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Clinicopathological Study of Locally Recurrent Breast Carcinoma with Special Reference to Resectability

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Abstract **Original Research Article**

The isolated local recurrence in a patient previously treated for early-stage invasive breast cancer presents a unique challenge to the oncologist. The main objectives of this study were to identify breast carcinoma patients who are prone to develop early recurrence, to study the feasibility of resection in case of locally recurrent breast carcinoma and determine the incidence of distant metastasis associated with locally recurrent breast carcinoma. The parameters namely age, previous clinical TNM staging, previous Histological grade, lymphovascular invasion, previous types of surgery, previous immunohistochemistry and previous chemoradiotherapy had shown very strong positive significance. There was significant association between previous findings of IHC and present findings of IHC (p=0.0087) but there was no significant association between clinical stage and resectability (p=0.95), between status of LVI and resectability (p=0.71) and between Histopathological Grade and resectability (p=0.43). Local recurrences after primary resection are seen to be mostly resectable with negative margin; however, whether it results in survival benefit can be studied in long term study.

Key words: Breast carcinoma, local recurrence, early recurrence, resectability.

INTRODUCTION

The isolated local recurrence in a patient previously treated for early-stage invasive breast cancer presents a unique challenge to the oncologist. The management of each patient requires a multidisciplinary approach that depends not only on factors specific to the recurrence itself but also on factors related to the original treatment. There is a paucity of clinical information, almost none prospective or randomized, to guide the clinician in choosing the optimal combination and sequence of surgery, radiation, and/or systemic therapy.

The clinical significance of an isolated local recurrence as a first event after treatment of early-stage invasive breast cancer, and its impact on survival, remains controversial. There is a strong association between local recurrence and the appearance of simultaneous or subsequent distant metastases. In many cases, local recurrence may be a manifestation of a more aggressive tumour biology that heralds the presence of distant metastases. Regardless of this association, durable local salvage is important in preventing the consequences of uncontrolled locoregional disease. However, if distant metastases are a common but not universal outcome after clinically isolated local recurrence, there may be a subgroup of patients for whom successful local salvage could result in long term disease-free survival or overall survival.

Approximately 10% to 15% of patients with stage I/II invasive breast cancer will develop a clinically isolated local recurrence. The standard management of an ipsilateral breast tumor recurrence following breast-conserving surgery and radiation is salvage mastectomy, while local excision and radiation are optimal treatment of a chest wall recurrence following initial mastectomy. Although there are few data regarding the efficacy of systemic therapy after isolated local relapse, chemotherapy and or hormonal therapy should be considered for most patients because of the high risk of subsequent distant relapse. However, local relapse does not always herald distant metastases. A prolonged interval between initial treatment and local recurrence is the most important prognostic factor for subsequent outcome, and when combined with other favourable characteristics, can predict 5-year survival rates of 70% or higher.

The incidence of local recurrence depends on multiple factors namely clinical (like young age, tumour size, gross multifocal or multicentric disease, genetic factors) and histopathological risk factors (like nodal status, extracapsular extension, margin status, extensive intraductal component, high-grade, lymphovascular invasion, oncogenes along with tumour suppressor genes, receptor status, previous adjuvant chemotherapy). It has been seen that overall survival after resection of local recurrence is improved.

MATERIAL AND METHODS

This was an institution-based, nonrandomized observational study conducted in Department of Surgery, Medical College, Kolkata, India from January 2016 to June 2017 (18 months). Informed consent was taken from all the patients. Sample size was 20 cases.

Inclusion Criteria: The following patients were included in the study population:

- Patients admitted at indoor, attended at out-patient department with recurrence of Breast Carcinoma lump at Breast Clinic, Department of General Surgery and Department of Radiotherapy, Medical College and Hospital Kolkata.

Exclusion Criteria: The following patients were excluded in the study population:

- Patients attended first time for resection.
- Patients already taking adjuvant therapy or neoadjuvant therapy after recurrence.
- Patients presented with local recurrence but do not have previous reports.

Thorough history and clinical examination of the selected patients were done. Previous investigations like routine blood investigations, histopathology, immunohistochemistry, bone scan and other suggestive reports were searched. The high-risk factors responsible for early recurrence were studied for their relevance.

After identification proper assessment for resectability of recurrent breast lump was done by clinical examination and relevant investigations. Any changes in receptor status of resected recurrent lump irrespective of whether the patients previously taken adjuvant chemotherapy, radiotherapy or not were looked for. Lastly assessment of incidence of distant metastasis with the help of whole-body scan in locally recurrent breast carcinoma was performed.

The main objectives of this study were

- To identify breast carcinoma patients who are prone to develop early recurrence in respect of risk factors with previous history obtained from the patient.
- To study the feasibility of resection in case of locally recurrent breast carcinoma and whether there is any change of receptor status to determine adjuvant therapy.
- The incidence of distant metastasis associated with locally recurrent breast carcinoma.

Statistical Analysis was performed with the help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC).

Descriptive statistical analyses were performed to calculate the means with corresponding standard deviations (s.d.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi-square (χ^2) test was performed to find the associations. In the cases where one of the cell frequencies were less than 5 corrected Chi-square (χ^2) was used to find the association between variables. $p<0.05$ was taken to be statistically significant.

RESULTS

A. Descriptive Statistics

I. Age Distribution

The mean age (mean ± s.d.) of the patients was 43.30±10.00 years with range 32 - 61 years and the median age was 40.5 years. Test of proportion showed that the proportion of the patients in the age group 30 - 45 years (60.0%) were significantly higher than other age groups ($Z= 2.82$; $p<0.001$).

II. Distribution of laterality of breast cancer

60.0% of the sites of breast cancer (BC) were in the left breast than that of right breast (40.0%) ($Z= 2.82$; $p<0.001$).

III. Distribution of Involved quadrant

Upper outer (50.0%) followed by lower outer (30.0%) were most common among the Involved quadrant than that of other quadrants ($Z= 2.88$; $p<0.001$). Only 1(5.0%) site was Lower Inner.

IV. Previous clinical TNM

Most of the previous TNM of the patients were between T2N1M0 and T3N1M0 (60.0%) ($Z=5.01$; $p<0.0001$). T3N1M0 constituted 30% followed by T2N0M0 (25%) and T2N1M0 (20%).

V. Distribution of clinical stage

85% of the cases were with Stage between IIA and IIIA (IIA & IIB – Both 30%, IIIA – 25%) ($Z= 9.89$; $p<0.001$). Only 15% of the patients were with Stage-I.

VI. Distribution of histopathogical grade

Most of the tumors were Grade-3 (65%) ($Z= 6.43$; $p<0.001$).

VII. Distribution of LVI

In 75% of the cases LVI (lymphovascular involvement) was positive than negative cases (25.0%) ($Z=7.07$; $p<0.001$).

VIII. Type of surgery underwent previously

MRM (65.0%) was the most common among the previous surgery (Z= 4.24; p<0.001). In rest of the cases (35.0%) BCS with axillary clearance done. All the cases were IDC (Infiltrating duct carcinoma).

IX. Findings of previous IHC

Table-1: Findings of previous IHC

Findings of Previous IHC	Number	%
ER-,PR-,HER-2-neu-	7	35.0%
ER-,PR-,HER-2-neu+	1	5.0%
ER-,PR+,HER-2-neu+	1	5.0%
ER+,PR-,HER-2-neu-	4	20.0%
ER+,PR+,HER-2-neu-	4	20.0%
ER+,PR+,HER-2-neu+	3	15.0%
Total	20	100.0%

Most of the cases were triple negative breast cancer (TNBC) (35.0%) (Z=2.37; p<0.05).

X. Previous Chemo-Radio Therapy

Previously most of the patients were treated with chemotherapy and radiotherapy (70.0%) (Z=5.65; p<0.0001).

XI. Distribution of interval period of recurrence after primary therapy

Table-2: Distribution of interval period of recurrence after primary therapy

Interval of recurrence (in months)	Number	%
<12	4	20.0%
12 - 24	5	25.0%
>24	11	55.0%
Total	20	100.0%

XII. Distribution of site of recurrence

80.0% of the site of occurrence on the previous incision line (Z=8.48; p<0.0001).

XIII. Distribution of type of recurrence

Nodular recurrence (85.0%) was significantly higher than that of DCWI (15.0%) (Z=9.89; p<0.0001). All the cases were IDC (Infiltrating duct carcinoma).

XIV. Findings of present IHC

Table-3: Findings of present IHC

Findings of present IHC	Number	%
ER-,PR-,HER-2-neu-	8	40.0%
ER-,PR-,HER-2-neu+	1	5.0%
ER-,PR+,HER-2-neu+	1	5.0%
ER+,PR-,HER-2-neu-	8	40.0%
ER+,PR+,HER-2-neu+	2	10.0%
Total	20	100.0%

Most of the cases were triple negative breast cancer (TNBC) (40.0%) and ER positive with HER-2-neu negative which was significant (Z=4.89; p<0.0001).

XV. Distant metastasis (by WBS) distribution

As per the findings of Whole-Body Scan most of the cases were free from distant metastasis (80.0%) (Z=8.48; p<0.0001).

XVI. Distribution of resectability and type of surgery they underwent

85.0% of the cases were resectable (Z=9.89, p<0.001). WLE (90.0%) was performed as re-surgery (Z=11.31; p<0.0001).

XVIII. Distribution of patients receiving chemotherapy and radiotherapy after resection

Only 35.0% of the patients required 2nd line chemotherapy and radiotherapy.

A. Inferential Statistics

I. Comparison of Previous findings of IHC and Present findings of IHC

Table-4: Comparison of Previous findings of IHC and Present findings of IHC

Previous findings of IHC	Present findings of IHC					TOTAL
	ER-,PR-,HER-2-neu-	ER-,PR-,HER-2-neu+	ER-,PR+,HER-2-neu+	ER+,PR-,HER-2-neu-	ER+,PR+,HER-2-neu+	
ER-,PR-,HER-2-neu-						
Row%	5	0	0	2	0	7
Col %	71.4	0.0	0.0	28.6	0.0	100.0
	62.5	0.0	0.0	25.0	0.0	35.0
ER-,PR-,HER-2-neu+						
Row %	1	0	0	0	0	1
Col %	100.0	0.0	0.0	0.0	0.0	100.0
	12.5	0.0	0.0	0.0	0.0	5.0
ER-,PR+,HER-2-neu+						
Row %	0	1	0	0	0	1
Col %	0.0	100.0	0.0	0.0	0.0	100.0
	0.0	100.0	0.0	0.0	0.0	5.0
ER+,PR-,HER-2-neu-						
Row %	1	0	0	3	0	4
Col %	25.0	0.0	0.0	75.0	0.0	100.0
	12.5	0.0	0.0	37.5	0.0	20.0
ER+,PR+,HER-2-neu-						
Row %	0	0	0	3	1	4
Col %	0.0	0.0	0.0	75.0	25.0	100.0
	0.0	0.0	0.0	37.5	50.0	20.0
ER+,PR+,HER-2-neu+						
Row %	1	0	1	0	1	3
Col %	33.3	0.0	33.3	0.0	33.3	100.0
	12.5	0.0	100.0	0.0	50.0	15.0
TOTAL	8	1	1	8	2	20
Row %	40.0	5.0	5.0	40.0	10.0	100.0
Col %	100.0	100.0	100.0	100.0	100.0	100.0

χ^2 =38.06; p=0.0087 S- Significant

Corrected Chi-square (χ^2) test showed that there was significant association between previous findings of IHC and present findings of IHC (p=0.0087).

However, out of the 7 cases of TNBC, 2(28.6%) cases were shifted from TNBC to ER+, PR-, and HER-2-neu-.

Out of the 4 cases of ER+,PR-,HER-2-neu-, 1(25.0%) case was shifted from ER+, PR-, HER-2-neu- to ER-,PR-, HER-2-neu- (TNBC).

Out of the 4 cases of ER+,PR+,HER-2-neu-, 1(25%). case was shifted from ER+,PR+,HER-2-neu- to ER+,PR+,HER-2-neu+.

Out of the 3 cases of ER+,PR+,HER-2-neu+, 1(33.3%) of cases were shifted from ER+,PR+,HER-2-neu+ to ER-,PR-,HER-2-neu- (TNBC) and another 1(33.3%) shifted to ER-,PR+,HER-2-neu+ .

II. Association between Clinical stage and resectability

χ^2 =0.65; p=0.95 NS- Not Significant

Corrected Chi-square (χ^2) test showed that there was no significant association between clinical stage and resectability (p=0.95). However, all the patients with Stage-I were resectable.

Table-5: Association between Clinical stage and resectability

Clinical stage	Resectable		TOTAL
	Yes	No	
IA	2	0	2
Row %	100.0	0.0	100.0
Col %	11.8	0.0	10.0
IB	1	0	1
Row %	100.0	0.0	100.0
Col %	5.9	0.0	5.0
IIA	5	1	6
Row %	83.3	16.7	100.0
Col %	29.4	33.3	30.0
IIB	5	1	6
Row %	83.3	16.7	100.0
Col %	29.4	33.3	30.0
IIIA	4	1	5
Row %	80.0	20.0	100.0
Col %	23.5	33.3	25.0
TOTAL	17	3	20
Row %	85.0	15.0	100.0
Col %	100.0	100.0	100.0

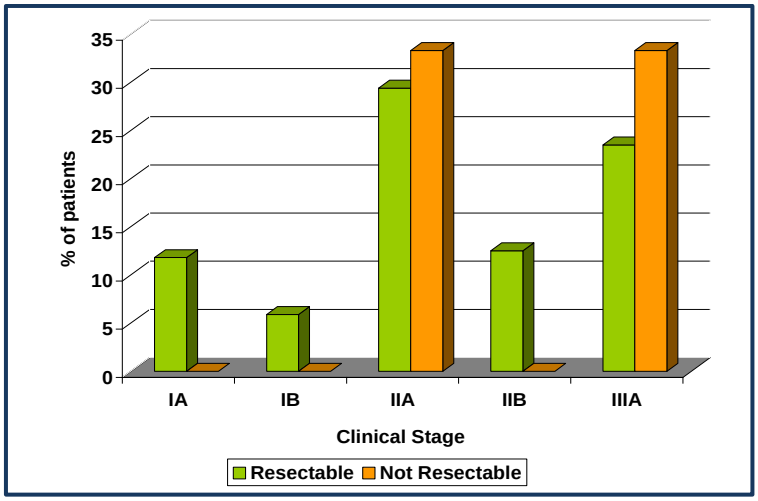

Chart-1: Association between Clinical stage and resectability

III. Association between status of LVI and resectability

χ^2 =0.13; p=0.71 NS- Not Significant

Corrected Chi-square (χ^2) test showed that there was no significant association between status of LVI and resectability (p=0.71). However, proportion of resectable cases was higher for LVI positive cases.

Table-6: Association between status of LVI and resectability

Status of LVI	Resectable		TOTAL
	Yes	No	
Positive	13	2	15
Row %	86.7	13.3	100.0
Col %	76.5	66.7	75.0
Negative	4	1	5
Row %	80.0	20.0	100.0
Col %	23.5	33.3	25.0
TOTAL	17	3	20
Row %	85.0	15.0	100.0
Col %	100.0	100.0	100.0

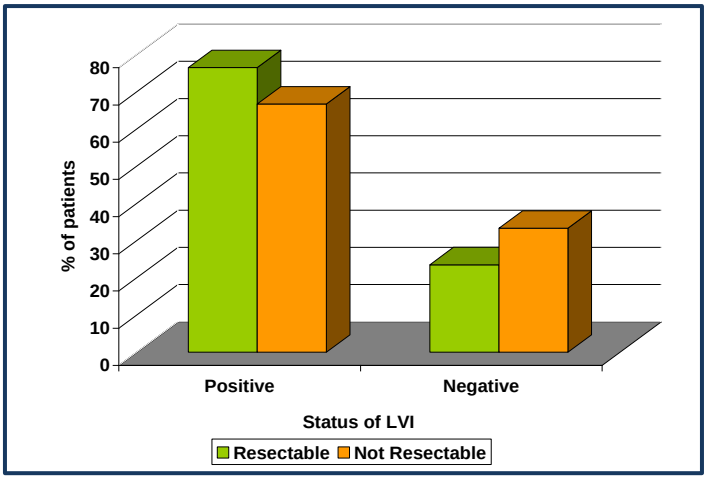

Chart-2: Association between status of LVI and resectability

IV. Association between Histopathological Grade and resectability

χ^2 =1.64; p=0.43 NS- Not Significant

Corrected Chi-square (χ^2) test showed that there was no significant association between Histopathological Grade and resectability (p=0.43). However, proportion of resectable cases was higher for Grade-III cases.

Table-7: Association between Histopathological Grade and resectability

Histopathological Grade	Resectable		TOTAL
	Yes	No	
I	2	1	3
Row %	66.7	33.3	100.0
Col %	11.8	33.3	15.0
II	3	1	4
Row %	75.0	25.0	100.0
Col %	17.6	33.3	20.0
III	12	1	13
Row %	92.3	7.7	100.0
Col %	70.6	33.3	65.0
TOTAL	17	3	20
Row %	85.0	15.0	100.0
Col %	100.0	100.0	100.

DISCUSSION

In our study, the median age in our study was 40.5 years, mean age 40.30 years, standard deviation of 10 years with the range of 32-61 years. Maximum cases i.e. 12 (60 %) were in the age group of 30-45 years. Test of proportion showed that the proportion of the patients in the age group 30 - 45 years (60.0%) were significantly higher than other age group (Z= 2.82; p<0.001). In India, the average age of the high-risk group is 43-46 years (mean in our study was 51 years) unlike in the west, where women aged 53-57 years are more prone to breast cancer [1]. Age groups of 35 years or less and 40 years or less have been associated with an increased risk of locoregional recurrence after mastectomy [1-3]. Lewis and Reinhoff reported a crude local recurrence rate of 67% for patients aged 20 to 29 years and 41% for patients aged 30 to 39 years in an early radical mastectomy series, whereas in women aged ≥ 40 years, local failure rates were 21% to 25% [1]. In another radical mastectomy series, Donegan et al. observed a similar crude failure rate of 67% for ages 20 to 29 years and 46% for ages 20 to 39 years, compared with <25% for those ≥ 40 years of age [2].

In our study, 16 patients were Hindu (80%) and 4 patients were Muslims (20%). Proportion of Hindu (80.0%) was significantly higher than that of Muslim (20.0%) (Z= 8.48; p<0.001).

In our study, 12 patients (60%) had left sided and 8 patients (40%) had right sided breast cancer. 60.0% of the sites of breast cancer (BC) were in the left breast than that of right breast (40.0%) (Z= 2.82; p<0.001). Many studies have shown that unilateral Breast cancer is more frequent in the left breast than in the right [4]. 50% patients (n=10) had cancer in upper outer (UO) quadrant of breast followed by lower outer (30.0%) were most common among the involved quadrant than that of other quadrants (Z= 2.88; p<0.001). Only 1(5.0%) site was Lower Inner which is consistent with previous studies [5].

Previous TNM of patients showed that T3N1M0 constituted 30% followed by T2N0M0 (25%) and T2N1M0 (20%). 85% of the cases were with Stage between IIA and IIIA (IIA & IIB – Both 30%, IIIA – 25%) (Z= 9.89; p<0.001). Patients with tumors ≥ 5 cm have a 25% or higher risk of isolated locoregional recurrence after mastectomy with or without adjuvant systemic therapy [1, 2, 6-12]. Tumors <5 cm are not associated with an increased risk of chest wall recurrence, and there is no significant distinction between T1 or T2 tumors in most studies [6, 7, 13, 14]. Most of the tumors were Grade-3 (65%) (Z= 6.43; p<0.001). High histological grade has been associated with an increased risk of locoregional recurrence after mastectomy in some series [15, 16].

In this study, LVI is positive (75%) in 15 patients out of 20 and LVI is negative (25%) in 5 patients out of 20 which is significant (Z=7.07; p<0.001). According to literature, in the aforementioned series of mastectomies for T1-2 tumors investigated by O'Rourke et al there was a 36% risk of chest wall recurrence with lymphovascular invasion, compared to a 19% risk without lymphovascular invasion [16]. MRM (65.0%) was the most common among the previous surgeries (Z= 4.24; p<0.001) followed by BCS+ Axillary clearance. All the cases were IDC (Infiltrating duct carcinoma).

In this study, most of the cases (7 out of 20) were triple negative breast cancer (TNBC) (35.0%) (Z=2.37; p<0.05). According to literature, Negative ER status, alone or in combination with negative progesterone receptors, has been associated with an increased risk of chest wall recurrence after mastectomy [6-8, 17]. Previously most of the patients were treated with chemotherapy and radiotherapy (70.0%) (Z=5.65; p<0.0001). According to Bonadonna et al. no significant difference (15% vs 13%) was found in the rate of locoregional recurrence as a first event, with or without chemotherapy [18]. However, as per Fisher *et al.* adjuvant systemic chemotherapy has been associated with a modest decrease in the risk of chest wall recurrence after mastectomy [19].

In this study, the mean duration of recurrence (mean ± s.d.) of the patients was 42.15±31.93 months with range 6 - 108 months and the median was 36 months. Most of the duration of recurrence was more than 24 months (55.0%) were significantly higher (Z= 4.33; p<0.001). Usually it takes 2 to 3 years for local recurrence as median time after mastectomy [13, 20-22]. The median interval to IBTR is 3 to 4 years after breast-conserving surgery and radiation [13, 23, 24], but this may be significantly prolonged after chemotherapy and/or tamoxifen therapy up to 5 to 7 years [25].

In this study, 80.0% of the sites of occurrence were on the previous incision line (Z=8.48; p<0.0001 and nodular recurrence (85.0%) was significantly higher than that of DCWI (15.0%) (Z=9.89; p<0.0001). The exact location of chest wall recurrence has not been specified in most of the literature, but it has been noted that involvement of mastectomy scar vary as low as 23% to a high of 70% cases [26]. The recurrence occurs in the same quadrant as the original primary tumor in approximately 50% to 90% of cases [27].

Regarding change in immunohistochemistry after previous chemoradiotherapy, out of the 7 cases of TNBC 2(28.6%) of the cases were shifted from TNBC to ER+, PR-, HER-2-neu-. Out of the 4 cases of ER+, PR-, HER-2-neu- 1(25.0%) of the cases were shifted from ER+, PR-, HER-2-neu- to ER-, PR-, HER-2-neu- (TNBC). Conversion from negative to positive may herald administration or continuation of Hormonal therapy in case of ER and PR cases. Conversion from positive to negative may herald discontinuation of Hormonal therapy in case of ER and PR cases.

As per the findings of Whole-Body Scan most of the cases were free from distant metastasis (80.0%) (Z=8.48; p<0.0001). Literature review shows that approximately 75% of patients present with an isolated recurrence in the breast only, 5% to 15% present with a clinically positive simultaneous regional nodal recurrence, and 5% to 15% present with simultaneous breast and distant metastases [27]. In this study, 85.0% of the cases were resectable (Z=9.89, p<0.001) and WLE was performed in 90% cases as re-surgery (Z=11.31; p<0.0001). Wide excision alone has been associated with a second local recurrence in over 60% to 70% of patients, despite its use in a more favorable group of patients with smaller tumor sizes and solitary nodules, compared to patients typically managed with surgery and radiation or radiation alone [28-30].

In our study, only 35.0% of the patients required 2nd line chemotherapy and radiotherapy. Elective irradiation of a clinically uninvolved axillary or internal mammary node region is not necessary [8]. The response rate to salvage chest wall irradiation after less than an excisional biopsy is high (73% to 96%), but approximately 60% to 70% will subsequently experience a second local failure [35, 8, 36, 8]. Systemic chemotherapy should be considered for most patients following treatment of a clinically isolated chest wall recurrence [30-33].

Corrected Chi-square (χ^2) tests were performed which showed several findings. There was significant association between Previous findings of IHC and Present findings of IHC (p=0.0087). But there was no significant association between clinical stage and resectability (p=0.95). However, all the patients with Stage-I were resectable. There was no significant association between status of LVI and resectability (p=0.71). However, proportion of resectable cases was higher for LVI positive cases. That there was no significant association between Histopathological Grade

and resectability (p=0.43). However, proportion of resectable cases was higher for Grade-III cases.

CONCLUSION

This study was conducted with the objective to identify breast carcinoma patients who are prone to develop early recurrence considering the risk factors with previous history obtained from the patients; to study the feasibility of resection in cases of locally recurrent breast carcinoma; any change of receptor status to determine the adjuvant therapy and to study the incidence of distant metastasis associated with the locally recurrent breast carcinoma. The parameters namely age, previous clinical TNM staging, previous Histological grade, lymphovascular invasion, previous types of surgery, previous immunohistochemistry and previous chemoradiotherapy had shown very strong positive significance. Other parameters that had shown positive significance are laterality, involved quadrant, types of surgery underwent previously, interval period of recurrence, site of recurrence and type of recurrence.

Larger portion of patients presented with local recurrence were resectable lump, main surgery offered to the recurrent patient were wide local excision. Significant number of patients showed change in immunohistochemistry after previous chemoradiotherapy. Significant number of patients who presented with local recurrence had distant metastasis determined by whole-body scan and 85% of patients had resectable lump. Significant number of patients did not need any treatment after resection of recurrent lump without distant metastasis that was determined by negative margin in excisional biopsy of recurrent lump and whole-body scan. All the patients with distant metastasis and small portion of patients without metastasis needed 2nd time chemoradiation after resection of recurrent lump.

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