# Histomorphologic Prognostic Factors in Invasive Breast Carcinoma-NST Affecting Loco-Regional Recurrence

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## ABSTRACT

**Background:** Breast carcinoma is one of the important and leading cause of mortality and morbidity in women. Locally advanced breast cancer constitutes more than 50-70% of the patients presenting for treatment in India.[1] Due to heterogeneous nature of the disease multi disciplinary approach is required to treat the disease. Numerous histopathological prognostic factors have been identified which helps in exploring the nature of disease and finding the probability of loco-regional recurrence.

**Material:** In current study all post operative MRM specimens 8 years retrospective ad 2 years prospective were included which came out to be IBC-NST. Detailed gross and histomorphological prognostics factors were studied and documented. Patients were followed up and were examined for loco regional recurrence. Statistical Bivariate analysis by Chi Square was done for all demographic and histomorphological factors with recurrence.

**Result:** Total 141 specimens were obtained and patients were followed up. Out of 141 cases 11 (8%) had recurrence. Minimum time for recurrence was 2 months and maximum was 34 months with mean of 14.4 months.

Statistically significant association (p<0.05) of recurrence was found with positive surgical margin, positive axillary lymph node and ER/PR status.

Borderline significant association (p nearing 0.05 but not less than 0.05) of recurrence was found with consistency of lump, tumor fixity to underlying tissue, tumor size, tumor emboli, multicentricity, overlying skin change, tumor grade and HER2.

No association was found with lump location, tumor necrosis, nipple-areola complex change, skin involvement by tumor.

**Conclusion:** The association of recurrence with histomorphological prognostic factors help us in assessing the outcome of the disease. It aids in calculating the probability of recurrence by studying the prognostic factors in MRM specimen. Clinician can assess the risk of recurrence and can offer better treatment to the patient.

*Key words:* Breast carcinoma, histomorphologic factors, prognostic factors, recurrence.

## INTRODUCTION

Breast carcinoma-NST is the most important malignancy studied in females. Any breast lump can be picked up early by self breast examination and can be accurately diagnosed by mammography and FNAC. MRM is the standard surgical procedure for Invasive breast carcinoma. A detailed and well elaborated histopathological report is very important in post surgical care of the patient. Numerous histopathological prognostic factors have

been identified which plays important role in post operative care, and in assessing the outcome of the disease. These includes tumor size, tumor grade, tumor consistency, tumor necrosis, tumor emboli, multicentricity, location of lump, nipple areola complex changes, skin changes, ER/PR, HER2 status etc. For ER/PR hormonal therapy is given for a longer period.[2] Recurrence is one of the rare complications of MRM. One study revealed that at time of diagnosis 3/4th of cases of breast cancer had already been spread.[3] The interval to recurrence (recurrence-free interval) and length of survival are basic measurements of prognosis. Factors associated with shorter post recurrence survival include short recurrence-free interval, visceral metastases, ER-negative, larger primary tumor size, the presence of axillary nodal metastases at diagnosis, and premenopausal menstrual status at the time of initial treatment.[4] Patients with breast cancer recurrences 2 to 4 years after diagnosis have a significantly greater risk of developing systemic metastases and poorer survival than those who manifest breast recurrence more than 4 years after initial treatment.[5] one study revealed that recurrence was found after 39 years of primary diagnosis.[6] Most recurrences are documented because patients present with symptoms or they are evident on physical examination.[7]

## MATERIALS & METHODS
The present study on breast carcinoma was carried out in department of Pathology, at a tertiary care hospital. Eight-year retrospective cases of breast carcinoma were included along with two years of prospective cases. Therefore, total of 10 years data was included. All the included cases were further followed up for loco-regional recurrence. In routine all the patients who underwent MRM were followed up regularly in our hospital and on every visit, they were examined for recurrence, metastasis and data is documented.

**Inclusion Criteria:** All the MRM specimens with axillary node dissection which were diagnosed to be invasive breast carcinoma-no special type on microscopy were included in the study.

**Exclusion Criteria:** Breast cancer cases other than Invasive carcinoma-NST, male breast cancer cases and those cases which were lost to follow-up were excluded.

**Ethics Clearance** from institute and patient consent was obtained.

**Gross of specimen:** All the gross findings of specimen were studied and recorded from the description of the specimen in the files. Histologic sections of specimen and axillary lymph nodes were retrieved and reviewed to confirm the findings of histopathology which were in the report given by Pathology department. In addition, all the slides were reviewed for additional prognostic factors if anything missing in original report. All data regarding tumor size, tumor grade, axillary lymph node, skin invasion, Paget's disease, nipple areola complex change, tumor consistency, tumor fixity to under lying tissue, ER/PR, HER2 status, tumor necrosis, tumor emboli, tumor margin, surgical margins were obtained.

## Follow-up
Patients were called for regular follow-up as per treatment protocol, more frequently in first three years after surgery. Every three to six months for the first three years after the first treatment, every six to 12 months for years four and five, and every year thereafter. Follow-up included detailed physical exam and history taking for recurrence, metastasis. Required tests were performed in follow-up including mammography of other breast, X-ray chest, USG, bone scan, FNAC was done if any nodule is found. All these follow up reports and history are documented in patient case files which were available with medical record section.

**Analysis**

Univariate analysis was done to study breast carcinoma distribution according to Age, Location, Site, Socio-economic status, Parity, Duration of symptoms, Tumor fixity to underlying tissues, Nipple-areola complex change, Skin changes, Microscopically skin involvement by tumor, Tumor consistency, Tumor size (tumor size was analyzed according to TMN staging), Tumor emboli (vascular and lymphatic), Tumor necrosis (any focus of necrosis was taken as positive), Surgical margin involved, Axillary LN involved, ER/PR status, HER2 status, Recurrence, Metastasis and Mortality.

## STATISTICAL ANALYSIS

To study the association of demographic and histomorphological factors. Bivariate analysis by Chi Square was done for all demographic and histomorphological factors separately with recurrence, metastasis and mortality.

All the analyzed demographic and histomorphological factors were then grouped into following three categories (wherever possible):-

A. Factors which are not associated
B. Statistically not significant factors but positive association (P value nearing 0.05)
C. Statistically significant prognostic factors (P< 0.05)

## RESULT

There were total of 141 cases of MRM which were followed up. Analyzing cases for recurrence showed that out of 141 cases, 11 (8%) cases had recurrence. Minimum time for recurrence was 2 months and maximum were 34 months with mean of 14.4 months.

All cases were analyzed and evaluated for association of "DEVELOPING RECURRENCE" with all demographic and histomorphologic factors.

No association of recurrence was found with:

1. Age
2. Parity
3. Socio-economic status
4. Lump location
5. Site of lump
6. Tumor necrosis
7. Nipple areolar complex change (nipple retraction, erosion, discoloration)
8. Skin involvement by tumor

Positive association of recurrence was seen with the following factors, but not statistically significant (P value was >0.05):

1. Duration of lump (recurrence was found in 5.7% cases if <6months duration as compared to 13.6% cases if >1year duration)
2. Consistency of lump (recurrence was found 8.6% cases when lump was hard as compared to 4% cases when lump was firm)
3. Tumor fixity to underlying tissues (recurrence was found in 12% cases when tumor was fixed as compared to 5.5% cases when tumor was mobile)
4. Overlying skin change (recurrence was found in 6.5% cases when skin was normal as compared to 10.2% cases when skin had peau-d-orange, ulceration, dimpling etc.)
5. Multicentricity (recurrence was found in 20% cases when tumor was multicentric as compared to 7.4% cases when tumor was unicentric)
6. Tumor size (recurrence was found in 7.2% cases when tumor size was up to 5 cm as compared to 11.1% cases when size was more than 5 cm)
7. Tumor emboli (recurrence was found in 9.3% cases when tumor emboli were present as compared to 5.5% cases if emboli were absent)
8. Tumor grade (no recurrence was found in grade-I, 6.5% cases recurred in grade-II and 10.3% cases recurred with grade-III)
9. HER2 (recurrence was found in 10.3% cases when HER2 was positive as compared to 6.9% cases when HER2 was negative)

| | Parameter name | Specifics of parameter | Recurrence percent | P-value |
|---|---|---|---|---|
| 1. | Duration of lump | <6 months | 5.7% | 0.418 |
| | | >1year | 13.6% | |
| 2. | Consistency | Firm | 4% | 0.435 |
| | | Hard | 8.6% | |
| 3. | Tumor fixity to underlying tissues | Mobile | 5.5% | 0.168 |
| | | Fixed | 12% | |
| 4. | Overlying Skin | Normal | 6.5% | 0.438 |
| | | Abnormal | 10.2% | |
| 5. | Multicentricity | No | 7.4% | 0.300 |
| | | Yes | 20% | |
| 6. | Tumor size | Up to 5cm | 7.2% | 0.402 |
| | | >5cm | 11.1% | |
| 7. | Tumor emboli | Absent | 5.5% | 0.406 |
| | | Present | 9.3% | |
| 8. | Tumor grade | Grade-I | 0% | 0.433 |
| | | Grade- II | 6.5% | |
| | | Grade-III | 10.3% | |
| 9. | HER2 | Negative | 6.9% | 0.502 |
| | | Positive | 10.3% | |

**Table 1: Association of recurrence and prognostic factors with P value**

**Statistically significant association of recurrence was found with:**

1. Surgical margins (recurrence was found in 5.3% cases when DSM was not involved as compared to 17.9% cases when DSM was involved)
2. Axillary lymph nodes involvement (recurrence was found in 4.7% cases when ALN were not involved as compared to 10.4% cases when ALN were involved)
3. ER/PR status (recurrence was found in 1.6% cases when both ER/PR were positive, 11% cases when both ER/PR were negative and 28.6% cases had recurrence when either one of ER/PR was negative.)

| Sr No | Parameter name | Specifics of parameter | Recurrence percent | P-value |
|---|---|---|---|---|
| 1. | Surgical margin | Free | 5.3% | 0.027 |
| | | Involved | 17.9% | |
| 2. | Axillary lymph nodes | Not involved | 4.7% | <0.001 |
| | | Involved | 10.4% | |
| 3. | ER/PR status | P/P | 1.6% | 0.015 |
| | | N/N | 11% | |
| | | Other (P/N, N/P) | 28.6% | |

**Table 2: Association of statistically significant factors with recurrence**

## DISCUSSION

Present study revealed 8% patient had recurrence. Minimum time for recurrence to occur was 2 months and maximum was 34 months with mean time of 14.4 months.

Demicheli et al[8] found 10.1% loco-regional recurrence rate within 10 years of surgery. Fritz et al[9] found 6.1% recurrence rate in invasive carcinoma patients with 5.86 years of average follow-up. A Danish study showed the incidence of local recurrence of 15%.[10]

According to the literature, cases of loco-regional and distant recurrences have been reported in 5 to 40% of cases.[11] One study concluded that in breast conservative surgery the recurrence after 10 years can be due to new primary tumor rather than recurrence of old tumor.[12]

In present study statistically significant association (P<0.05) of recurrence was found with positive surgical margins, ER/PR and Positive axillary lymph nodes and positive association (not statistically significant) of recurrence was found with many other important prognostic factors.

### Surgical Margins and recurrence:

Present study showed 5.3% recurrence rate in cases with free surgical margins whereas

17.9% recurrence rate was observed with positive surgical margin (deep surgical margin). Ahlborn et al reported a slightly higher incidence of loco-regional recurrence in patients with close surgical margins.[13] Many studies have shown that patients with histologically positive surgical margin have increased recurrence rate as compared to patients with negative margins.[14]

**Lymph node and recurrence:**
Present study showed 4.7% recurrence when no lymph was involved, 20% recurrence with 8-10 lymph nodes and 35.7% with >10 lymph nodes involved. Fisher et al[15] found 8% recurrence with no lymph node, 24% with 1-3 lymph node positive and 31% when >4 lymph node is positive. Similarly Lee et al[16] found 8% recurrence when no lymph node involved, 11% with 1-3 lymph and 37% with >4 lymph node positivity. Study by Stankov et al[11] showed that positive lymph node as the most important prognostic factor for recurrence.

**ER/PR and recurrence:**
Present study revealed 1.6% recurrence with ER/PR positive, 11% recurrence with ER/PR negative and 28.6% recurrence when one of ER or PR is positive. Stankov et al[11] observed that patients with positive hormone receptors had recurrence at a later stage as compared to patients with negative hormone receptors. Pan et al showed that patients on hormonal therapy who were ER positive had 13-41% risk of recurrence which further depended on tumor and nodal status of patient.[17] Similar findings were found in other studies as well. [18,19] One study showed that in ER negative tumors recurrence occurred within 5 years of surgery.[20] Another study showed that in ER positive tumors the recurrence happened in 5-10 years.[21]

**Tumor emboli and recurrence:**
Present study revealed 5.5% recurrence rates with absence of tumor emboli as compared to 9.3% with presence of tumor emboli. Fisher et al[22] found 13.8% recurrence rate with presence of tumor emboli and 7% when tumor emboli were absent.

**Tumor size and recurrence:**
Present study revealed 7.2% recurrence rate in tumor size up to 5 cm and 11.1% with tumor size >5 cm. According to Bjorn et al, the single characteristic primary tumor that contributed most to the information to prediction of early recurrence was tumor size.[23] Donegan et al found that as the tumor size increased, there is increased incidence of loco-regional recurrence.[24]

**Tumor grade and recurrence:**
Present study revealed no recurrence in grade-I tumors, 6.5% in grade-II and 10.3% in grade-III tumors. One study showed that grade 3 tumors have a relative recurrence risk of 4.4 times higher compared to the reference group.[11] Donegan et al[24] found as the tumor grade increases percentage of recurrence also increases. Similar finding was found by Jensen et al.[25]

## CONCLUSION
Patient with breast carcinoma who underwent MRM is not the end of treatment. A detailed report file with all the demographic, socio-economic parameters of the patient is necessary. An exhaustive pathological report with gross morphology of MRM specimen and histomorphologic prognostic factors is indispensible for giving proper post operative care to the patient. As this study showed that many of the histology factors can very well predict which patient might be a candidate for recurrence or have higher chances of getting recurrence. These patients can be followed up very closely and investigated regularly to avoid further morbidity and mortality. Description of histomorphological prognostic factors by a pathologist is an important tool in the hands of clinician by which the treatment protocol can be changed or altered for the betterment of the patient.

## REFERENCES

1. Chopra R. The Indian Scene. Journal of Clinical Oncology. 2001; 19(18 Suppl):106S-111S.
2. Dowling RJO, Kalinsky K, Hayes DF, et al. Toronto workshop on late recurrence in estrogen receptor-positive breast cancer: part 1: late recurrence: current understanding, clinical considerations. JNCI Cancer Spectr. 2019;3(4): pkz05. doi:10.1093/jncics/pkz050
3. Friberg S, Nyström A. Cancer metastases: early dissemination and late recurrences. Cancer Growth Metastasis. 2015; 8:43–49. doi:10.4137/CGM.S31244.
4. Vogel CL, Azevedo S, Hilsen beck S, Dawn X, East RN, Jorge A. Survival after first recurrence of breast cancer. The Miami experiences. Cancer. 1992; 70(1):129-135.
5. Haffty BG, Reiss M, Beinfield M, Fisher D, Ward B, McKhann C. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. J Clin Oncol. 1996; 14(1):52-57.
6. TashimaY, KawanoK.A case of local recurrence developing thirty-nine years after mastectomy for breast cancer. Gan To Kagaku Ryoho. 2014;41(3):357–359.
7. Mansi JL, Earl HM, Powles TJ, Coombes RC. Tests for detecting recurrent disease in the follow-up of patients with breast cancer. Breast Cancer Res Treat. 1988; 11(3):249-254.
8. Demicheli R, Abbattista A, Miceli R, Valagussa P, Bonadonna G. Time distribution of the recurrence risk for breast cancer patients undergoing mastectomy: further support about the concept of the tumor dormancy. Breast Cancer Research and Treatment. 1996; 41(2):177-185.
9. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991; 19(5):403-410.
10. LyngholmCD, LaurbergT, AlsnerJ, Damsgaard TE, OvergaardJ, ChristiansenPM. Failure pattern and survival after breast conserving therapy. Long-term results of the Danish Breast Cancer Group (DBCG) 89 TM cohort. Acta Oncol Stockh Oncol. 2016;55(8):983–992. doi:10.3109/0284186X.2016.1156741.
11. Stankov A, Bargallo-Rocha JE, Stankova-Ninova K, Ramirez MT, Silvio AN, Meness-Garcia A. Prognostic Factors and Recurrence in Breast Cancer: Experience at the National Cancer Institute of Mexico. ISRN Oncology. 2012; 4(2):25-28.
12. LaurbergT, LyngholmCD, ChristiansenP, Al snerJ, OvergaardJ.Long-term age-dependent failure pattern after breast-conserving therapy or mastectomy among Danish lymph node-negative breast cancer patients. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2016;120(1):98–106. doi: 10.1016/j.radonc.2016.05.006.
13. Ahlborn TN, Gump FE, Bodian C, Hakif DV, Kister S. Tumor to fascia margin as a factor in local recurrence after modified radical mastectomy. Surg Gynec Obstet. 1988; 166(6):523-526.
14. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Solin LJ et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast conserving surgery. Eur J Cancer. 2010; 46(18):3219-3232.
15. Fisher B, Slack NH, Gandner B, Cavanaugh PJ, Ravdin RG. Postoperative radiotherapy treatment of breast cancer: result of the NSABP clinical trial, Ann Surg. 1970;172(4):711-718.
16. Lee YN. Breast carcinoma: patterns of recurrence and metastasis after mastectomy. Am J Clin Oncol. 1984; 7(5):443-449.
17. PanH, GrayR, BraybrookeJ, et al. EBCTCG. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377(19):1836–1846. doi:10.1056/NEJMoa1701830.
18. KostevK, KalderM.20-year risk of breast cancer recurrence. Breast Cancer Res Treat. 2018;168(3):765–766. doi:10.1007/s10549-017-4636-3.
19. YuNY, IftimiA, YauC, et al. Assessment of long-term distant recurrence-free survival associated with tamoxifen therapy in

postmenopausal patients with luminal A or luminal B breast cancer. JAMA Oncol. 2019;5(9):1304–1309. doi:10.1001/jamaoncol.2019.1856.

20. ColleoniM, SunZ, PriceKN, et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the international breast cancer study group trials I to V. J Clin Oncol. 2016;34(9):927–935. doi:10.1200/J Clin Oncol.2015.62.3504.

21. DowsettM, SestakI, ReganMM, et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor–positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol. 2018;36(19):1941–1948. doi:10.1200/J Clin Oncol.2017.76.4258.

22. Fisher E R, Sass R, Fisher B et al. Pathologic findings from the national surgical adjuvant project for breast cancers (protocol no. 4) and discriminants for tenth year treatment failure. Cancer. 1984; 53(5):712-723

23. Stenkvist B, Bengtsson E, Dahlquist B, Eklund G, Eriksson O, Torsen J et al. Predicting breast cancer recurrence. Cancer. 1982; 50(12):2884-2893.

24. Dnoegan WL, Perez Mesa CM, Watson RF. A bio statistical study of locally recurrent breast carcinoma. Surg Obstet. 1966; 122(3):529-540.

25. JensenM-B, LaenkholmA-V, OffersenBV, et al. The clinical database and implementation of treatment guidelines by the Danish Breast Cancer Cooperative Group in 2007-2016. Acta Oncol Stockh Oncol. 2018;57(1):13–1. doi:10.1080/0284186X.2017.1404638.

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