Retrospective Study of Prognostics Factors in Operated Breast Cancer Patients in the Western Indian Population

Dr. Shilpa L. Chudasama[1], Dr Taher Gandhi[2], Dr Mihir Joshi[3], Dr Ajith P.[4]

[1]Associate Professor, Department of Radiodiagnosis, Shri M P Shah Medical College, Jamnagar, Gujarat
Email: *shilpadoppler[at]gmail.com*

[2]Senior Resident, Department of Radiodiagnosis, Shri M P Shah Medical College, Jamnagar, Gujarat
Email: *gandhitaher27[at]gmail.com*

[3]Resident, Department of Radiodiagnosis, Shri M P Shah Medical College, Jamnagar, Gujarat
Email: *mihirace.joshi[at]gmail.com*

[4]Resident, Department of Radiodiagnosis, Shri M P Shah Medical College, Jamnagar, Gujarat
Email: *ajithp073[at]gmail.com*

Abstract: *Breast cancer is among the most prevalent and growing malignant diseases among Indian women in the past three decades. This disease affects all physical, mental, and social aspects of women's life. On the other hand, such as social and mental support during the illness can reduce the damage. This study investigates different factors and their association with recurrence in the form of locoregional and distant metastasis in operated cases of primary invasive breast carcinoma. Prognostic factors for the risk of breast cancer and subsequent recurrences or distant metastases (DM) breast cancer recurrence are well known. As current follow - up is still consensus - based, more information on the patterns and predictors of subsequent recurrences can inform more personalized follow - up decisions. [1]. Methods: Women diagnosed with invasive ductal breast cancer who were operated on with modified radical mastectomy (MRM) with curative intent were selected from the G. G. Hospital registry (N = 106). A retrospective study was undertaken to assess their likeliness of association with subsequent recurrences after MRM. Patients treated with lumpectomy, radical mastectomy, and other histopathological variants like lobular carcinoma, and medullary carcinoma were excluded from this study. Results: The risk of first recurrence was highest during the first - year post - diagnosis (39 percent). Out of 26 symptomatic patients, 20 patients were found positive for recurrence on CT follow - up scans. The rate of recurrence is found to be slightly higher in patients of the non completion group as compared to those that completed their chemotherapy cycles and statistically insignificant (p value=0.233). And patients of age less than 50 were found to have a higher association for the recurrence but statistically insignificant (parietal - value: 0.96). The majority of the patients were ER +, PR +, and Her 2 - ve with equal recurrence rates. Triple - negative patients showed higher rates of recurrence with an Odds ratio: of 4.7 and statistical significance (P value: 0.03). Conclusions: Higher recurrence rates in the first two years post – surgery suggest more intensive follow - up and better modalities needed for early detection subsequent to primary treatment especially during the first 2 years. Most variables like IHC markers, age groups (age less than 50 or more than 50), and treatment completion known in various literature as established prognostic factors were found to be of no statistical significance (except for the data on the relation of triple - negative status emphasizing on its role as a poor prognostic marker) possibly due to cultural difference, literature deficiency and difficulty in accessing timely health care services in our region.*

Keywords: Breast cancer, breast cancer risk factors, post - operative recurrence breast cancer, Breast cancer prognosis, breast cancer follow - up

1. Introduction

Breast cancer is the commonest malignancy among women globally. [2] From being fourth on the list of most common cancers in India during the 1990s, it has now become the first. [3]

As a result of early detection and improved treatment survival after breast cancer has improved significantly. Consequently, an increasing number of women are in need of follow - up care after curative treatment. [4] The main aim of follow - up is the early detection of recurrences and second primary tumors.

Follow - up schedules vary internationally. Guidelines issued by the American Society of Clinical Oncology in 1999 recommend monthly breast self - examination, annual mammography of the preserved and contralateral breasts, and a history and physical examination every three to six months for three years, then every six to 12 months for two years, then annually. [5]

Routine follow - up protocols in use today are based on two hypotheses:
1) That most recurrences are detected at anearlier stage through follow - up and
2) That the earlier treatment of recurrences offers a better chance of cure, longer survival, or improvement in quality of life.

Although many risk factors have been associated with the possible disease initiation and progression, nothing concrete is established that can potentially prevent the primary disease or its progression and metastases.

Additionally, there are well - studied disparities in breast cancer that include socioeconomic disparities as well as racial disparities. All this information seems to suggest that no two women have equal chances of developing the disease. Even when comparing breast cancer patients, there are not very reliable predictors of aggressiveness. [6]

When analyzing the presentation of recurrent breast cancer, a distinction has been made between loco regional and metastatic disease. [7]

Metastatic disease is incurable, and it has been demonstrated that no survival advantage is gained from diagnosing it at an asymptomatic stage by means of routine investigations.

Whether early detection of loco regional recurrence leads to a survival benefit, however, is still controversial, with the current evidence suggesting that early detection and treatment of asymptomatic loco regional recurrence has no benefit to overall survival compared with the treatment of symptomatic recurrence. [8 - 11]

2. Materials and Methods

We conducted a retrospective study of 106 patientswho attended G. G. Hospital OPD with a diagnosis of primary invasive breast cancer.

Ethical approval to conduct the study was obtained from thehospital ethics committee, and the study was conducted with due attention to patient confidentiality

Women with primary invasive breast cancer diagnosed in G. G. Hospital in 2021 were included. Eligibility criteria were invasive breast cancer, no previous
or synchronous cancer, modified radical mastectomy, and chemotherapy in a G. G. hospital. Patients with macroscopic residue after surgical treatment or microscopic residue, patients treated with lumpectomy, radical mastectomy, and other histopathological variants like lobular carcinoma, and medullary carcinoma were excluded from this study.

Gold standards to diagnose relapse includes CT findings of distant metastasis or regional lesions. However, histopathological confirmation was not done for all patients.

Chief symptomology and history were taken via an online form and case files of patients reporting for follow - up scans.

Variables Tested
Variables were selected based on the literature and availability of the data. Estrogen receptor (ER), Progesterone receptor (PR), and Her2neu status were described as (ER / PR positive, ER/ PR negative, and Her2neu). Ageat diagnosis of the primary tumor as<50 years and > 50 years), treatment status (completed chemotherapy course and not opting for chemotherapy, immunohistochemistry status [(E+, P+, HER+), (E+, P+, HER - ve), (E - ve, P - , HER - ve) and others] were recorded and analyzed.

3. Observation

Recurrence occurred in 56out of 106 patients, of which many (46%) took complete their chemotherapy course as per existing hospital protocols.

Table 1: Distribution of age in patients with and without recurrence

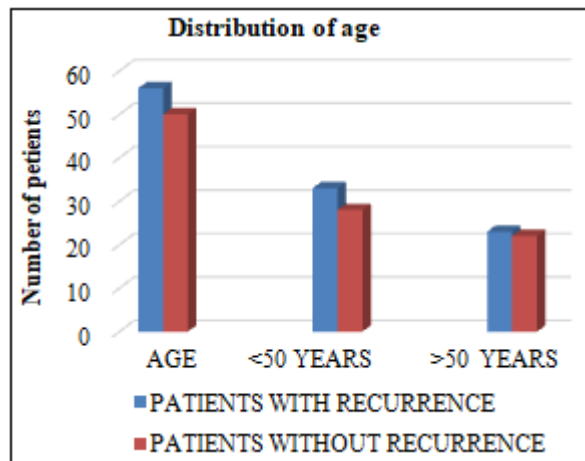| Age	Patients with recurrence	Patients without recurrence
<50 Years	33	28
>50 Years	23	22

Figure 1: Distribution of age in patients with and without recurrence

The odds of occurrence of relapse in patients with age less than 50 years is 1.12 times more than the odds of occurrence of relapse with age more than 50. An ageless than 50 years might have a higher risk of recurrence. However, the data on the relation between age and relapse rate is not found to be statistically significant in our study. (P=0.962, OR = 1.273)

Table 2: Distribution of IHC markers in patients with and without recurrence

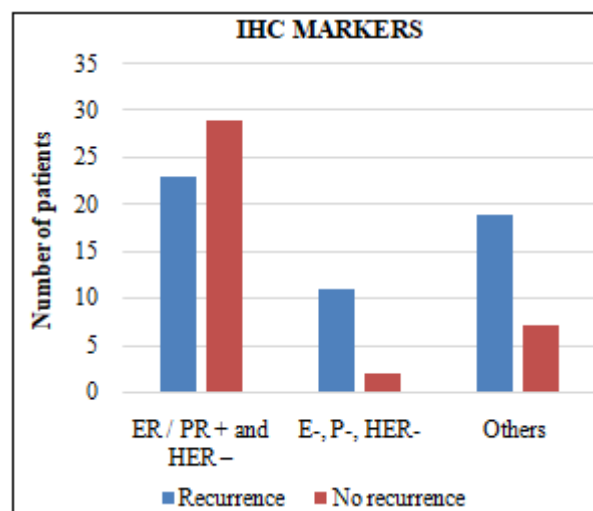|	Recurrence	No recurrence
ER / PR + and HER –	23	29
E - , P - , HER -	11	2
Others	19	7

Figure 2: Distribution of IHC markers in patients with and without recurrence

Out of 106 patients, immunohistochemistry data was available for 89 patients out of which most patients (52) were ER +, PR +, and Her 2 - ve with equal results in recurrence rates. There were higher rates of recurrence in triple - negative patients. (Odds ratio: 4.7, P value: 0.03)

Pointing towards the role of triple - negative status as a poor prognostic marker.

There was a higher rate of recurrence in patients with other IHC statuses but due to limited patient data, no significant conclusion can be made.

Table 3: Data representing time period of recurrence post MRM.

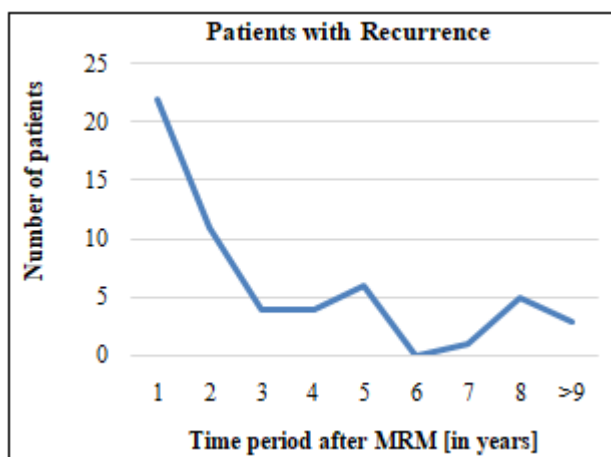| Interval Year	Patients with Recurrence
1	22
2	11
3	4
4	4
5	6
6	-
7	1
8	5
>9	3

Figure 3: Data representing time period of recurrence post MRM.

22 out of 56 patients were found to have a recurrence in the first year of follow - up (39.3 percent), 11 out of 56 in the second year (19.6 percent), and 3 out of 56 after 9 years of follow - up (5 percent).

Table 4: Data representing recurrence and parity

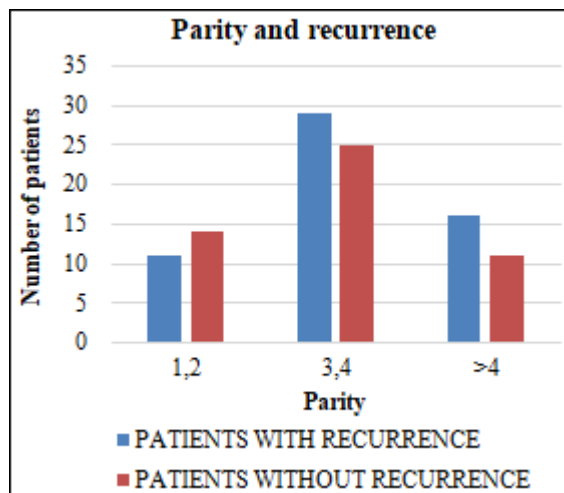| Parity	Patients With Recurrence	Patients Without Recurrence
1, 2	11	14
3, 4	29	25
>4	16	11

Figure 4: Data representing parity and recurrence

Recurrence occurred in 56 out of 106 patients, of which most were multiparous. The same distribution was noted in patients without recurrence suggesting no significant relationship between them. It rather indicates poor population control.

Table 5: Years of breastfeeding and recurrence

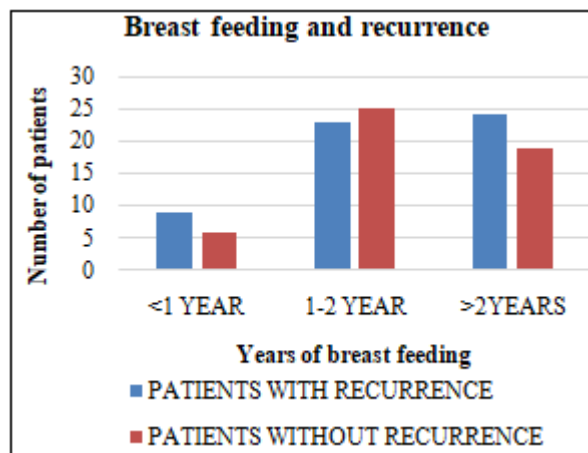| Breastfeeding	Patients with Recurrence	Patients without Recurrence
<1 Year	9	6
1 - 2 Year	23	25
>2years	24	19

Figure 5: Years of breastfeeding and recurrence

Recurrence occurred in 56 out of 106 patients, of which most were feeding for duration of more than 1 year The same distribution was noted in patients without recurrence suggesting no significant relationship between them.

Table 6: Distribution of patients' treatment status in patients with and without recurrence

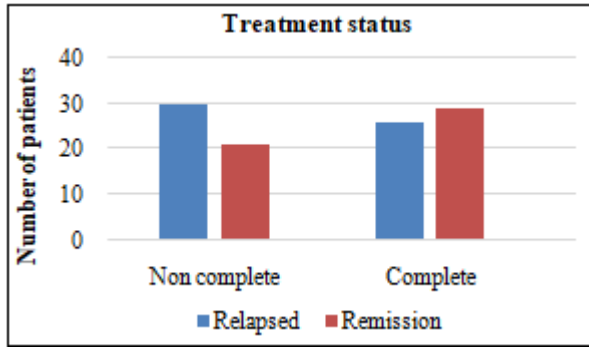| Treatment	Relapsed	Remission
Non complete	30	21
Complete	26	29

Figure 6: Distribution of patients' treatment status in patients with and without recurrence

Recurrence occurred in 56 out of 106 patients, out of which almost equal proportion of patients decided to opt out of chemotherapy. The odds of occurrence of relapse in the treatment non completion group is 1.69 times greater than the treatment completion group. (OR = 1.69) But after applying the chi - square test of independence it was shown that there was no significant association between treatment non - completion and relapse, $X2$ ($N = 106$) =1.4, $p = 0.23$.

Table 7: Distribution of patients' symptoms and their radiological findings

Symptom	No of patients	C T Finding
Anterior chest wall swelling and pain	8	Local recurrence (6), infective etiology (1), NAD (2)
Speech abnormalities, tingling sensation	1	Mets's brain
Globus sensation	1	NAD
Axillary Swelling	1	AXILLARY METS
Lower Back Pain	7	SKELETAL METS (6), NAD (1)
Upper Abdominal Pain	5	LIVER METS (3), NAD (2)
Neck Swelling	1	CERVICAL METS (1)
Headache	2	BRAIN METS
Follow up	80	Mets (36), NAD

Among patients presenting with no complaints, 35 were found to have recurrence and 39 had successful remissions (52 percent), meanwhile those with symptoms (total of 26), 6 patients had no evidence of recurrences (33 percent) undermining the role of symptoms as a predictor marker of recurrence as compared to routine follow - up. Nonetheless, their role is still of utmost importance

4. Discussion

The pattern of recurrence was mostly found to be dominated by distant metastasis, which is in line with other studies.

In our study, recurrences were higher in the first year followed by a decreasing trend. In a study done by Howell et al and Saphner Temporal et. al, recurrence was highest during the interval of 1 to 2 years in patients post - surgery, which matches with our study findings [12, 13, 14, 3]

We found the odds of occurrence of relapse in patients with age less than 50 years is 1.12 times more than the odds of occurrence of relapse with age more than 50 but found to be statistically non significant. In a study done by Brandt et. a, poor prognosis was found in patients younger than 40 years

and over 80 years. [15] There is a discrepancy between our studies possibly due to prolonged lead time in patients with easily treatable breast carcinoma resulting in almost similar prognoses irrespective of age.

In our study, the majority of patients were E+, P+, and Her - ve with almost the same rates of recurrence. However, the odds of recurrence were higher in triple - negative patients and were found statistically significant. In a study done by Brewster AM et. al. for patients not taking hormone replacement therapy, no statistically significant association between recurrence risk and receptor status was found. [16]. This was comparable to our study findings indicating no major prognostic value of IHC status in resource - poor settings.

In a study done by Lee et al, recurrence was found higher in patients with triple - negative and Her 2 positive status which was found comparable to our study. [17]

No significant conclusion can be made from other IHC types due to a limited number of patients.

Recurrence occurred in 56 out of 106 patients among which almost half had not completed their treatment. For those who had completed their chemotherapy course, slightly less chance of recurrences was found. The odds of occurrence of relapse in the treatment non completion group is 1.69 times greater than the treatment completion group and statically non significant. (P value: 0.23).

Most of the variables that were tested for their role in the recurrence of operated cases of breast carcinoma were found to be statistically non - significant.

However, the relation between triple - negative IHC status and higher recurrence was found to be statistically significant.

Apart from the usual risk factors of incidence of breast cancer which may play a role in the recurrence in operated cases of breast carcinoma, there exist socio - economic as well as racial disparities, especially in a heavily populated diversified country like India.

After analyzing 106 patients' history and presentation post - procedure it has been observed that there is no single specific factor that would contribute to recurrence but rather multiple interlinked factors which in turn depend largely on the patient's socio - economic and cultural background.

Most patients had metastasis on their CT reports suggesting the need for better modalities of follow - up. reasons for not completing their intended treatment were medicine side - effects most common of which were constant nausea and weakness, financial constraints on traveling, choosing alternate medicines over chemotherapy

Moving Forward
In a resource - poor country like ours, it is difficult to ensure timely screening practices, routine follow - ups, and mammograms for every patient.

A major widespread challenge in India is the paucity of skilled/ trained cancer screening manpower and adequate healthcare infrastructure. The country lacks enough qualified radiologists, pathologists, technicians, nurses, and auxiliary healthcare workers for organized breast cancer screening programs. The availability of facilities and infrastructure (mammography equipment, treatment facilities, information systems, data, and recording keeping) for cancer screening is highly limited in India and unable to meet the excess demand for services from a screening program.

Along with economic constraints, social perception of routine self - breast examination, stigma related to chemotherapy, and inability to deal with psychological barriers cancer patients deal with the need to be handled with care and sensitivity.

Hence, a country like India should focus on promoting early clinical diagnosis through breast awareness, BSE and CBE, diagnostic imaging with mammography with or without ultrasonography, fine needle aspiration cytology (FNAC), and /or biopsy linked with prompt and adequate treatment. This approach is called 'triple diagnosis' or 'triple assessment' and includes a physical examination, imaging (diagnostic mammography and/or ultrasonography) and biopsy (FNAC or core/excisional biopsy) is more accurate (around 99% accuracy) than any single modality for early diagnosis. The existing healthcare infrastructure needs to be further strengthened in a phased manner to meet the demand for triple assessment for early diagnosis. Conducting awareness campaigns is the right approach to educating the masses on breast cancer and other cancers and their prevention.

Since the backbone of health care is the primary level, follow - up on breast cancer patients should not be restricted to tertiary care hospitals and the need to decentralize and incentivize general care practitioners at the rural village level should be considered.

References

[1] Geurts, Y. M., Witteveen, A., Bretveld, R. *et al.* Patterns and predictors of first and subsequent recurrence in women with early breast cancer. *Breast Cancer Res Treat* **165**, 709–720 (2017). https: //doi. org/10.1007/s10549 - 017 - 4340 - 3

[2] Schapira DV. Breast cancer surveillance—a cost - effective strategy. Breast Cancer Res Treat 1993; 25: 107–11.

[3] Mehrotra R, Yadav K, et al Breast cancer in India: Present scenario and the challenges ahead. World J Clin Oncol.2022 Mar 24; 13 (3): 209 - 218. doi: 10.5306/wjco. v13. i3.209. PMID: 35433294; PMCID: PMC8966510.

[4] van Laar C, van der Sangen MJC, Poortmans PMP et al (2013) Local recurrence following breast - conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population - based cohort of 1143 patients. Eur J Cancer. doi: 10.1016/j. ejca.2013.05.030

[5] Hiramanek N. Breast cancer recurrence: follow up after treatment for primary breast cancer. Postgrad Med J.2004 Mar; 80 (941): 172 - 6. doi: 10.1136/pgmj.2003.010728. PMID: 15016942; PMCID: PMC1742945.

[6] Geurts YM, Witteveen A, Bretveld R, Poortmans PM, Sonke GS, Strobbe LJA, Siesling S. Patterns and predictors of first and subsequent recurrence in women with early breast cancer. Breast Cancer Res Treat.2017 Oct; 165 (3): 709 - 720. doi: 10.1007/s10549 - 017 - 4340 - 3. Epub 2017 Jul 4. PMID: 28677011; PMCID: PMC5602040.

[7] Donnelly J, Mack P, Donaldson LA. Follow up of breast cancer: time for a new approach? Int J Clin Pract2001; 55: 431–3

[8] Churn M, Kelly V. Outpatient follow - up after treatment for early breast cancer: updated results after 5 years. Clin Oncol 2001; 13: 187–94.

[9] Tomin R, Donegan WL. Screening for recurrent breast cancer—its effectiveness and prognostic value. J Clin Oncol 1987; 5: 62–7.

[10] Dewar A, Kerr GR. Value of routine follow - up of women treated for early carcinoma of the breast. BMJ 1985; 291: 1464–7.

[11] Clemons M, Danson S, Hamilton T, et al. Locoregionally recurrent breast cancer: incidence, risk factors and survival. Cancer Treat Rev 2001; 27: 67–82

[12] Howell A. An early peak of relapse after surgery for breast cancer. Breast Cancer Res.2004; 6 (6): 255 - 7. doi: 10.1186/bcr946. Epub 2004 Oct 11. PMID: 15535855; PMCID: PMC1064089.

[13] Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol.1996 Oct; 14 (10): 2738 - 46. doi: 10.1200/JCO.1996.14.10.2738. PMID: 8874335.

[14] Mansell J, Monypenny IJ, Skene AI, et al. Patterns and predictors of early recurrence in postmenopausal women with estrogen receptor - positive early breast cancer. Breast Cancer Res Treat.2009; 117: 91–98. doi: 10.1007/s10549 - 008 - 0291 - z. [PubMed] [CrossRef] [Google Scholar]

[15] Brandt, J., Garne, J. P., Tengrup, I. et al. Age at diagnosis in relation to survival following breast cancer: a cohort study. World J SurgOnc 13, 33 (2015). https: //doi. org/10.1186/s12957 - 014 - 0429 - x

[16] Brewster AM, Do KA, Thompson PA, Hahn KM, Sahin AA, Cao Y, Stewart MM, Murray JL, Hortobagyi GN, Bondy ML. Relationship between epidemiologic risk factors and breast cancer recurrence. J Clin Oncol.2007 Oct 1; 25 (28): 4438 - 44. doi: 10.1200/JCO.2007.10.6815. Epub 2007 Sep 4. PMID: 17785707; PMCID: PMC6559726.

[17] Lee, Y., Kang, E., Lee, A. S. *et al.* Outcomes and recurrence patterns according to breast cancer subtypes in Korean women. *Breast Cancer Res Treat* **151**, 183–190 (2015). https: //doi. org/10.1007/s10549 - 015 - 3390 - 7