0	36	36
	N1	41	41
	N2	9	9
	N3	14	14

Table 2: List of prognostic factors of primary and recurrent disease affecting outcome

Factor	DFS	OS
Menopausal status at presentation	0.630	0.339
Menopausal status at recurrence	0.929	0.873
Laterality	0.378	0.056
Clinical stage	**0.003**	**0.000**
Quadrant	0.526	0.664
Clinical T stage	0.414	0.228
Clinical nodal stage	0.065	**0.034**
Response to therapy	**0.025**	**0.009**
Type of surgery	0.090	0.095
Pathologic tumor size	0.155	0.086
Grade	0.115	0.618
EIC	0.603	0.865
PNI	0.127	**0.038**
LVE	**0.024**	**0.004**
Pathologic node positive	**0.000**	**0.006**
Perinodal extension	**0.000**	**0.004**
Skin involvement	0.463	0.666
ER status (primary)	0.324	0.185
PR status (primary)	0.876	0.223
Her2neu (primary)	0.926	**0.052**
RT fractionation	0.781	0.102
Regional (SCF) RT	**0.033**	**0.010**
RT boost	**0.017**	**0.023**
Adjuvant HT	0.237	0.081
Site of recurrence (L/R/L+R)	**0.000**	**0.000**
ER status (recurrence)	0.959	0.237
PR status (recurrence)	0.849	0.373
Her2neu (recurrence)	0.773	0.182
Intent of treatment	**0.007**	**0.000**

DISCUSSION

This is prospective study of women with breast cancer who were optimally treated either at Tata Memorial Hospital (TMH) or outside centre for primary breast cancer and presented to TMH with recurrent disease. In this study we evaluated various risk factors affecting outcome in women who presented with clinically suspected local or loco-regional recurrence (with or without distant recurrence) in 100 consecutive women with a primary diagnosis of nonmetastatic breast cancer treated, preferably treated at TMH, Mumbai. The overall and disease-free survival was analyzed for different prognostic factors as shown in Table 2. It has been reported that disease free interval (DFI) before a LRR is a strong prognostic factor for overall survival and women with longer DFI have longer survival. Besides the DFI, age and surgical removal of the recurrence were significantly associated with survival after recurrence. DFI as a prognostic factor was reported by Annemieke *et al.*[13] After adding covariables in the multivariable analysis, length of the DFI before a LRR

remained of significant influence on survival after the LRR, which suggests that it is an independent prognostic factor. Patients with a short DFI and a LRR show on average less differentiated cells (grade III) and a larger primary tumour compared to the patients with medium and long DFIs, which suggests a more biological aggressive form of breast cancer. Moreover, short DFIs are significantly associated with subsequent distant metastases. Consistent with previous studies, good differentiation of the tumour cells (grade I, II), smaller tumour size, negative lymph nodes, positive hormone status, no axillary lymphnode dissection, radiotherapy and surgical removal of the recurrence have been identified to be associated with better survival. Both chemotherapy and hormone therapy are known to have a positive influence on survival after primary breast cancer. Yet after adding covariates in the proportional hazards models chemotherapy and hormone therapy was not of significant influence on survival after a LRR in the study by Annemieke *et al.* In the univariable analysis women who received chemotherapy or hormone therapy showed worse survival compared to those without recurrence of the breast cancer, possibly even during the adjuvant treatment period, might suggest resistance to the treatment. Of the total 100patients with a LRR, 69 patients not receive surgery for their recurrence. Typical reasons for withholding from surgical treatment include diffuse infiltration, inflammatory changes, subsequent DM, high age or patient preference. LRRs show differences in characteristics and prognosis and therefore need an individualized approach. In the current study, we showed that various clinic-pathological risk factors of the primary tumor such as clinical stage, clinical and pathological nodal status, lymphatic invasion and perineural invasion affected DFS as well as OS after re-treatment of the LRR. Amongst the initial treatment variables for the primary diagnosis, none of the surgical, radiation or systemic therapy related factors affected outcome after retreatment. Women who had received regional nodal irradiation primarily to the supraclavicular fossa had improved outcome. Similarly, RT boost to primary tumor bed also reduced the chance of LR. Similarly, patients presenting with only local or regional recurrence had better OS and DFS in comparison to those who had both. Women who are treated with curative intent had better OS and DFS in comparison with patients who are treated with palliative intent. The current study accrued women with LRR who were treated at variable time points. Overall, of all the consecutive 100 patients, about two third (60%) had concurrent distant metastases. Hence these were treated with palliative intent and rest was treated curatively. Not only has the site of the recurrence but its size and number also provided important information about the risk of developing distant disease. Patients with recurrences <1 cm had a lower distant recurrence risk compared to patients with local recurrences >1 cm.[13] Although this seems to point towards a potential benefit of early detection of local recurrence, it can also be explained by a different biological behaviour, associated with certain clinical and mammographic features that facilitate detection. In a study by Voogd *et al.*,[13] prognostic factors were almost similar for patients with a local recurrence within three years after diagnosis of the primary tumor and the group with a recurrence-free interval of more than three years, except for the axillary nodal status of the primary tumor that was the only important factor. Many studies have been performed to distinguish the local recurrences associated with a good or a poor prognosis and to identify risk factors for the development of distant metastases. The question is whether optimal loco-regional therapy is sufficient treatment or should it be followed by systemic treatment, depending on the risk for distant relapse. There is currently no good evidence that adjuvant systemic treatment is effective in patients with local recurrence. In a recent Cochrane systematic review of three randomized-controlled trials comparing systemic the rapy versus observation for women with loco-regional recurrence following mastectomy or breast-conserving treatment who did not have previous or synchronous distant metastases, provided insufficient evidence for an improvement in the overall survival.[14] However, when considering the available evidence for its effectiveness in primary breast cancer, adjuvant systemic (re-)treatment may be considered in patients with unfavourable prognostic factors. Local recurrence at or near the site of the original tumour, skin involvement, diffuse growth of recurrence, a short disease-free interval and an unfavourable initial tumour stage have been found to be predictors of a poorer prognosis in more than one study. Patients with a recurrence remote from the primary tumour appear to have a better prognosis than those with a recurrence at or near the site of the primary tumour. The most likely explanation for this finding is that the first group consists largely of new primary tumours, whereas the recurrences that are located at or near the site of the primary tumour are true recurrences, originating from tumour tissue not removed by the primary excision or radio-resistant clone. The distinction between a true recurrence and anew primary is not always a clear-cut case. In most studies, the diagnosis “new primary” was applied when the recurrence was located elsewhere in the breast, had a different histology.

CONCLUSION

Numerous prognostic factors affect survival after diagnosis of recurrence. These include clinical stage at primary diagnosis, nodal positivity, presence of

lymphovascular invasion and perinodal extension as well as site/s of recurrence. The risk of recurrence must be evaluated on an individual basis and the treatment plan must consist of multimodal therapy which takes the individual tumor biology into consideration. As these patients need a multi-modality management, decision regarding choice of treatment should be taken in a multi-disciplinary tumor board meeting, taking into account the previous locoregional and systemic treatment, expected risk of recurrence, clinical benefit and toxicity of retreatment.

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