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Research Article

Breast

A study of predictive and prognostic histopathologic factors in breast conservation therapy

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Background: Breast cancer is the second most common cancer after cervical cancer in Indian. Presently breast conservation therapy (BCT) is the preferred treatment for stage I and II breast cancer. Therefore, the present study was undertaken to identify and study these histopathologic factors and correlate them with local recurrence rate. **Method:** The pathology records of a tertiary cancer referral hospital were systemically scrutinized for two years and 106 women in the age group of 25-70 years with primary operable invasive breast cancer treated by breast conversation therapy (BCT) were studied in depth. Follow-up ranged for 2 to 3 years. Every patient was followed up every 6 monthly by the onco-surgeon and radiotherapist. Cases in which the pathology slides and / or blocks were not available were excluded. **Result:** The mean age of all the patients was 43.1 years. (Range: 25-67 years.) Majority of the patients are in the age group of 35-44 years (44.3%). Most of the tumours occurred in the upper outer quadrant (62.3%). IDC forms the main group (93.4%) in the various cases studied. Out of 99 IDC only 89 are pure IDC and 10 are with other components. Majority of the cases belongs to grade-III (63.2%). Maximum tumour size is in the range of 2-5 cm (52.8%). Necrosis was one of the main histological factor observed in the present study (12.3%). Overall 7.5% of our patients developed local recurrence, most of them occurred within the first year. **Conclusion:** Predictive and prognostic histopathologic factors which increase the risk of recurrence are, Presence of extensive intraductal component, Positive cut margin of resection, Presence of Lymphovascular invasion.

Keywords: Breast Conversation Therapy (BCT), Breast Cancer, Histopathology, Recurrence rate

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Introduction

Breast cancer is the second most common cancer after cervical cancer in Indian women, except in Mumbai where it has exceeded cervical cancer. Currently approximately 75,000 new cases of breast cancer are estimated to occur in Indian women per year. It is estimated that one out of about 55 urban Indian women would develop breast cancer by the age of 64 [1]. The annual age adjusted incidence rate in urban areas is 21.9-28.3/1,00,000 as per 1992 ICMR report [2]. In contrast the incidence in the Indian rural area of Barshi (1992), has been reported to be as low 8.6 / 1,00,000 [3]. This supports the concepts that this disease is related to lifestyle habits and is least partially the result of urbanization. Breast cancer is a highly heterogeneous disease with diverse clinical and genetic characteristics [4].

Treatment of the breast cancer depends upon the stage of the disease. Stage I and II disease are treated with curative intent. The goal of treatment is to produce cure with the least disability and morbidity. Treatment of stage I and II has undergone a significant change over the past 20 years. Initially, radical mastectomy described by Halsted [5] was the standard therapy and it was composed of complete removal of breast tissue with its overlying skin, both the pectorals muscles and Axillary nodes. It was based upon Halstedian principles of en block resection. This was followed by the extended radical mastectomy where the surgery involved complete removal of breast, pectoralis muscles and Axillary nodes in addition to removal of intra mammary nodes. However, the results were the same as for Halsted's radical mastectomy [6, 7]. Due to the changing principles in the treatment, newer procedures included Patey's modified radical mastectomy, which is a widely used surgical procedure and gives equal overall survival. This procedure conserves the pectoralis major muscle [8]. All the above-mentioned surgeries include at least removal of complete breast with nipple, areola, muscle and Axillary nodes, but the treatment does not consider the cosmesis. The treatment outcome for patients with breast cancer has improved due to development of various treatment methods including chemotherapy, endocrine therapy, and radiation therapy [9]. Apart from improving the overall survival period, today with an increasing number of patients being young, the quality of life is very important.

The focus is now also on good cosmesis and conservation of the breast. With availability of effective combined treatment in the form of radiotherapy, chemotherapy, hormonal therapy and minimal surgery, these goals are being realized. It is understood for mortality, recurrence is one of the independent prognostic factors [10].

There have been several reports on potential predictive factors for recurrence and survival, including tumor size, histological type, differentiation degree of the tumor, nuclear grade, presence of lymph node metastasis, estrogen receptor (ER) and progesterone receptor (PR) status, and gene expression [11, 12]. Presently breast conservation therapy (BCT) is the preferred treatment for stage I and II breast cancer [13]. However, in BCT there is some degree of increased risk of local recurrences which is circumvented with adequate post – operative radiotherapy. These risks can be predicted or anticipated, by examining several histopathologic parameters in the lumpectomy specimen. Some of the most important histopathologic factors are positive cut margins, extensive intraductal component, tumour size and grade, lymphatic and vascular invasion. Therefore, the present study was undertaken to identify and study these histopathologic factors and correlate them with local recurrence rate.

Objectives

To determine the relation between different histo-pathologic factors and local recurrence in BCT.

Material and Methods

The pathology records of a tertiary cancer referral hospital were systemically scrutinized for duration of two years i.e. from Jan 2016 to Dec 2017and 106 women in the age group of 25-70 years with primary operable invasive breast cancer treated by breast conversation therapy (BCT) were studied in depth by selecting randomly. Follow – up ranged for 2 to 3 years. Every patient was followed up every 6 monthly by the oncosurgeon and radiotherapist. Cases in which the pathology slides and / or blocks were not available were excluded.

Data collection procedure: The files of these patients were retrieved from the Medical Records Department and the clinical data was collected. Patients with gross positive margins and other risk factors like extensive intraductal component were re-scheduled for surgery and MRM was done.

These patients could not be included in the analysis for recurrence.

All the above BCT patients completed the post – operative radiotherapy treatment (4-5 weeks after surgery), a dose of 45 Gy was given in 25 fractions over 5 weeks followed by tumour bed boost of 15-20 GY with or without chemotherapy and / or hormonal therapy depending on the nodal and hormonal receptor status. The slides and paraffin blocks of all the cases were retrieved. If required, the blocks were re – sectioned and stained wherever required.

Hematoxylin and Eosin stained sections were examined microscopically, and the histologic parameters were documented.

Tumour Grade: For purpose of grading Elston's modification of the Richardson Blooms scoring [14] was used. This scoring system is based on three principle criteria's namely, tubule formation, nuclear plemorphism and mitotic activity.

All these three criteria's have to be objectively scored on a scale of 1-3 and the scores are then added to give the final grade, which may vary between 3-9.

The maximum score that can be attained is 9. Tumours which attain a score of 3-5 are of grade I malignancy, those with a score of 6-7 are grade II and those that attain a score of 8-9 are grade III tumours. This scoring has been directly co-related with the patient's survival.

ER and PR Status: ER–PR studies performed using an Avidin – Biotin Complex (ABC) method. Scoring for steroid hormone receptor positivity [15] was used.

The tumour was assessed for both the number of cells stained and the intensity of staining. The two scores so obtained were multiplied together. Tumours with the score of 1-3 were considered weakly positive those with score 4-6 were moderately positive and those with scores more than 6 were strongly positive. Institution ethical clearance was obtained prior to begin the study.

Statistical analysis: Data collected was fed into a computer and run on a statistical program which calculated the frequencies. The Chi square test was used to determine significance. A p-value less than 0.05 were considered as significant.

Results

A total of 106 patients with stage I and II breast cancer were treated by breast conservation therapy and followed up for an average of two years.

Table-1: Basic characteristics

Characteristics	Frequency	Percentage
Age (years)		
25 -30	15	14.2
35-44	47	44.3
45-54	26	24.5
55-64	15	14.2
65 – above	3	2.8
Menopausal status		
Premenopausal	46	43.3%
Perimenopausal	3	2.8
Postmenopausal	30	28.4
Unknown	27	25.5
Family History		
Yes	3	2.8
No	95	89.6
Unknown	8	7.6

The mean age of all the patients was 43.1 years. (range: 25-67 years.) Majority of the patients are in the age group of 35-44 years (44.3%). At presentation 28.3% of the patients were postmenopausal. Only 3% of our patients had a family history of breast cancer. The vast majority had no family history of breast cancer (Table-1).

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Table-2: Distribution of cases according to tumour characteristics

Characteristics	Frequency	Percentage
Tumour site		
Upper outer	66	62.3
Lower outer	16	15
Lower inner	4	3.7
Upper inner	11	10.5
Central	1	1
More than 1	7	6.6
Missing	1	0.9
Types of carcinomas		
IDC	99	93.4
DCIS	3	2.8
ILC	1	0.97
Metaplastic	1	0.9
Tubular	1	0.97
Mucinous	1	0.97
Tumour grade		
I	4	3.8
II	35	33
III	67	63.2
Tumour size		
<2 cm	44	41.5
2 – 5	56	52.8
>5 cm	6	5.7

Most of the tumours occurred in the upper outer quadrant (62.3%). IDC forms the main group (93.4%) in the various cases studied. Out of 99 IDC only 89 are pure IDC and 10 are with other components. Majority of the cases belongs to grade-III (63.2%). Maximum tumour size is in the range of 2 – 5 cm (52.8%) (Table-2).

Table-3: Distribution of other histologic factors

Factors	Frequency	Percentage
Necrosis	13	12.3
Elastosis and desmoplasia	12	11.3
Calcification	6	5.7

Necrosis was one of the main histological factor observed in the present study (12.3%) (Table-3).

Table-4: Distribution of Other benign pathologies

Benign Pathology	Frequency	Percentage
Sclerosing adenosis	2	1.9
Ductal hyperplasia with cystic change	3	2.8
Granuloma	2	1.9

Ductal hyperplasia with cystic change was one of the main benign pathologies observed in the present study (2.8%) (Table-4).

Table-5: Association of recurrence with different variables

Variables	Recurrence		Total	P-value
	Yes	No		
Tumour Size				
0 – 2	4	40	44	0.74
2- 5	4	48	52	
>5	0	6	6	
Tumour grade				
I	0	4	4	0.31
II	1	33	34	
III	7	57	64	
Tumour type				
IDC	7	89	96	0.15
DCIS	0	3	3	
ILC	0	1	1	
Tubular	0	1	1	
Mucinous	1	0	1	
EIC				
Positive	31	7	38	0.002
Negative	63	1	64	
Cut margin status				
Gross positive	1	7	8	0.003
Focal positive	4	9	13	
Negative	3	78	81	
LVE				
Present	5	22	27	0.016
Absent	3	72	75	
ER				
Positive	2	17	19	0.6
Negative	6	77	83	
PR				
Positive	3	26	29	0.5
Negative	5	66	73	

Overall 7.5% of our patients developed local recurrence, most of them occurred within the first year. There was no significance relationship observed between recurrence and tumour size (p=0.74), tumour grade (p=0.31), tumour type (p=0.15), ER (p=0.63) and PR (p=0.55) whereas there was significance relationship observed between recurrence and Extensive intraductal component (p=0.002), cut margin status (p=0.003)

And Lymphovascular invasion (p=0.016) (Table-5).

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Tumour type				
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DCIS	0	3	3	
ILC	0	1	1	
Tubular	0	1	1	
Mucinous	1	0	1	
EIC				
Positive	31	7	38	0.002
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Negative	5	66	73	

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Discussion

In this study, basically the clinical details and histo-pahtologic factors by gross and microscopic examination were studied and then analysed the relationship between different prognostic factors and the recurrence. Out of these 106 patients, 4 patients showed gross positive cut margins and extensive intraductal component positivity and they underwent modified radical mastectomy as a final treatment procedure. Patient's final surgery was MRM so for recurrence analysis these were not considered, but because these patients were initially considered for BCT they were included in the frequency analysis.

In the present study local recurrence rate was 7.5% and minimum follow up was 2 years (24 months). BCT can be offered for patients in any age group, provided they were in stage I/II. Several trials have been carried out in the world where patients in all age groups were considered. Roses et al study of predictors of recurrence in stage I/II breast cancer studied cases in the age group of 28 to 83 [16]. Fourquet et al studied patients in the age group of 26 to 77. (mean age = 47.6) [17]. Locker et al concluded that along with the other factors like nodal status, tumour size, presence of definite vascular invasion, patients age is an independent significant factor predictive of local recurrence after BCT. He found increased rate of local recurrence with young age [18]. Haffty et al also found that young age was the most significant prognostic factor for local recurrence in BCT (P <0.03). Local recurrence rate was higher in young patients [19].

A study by Kurtz showed that an increase in local recurrence in young patients correlated with a higher incidence of EIC in women younger than 50. In addition, they documented a mononuclear cell reaction & high histological grade in women younger than 40 and in this study by Cox multivariate analysis only EIC positivity, high nuclear grade & mononuclear cell infiltrate proved significant as risk factors, for local recurrence after BCT [20]. In the present study age was indirectly related to local recurrence.In addition, they documented a mononuclear cell reaction & high histological grade in women younger than 40 and in this study by Cox multivariate analysis only EIC positivity, high nuclear grade & mononuclear cell infiltrate proved significant as risk factors, for local recurrence after BCT [20]. In the present study age was indirectly related to local recurrence.

In the present study the patients were in the ager group of 25-67 years and the mean age was 43.1 years. The highest rate of recurrence is seen in the age group of 36-45. Statistical analysis did not reveal any relationship between age and recurrence. The follow up period in the present study is too early as yet to draw long term conclusions.

In the present study 62.2% of tumours were seen in the upper outer quadrant. This is a known fact that about 50% are in the upper outer quadrant because the amount of breast parenchyma is more in the upper outer quadrant as compared to other quadrants [21]. In the present study, tumour sizes varied from 0.5 to 5 cm. Most of the tumours were T2 tumours i.e., between 2-5 cm in size. Statistically there was no relationship between size of the tumour and local recurrence rate.

Fisher et al reported that tumours measuring $\geq$ 2.0 cm, with a high histologic and nuclear grade or intra-lymphatic extension have a statistically significant increase in local breast recurrence [22].

In contrast to above study our results are at variance because our patients were treated with lumpectomy followed by postoperative radiotherapy, which reduced the recurrence rates. In BCT the only relative risk is local recurrence and it is a known fact that microscopic examination is the only usuful tool for assessing the risk of local failure which is quite low for the majority of patients treated with breast conservation therapy [20]. Histologically, out of the 106 tumours, 99 were infiltrating duct carcinomas making up 93.4% of the total tumours. This is the commonest tumour type. In the present study 63.2% of all tumours were grade III i.e. high-grade cancers.

Statistically there was no relation between tumour with the studies done by Kurtz et al and Fisher et al who showed a significant relation between tumour grade and local recurrence i.e. increased local recurrence rate in high grade tumour [20, 22]. In the study done by Fisher et al these patients did not receive post – operative radiotherapy as opposed to our patients who all received post lumpectomy radiotherapy [22].

In one of study published by Roses et al 44 the histologic type was also predictive of recurrent disease. In this study 18% (18/101) of patients with invasive ductal or lobular carcinoma developed recurrence, while none of the group of 21 patients with other types suffered a recurrence (P = 0.036).

This study suggests out that there is an increased risk of local recurrence related to the histologic type of carcinoma, i.e. invasive ductal and lobular carcinoma [16].

In the present study, 51 patients with IDC showed associated duct carcinoma in situ i.e. 49.9%. Out of these only 42 showed extensive intraductal component, 8 showed minimal duct carcinoma in situ, and 1 showed lobular carcinoma in situ. On analysis of these 42 patients with extensive intraductal component, it was observed that 7 patients out of these 42 who showed local recurrence and only 1 patient recurred locally who did not have extensive intraductal component. Statistically these results indicate a significant relationship between the presence of extensive intraductal component and local recurrence.

In breast conservation therapy postoperative radio-therapy ideally should take care of these residual foci of DCIS. The present study showed a definite relation local recurrence and with extensive intraductal component i.e.; increased local recurrence in EIC + ve patients.

The study done at the joint center for Radiation Therapy (JCRT) in Boston by Osteen et al, found that local recurrence was related to the presence of an extensive intraductal component. At 5 years follow up, they found a 3% local failure rate without an EIC as opposed to the 22% failure rate in patients with EIC (p< 0.001) [23].

The study by Schnitt et al concluded that a combination of EIC, high nuclear grade and high mitotic index were the histologic features associated with a significantly increased local recurrence risks at 5 year follow up (P = 0.004) They attributed this to the EIC being related to multicentricity [24]. Kurtz et al reported that, histologic high grade and monocular cell infiltrate were the factors related to increased local recurrence [20].

Bertelink et al in Nethlands Cancer Institute studied 585 patients between 1979 to 1984 and found a small but significant increase in local recurrence rate n EIC positive patients (P <0.03) [25]. Smaller results were documented by Separovic V. et al [26]. Thus, all the studies concluded that EIC positivity is a major risk factor for local recurrence in BCT and hence if EIC is positive then there should be negative and clear excision margins which would minimize the chances of local recurrence and patients should be given postoperative (within 6 weeks) radiotherapy.

If margins are positive at histology, then re – excision is necessary. In the present study 4 patients had positive margins as well as extensive intraductal components, these patients after counselling underwent modified radical mastectomy and presently are completely controlled.

The major histologic predictive factor in breast conservation therapy is surgical cut margin status which is very important in assessing the risk of local recurrence. IT is very essential to achieve negative cut margins without compromising cosmesis. Negative cut margin status can be achieved by removing large amounts of normal breast parenchyma around the tumour, but this does not give good cosmesis, hence it is essential to give negative cut margin but without large amount of normal parenchyma.

After a statistical analysis, which denotes that there is a relationship between margin positivity and local recurrence (p=0.003). Local recurrence increases with positive cut margins.

Gage et al found that the 5-year rate of local recurrence in patients with negative margins was 2% and in patients with positive margins was 16% and statistical analysis (P <0.0001) showed that if margins are positive then there is an increased rate of local recurrence. He further studied recurrence rate and type of positive margins like focally positive margin and more than focally positive margin and found that the rate of recurrence is related to significantly involved margins [27].

Spivack et al found that the overall rate of local recurrence was 6.3%. Local recurrence was more frequent (P = 0.0001) in patients with histologically positive margins (18.2%) than in those with histologically unknown margins (7.1%) or negative margins (3.7%) [28]. Univariate analysis done by Noguchi et al, in his study showed that the positive surgical margin (P< 0.001) and positive P53 immunostaining (P<0.001) were significant risk factors for local recurrence [29].

Smitt et al followed 289 patients for 20 years and found that actuarial probability of local control at 10 years was 98% for those with negative surgical margins versus 82% for patients with positive margins (P = 0.007). The local control rate at 10 years was 97% for patients who underwent re – excision and 84% for those who did not. Re – excision appears to convey a local control benefit for those patients with close, in-determined or positive margins [30].

Pittinger et al who do not agree with the above results and concluded that even if the margins are positive, then post – operative radiotherapy is enough to take care of those foci of tumours and will give equivalent results of local recurrence as seen in negative margins [31]. There are a few studies which consider cut margin positivity and EIC positivity together as a major risk factor Abner et al showed that patients with EIC positivity and positive cut margin are at high risk for local recurrence [32]. These two factors simultaneously analyzed against recurrence and found that patients with EIC positivity and positive cut margin had a higher chance of local recurrence. (P = 0.032).

Lymphovascular invasion (LVI) in patients was also looked upon. In the present study 27 tumours showed presence of lymphovascular invasion. Out of these 5 patients showed presence of local recurrence and in 75 patients without lymphovascular invasion, 3 patients showed local recurrence. Thus, by statistical analysis it was observed found (P = 0.029) that there is relation between presence of lymphovascular invasion and local recurrence. Thumours with lymphovascular invasion or embolization are more likely to have local recurrence after BCT. Roses et al found that lymphatic invasion was the most significant predictor of recurrence, Recurrence was present in 32% (8/25) of patients who had lymphatic invasion and in 10.3% (10/97) of patients who did not show LVI (P = 0.006) i.e, lymptatic invasion increases rate of local recurrence [16].

Pinder et al also found that histological assessment of vascular invasion provides independent prognostic information in primary operable breast cancer. They considered vascular invasion as lymphatic or capillary invasion. Definite vascular invasion was seen in 22.8% of cases. In multivariate analysis, presence of vascular invasion was of independent prognostic significance for both, survival and for local recurrence of the tumour. They found that presence of vascular invasion decreases survival and local disease control [33]. Fishter et al carried out a study and found that intralymphatic invasion was the only factor found to be related to increased local recurrence in the lumpectomy and irradiation group [22]. In the present study, 13 patients i.e. 11% showed presence of necrosis, but out of them only two patients showed recurrence and thus, there is no relation between the presence of necrosis in the tumour and local recurrence rate in the present study.

Study done by Mate et al revealed that tumour necrosis was a histopathlogic factor associated with an increased risk of both overall and local recurrence in BCT most notably in stage II patients [34].

Six patients who had showed presence of calcification in the tumour and psammoma bodies, but these patients did not have local recurrence.

Elastosis and desmoplasia is seen in 12 patients but there is no evidence of recurrence in these patients. Six tumours showed presence of intense lymphocytic infiltration in the tumour some in the form of lymphoid nodule formation but these patients were controlled locally till the last follow up. These features showed no relation with local recurrence of breast cancer.

The other factors include presence of axillary node metastasis, ER and PR status. No relationship between axillary node metastasis and local recurrence as well as ER – PR status and local recurrence was observed.

Limitations of the present study: Further study in large number of patients is required to get more depth knowledge of predictive factors and correlation with local recurrence rate.

Conclusions

Predictive and prognostic histopathologic factors which increase the risk of recurrence are, presence of extensive intraductal component, positive cut margin of resection, presence of lymphovascular invasion.

What the study adds to the existing knowledge?

Literature on predictive and prognostic histopathologic factors in breast conservation therapy has shown different degree of increased risk of local recurrences which make a meaningful adding in existing literature by conducting the present study in an area to timely recognition and understanding of common issues related to BCT.

Author's contribution

Dr. Gauri Kelkar: Study design and manuscript preparation.

Dr. Nivedita S.B.: Study design and manuscript preparation.

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