



STUDY OF BREAST MALIGNANCY RECURRENCES IN RELATION TO HISTOPATHOLOGICAL FACTORS

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ABSTRACT

Malignancy of the breast is found to have so many factors influencing its growth or control. Many factors in the past like early detection, oestrogen progesterone receptors and its effect on the treatment, lymph node status and its effect on prognosis of the disease, types of primary pathology, age and sex of the patient, clinical stage of the disease have been studied in detail by different authorities from time to time. The present study was undertaken to elucidate the predictive value of the special histopathological characteristics in addition to histopathological grading and typing. In the series of 327 women with breast cancer with special emphasis on recurrences assessing wheather they are of any value in predicting some times unfavourable histopathology which can lead to recurrences were studied retrospectively; so that effective detection and its treatment can be instituted well in advance.

KEYWORDS: Malignancy, Histopathology, Recurrence.

INTRODUCTION

Breast is a complicated orqan so far as circulation, lymphatic drainage and situation is concerned. This has been further complicated by extreme sensitivity and dependency for its growth on oestrogen and progesterone. The diseases of breast including malignancy have important bearing for these factors to which feeding to infant by breast can be added further.

Malignancy of the breast is found to have so many factors influencing its growth or control. Many factors in the past like early detection, oestrogen progesterone receptors and its effect on the treatment, lymph node status and its effect on prognosis of the disease, types of primary pathology, age and sex of the patient, clinical stage of the disease have been studied in detail by different authorities from time to time.^[1]

It has been seen and reported by many authors that the progress of disease depends not only on one factor but on many factors which includes tumor doubling time which entails the subclnical cause of the disease and the opportunity that disease have to spread to rest of the body.

Inspite of so many attempts to find out the factors influencing disease, recurrences continue to occur. This

opened the minds of the authors to change the battery of investigations towards histopathological elements in the tumors.

The present study was undertaken to elucidate the predictive value of the special histopathological characteristics in addition to histopathological grading and typing. In the series of 327 women with breast cancer with special emphasis on recurrences assessing wheather they are of any value in predicting some times unfavourable histopathology which can lead to recurrences were studied retrospectively; so that effective detection and its treatment can be instituted well in advance.^[2]

MATERIAL AND METHODS

This study was carried out at Government Medical College, Naqpur from the period JULY 1992 to JULY 1994.

The cases of BREAST MALIGNANCY RECURRENCES admitted in the six teaching surgical units of the Surgery Department in Government Medical College and Hospital, Nagpur were entered in this study.

The data related to the BREAST CANCER was collected from CANCER REGISTRY, attached to the Department

of Surgery. Government Medical College and Hospital, Nagpur.

Those patients who had recurrences were given special attention so as to analyse them retrospectively.

Hence the study comprises of the review of the cases operated even before five years. Some patients having operated in Government Medical College and hospital, Nagpur visited RASHTRASANTA TUKDOJI CANCER, HOSPITAL'S cobalt unit for adjuvant radiotherapy were also traced from that institute.

The patients in their postoperative period are advised to attend the Department of Radiotherapy in the Hospital for adjuvant radiotherapy and hence the data is also collected from that department.

Revealed recurrences were noted yearwise so as to calculate in relation to the case of that year.

All the cases were studied from the records available from MEDICAL RECORD SECTION of the Government Medical College and Hospital. Clinical evaluation was possible for the following patients.

- a. Patients presented with recurrences.
- b. Patients came for followup.
- c. Patients operated during the course of the study.

The patients with recurrences and the operated patients during the course of study were subjected to histopathological study on the lines stated as under.

Total number of the cases reviewed were 711, however less than 50% i.e. 327 were included in a group of operated and hence the study was done out of 327 patients who were operated and studied for recurrences. Those patients not subjected to the surgery were excluded from the study. Nagpur being an adjoining area to Madhya Pradesh, in addition to Vidarbha, it also acted as referral centre from adjoining area of Madhya Pradesh. There is constant and significant flow of the cases. There are large number of cases i.e. 711 in 4 years out of which 327 cases were operated. These 327 operated cases were

observed for recurrences and their specific histopathology.

Head of the Department of Pathology, Government Medical College and hospital Nagpur was approached for reading the slides by two certified pathologists for the unanimity of the opinions. Out of 327 cases operated the recurrences were observed in 55 patients, of which only 20 patients were available for histopathological study in comparison with the original slides of primary pathology.

Due to difficulty in reading the slides since their staining was faint the 100 slides in fair condition were selected for review where there were no recurrences.

The 55 slides with recurrences were also reviewed and compared with the slides of the primary pathology where there were no recurrences.

The findings were entered in the proforma for analysis, patients with recurrences were subjected to FNAC (Fine Needle Aspiration cytology). from the site of recurrence with 23 Gauge needle with sterile technique. Samples were preserved in alcohol and subsequent staining with haematoxylin and eosin on the slides. They were examined and reported.

The nature of the biopsy from recurrence was related with the nature of the recurrence. The method adopted for biopsy was excision with adequate clearances where recurrence was smaller than 2 cm or 2 cm in its greatest diameter and was not adherent to the underlying structures.

Incisional biopsy was avoided as far as possible and was undertaken as a last resort.

Samples so collected were sent to histopathology for staining and reading the slides.

OBSERVATION AND RESULTS

The results of the study have been shown in the following tables.

Table 1: Total Admitted Cases of Breast Malignancy.

Year	Total Registered Cases	Total Operated Cases
1990	152	71
1991	192	84
1992	197	80
1993	170	85
Total	711	320

Table 2: Year Wise Distribution of Recurrences.

Year	Total Registered Cases	Recurrence
1990	84	11
1991	76	17
1992	90	18
1993	77	9
Total	327	55

Table 3: Incidence of Carcinoma Breast Site Wise.

Year	Left Breast	Right Breast
1990	51	33
1991	43	33
1992	51	39
1993	44	33
Total	189 (57.79%)	139 (42.2%)

Table 4: Age Distribution.

Age Group	Total No. of Patients	Recurrence
30-40 yrs.	27 (8.25%)	9 (33.5%)
40-50 yrs.	213 (65.13%)	34 (15.94%)
50-65 yrs.	87 (26.60%)	12 (13.79%)
Total	327	55 (16.81%)

Table 5: Recurrences in Relation with Time Interval after Surgery.

Time Interval	Recurrence	Percentage
0-1 yr.	6	10.99%
1-2 yrs.	23	41-18%
2-3 yrs.	15	27.27%
After 3yrs.	11	20.00%
Total	55	

Table 6: (A) Relation of Recurrences with Modality of Treatment.

Type of Treatment Received	No. of Patients	Recurrence
Radical + Radiotherapy	300	38 (12.36%)
Simple + Radiotherapy	27	17 (62.65%)
Total	327	55 (16.81%)

Table 6: (B) Relation of Recurrences with Modality of Treatment.

Recurrence	Radical Mastectomy + Radiotherapy	Simple Mastectomy + Radiotherapy
1. Local	11	4
2. Locaoregional	25	12
3. Distant metastases	2	1
Total	38	17

Table 7: Recurrences Verses Menstrual Status.

No. of cases	Premenopausal	Postmenopausal
55	20 (36.36%)	35 (63.63%)

Table 8: Comparison between Primary Tumor and Recurrences.

Histological Factors	Primary Malignancy	Recurrence
1. Histological type • Infiltrating ductal carcinoma:	155	55
2. Histological grade: i. Moderate ii. Poor	97(62.97%) 58(37.33%)	6(10.9%) 40(89.09%)
3. Tubule formation	38(24.67%)	4(7.2%)
4. Intraductal growth pattern	56(36.5%)	3(5.5%)
5. Tumor necrosis: i. Extensive ii. Minimal	88(57.14%) 67(42.8%)	39(70.9%) 16(29.1%)
6. Nuclear pleomorphism: i. Extensive ii. Minimal	93(59.74%) 62(40.26%)	43(78.2%) 12(21.8%)
7. Inflammatory cell reaction i. Extensive ii. Minimal	95(61.3%) 60(38.7%)	45(81.8%) 10(8.2%)
8. Lymphatic invasion	155(100%)	55(100%)
9. Vascular invasion	151(98%)	55(100%)
10. Tumor margin circumscription	Could not be commented upon	

DISCUSSION

This study is the retrospective study of the BREAST MALIGNANCY RECURRENCES. Cancer of the breast is one of the leading factors killing the female patients. Women who have a first degree relative with breast cancer have a risk of two to three times that of the general population. This risk is increased further if the relative was affected at an early age or had bilateral disease. It is estimated that women who have first degree relative with bilateral breast cancer detected premenopausely have a nine fold increased risk of breast cancer. Breast cancer also affects the quality of the life because of the morbidity it provides and it is further increased by the terminal events caused by the recurrences and the metastatic disease. And hence the study was carried out to study the histopathological factors responsible for the recurrences in breast malignancy in addition to the age at first detection of the disease, menopausal status of the patients, time interval required for the recurrence and type of modality of the treatment in relation to occurrence of the recurrences.

This study was carried out at Government Medical College and Hospital Nagpur. Total 327 patients with operated breast cancer was observed for recurrences.

Recurrences were detected in 55 patients. In this study all the patients with operated breast cancer were females.

In relation to the age at diagnosis, the peak incidence of female breast cancer was found in perimenopausal period, i.e. 40 - 50 years.

Levi F. has observed that the incidence of the breast cancer is highest in the perimenopausal period or in the age group of 40 - 50 years, and survival during this period is on the peak with lower survival at younger and older ages.^[3]

This can be interpreted in terms of selection and modifying effects on the incidence and survival of hormone dependency of proportion of breast cancers, the growth of which could be accelerated during premenopause and the survival in contrast, favourably influenced by decline in contrast, in steroid hormone levels after menopause. But the recurrences are maximum in the younger patients because of direct influence of steroid hormones. Most authors found a positive relationship between receptor status and histopathological characteristics. But Molino Annamaria in his study found no relation between ER and PR status and tumor size which influenced the recurrences.^[4] Williams and Hauvkins et al also have the same opinion. He added that receptor status is neither predictive of nodal involvement nor correlated with tumor size or age, receptor status is predictive of prognosis only in relation in nodal status more than 4 and premenopausal groups.

In this study most of the patients had axillary nodal metastases. This might have contributed to the incidence of the recurrence.

The application of ER data to predict the clinical course of breast cancer patients has been suggested by Waif and colleagues and by Knight and co-workers who observed an earlier recurrence in patients whose primary lesions were ER Negative. Several breast cancer study groups have obtained similar results; while others failed to find a significant difference in disease free interval and recurrences for women with ER positive and ER negative tumors.

The recurrences noted in this study occurred within 24 months of the surgery were maximum. By definition it was early recurrence.

Most studies of series of patients having had radical mastectomy show 15 to 25% incidence of locoregional recurrence, Conway and Neuman demonstrated a correlation between the size of primary tumors and local recurrences. Most of the recurrences appear within 2 years of the surgery.

Zimmerman K. W. et al reported that more than 70% of the recurrences were found within first 2 years of surgery.^[5]

Relatively few publications are available giving information on the frequency and anatomical distribution of local recurrences i.e. recurrences on chest wall, axilla, supraclavicular area and parasternal region.

Study of Lewis and Reinhoff who reviewed 541 patient seen at Johns Hopkins from 1889 to 1930 who have had a radical mastectomy and on whom there was adequate follow up information. Local recurrences had developed in 144 patients (26.67%). The majority of the recurrences were on chest wall, the incidence being great in younger patients.^[6]

Zimmerman K.w, et al also found the similar results. He compared radical mastectomy alone with radical mastectomy with pre or postoperative radiation and found the recurrence on the chest wall was more than 70%.^[7]

Auchincloss found a correlation between local recurrences and positive axillary nodes. Further more, approximately half of the recurrences were parasternal leading the author to the statement.

"The concept that most local recurrences are in reality outgrowths of tumor from preexisting foci in lymphatics of the chest wall, especially internal mammary chain nodes.

In this study, the main site of recurrence was chest wall either along the mastectomy scar or diffusely on the chest wall.

In 90% of the patients in the radical mastectomy group the chest wall recurrence was the first manifestation of the disease. The results of this study almost coincides with many other studies carried out by different authors.

Most significant reason being incomplete removal of the disease and failure to receive adjuvant radiotherapy. The other factors are also important like lymph node status at the time of operation, steroid receptor status, menstrual status of the patient and histopathological elements of the tumor.^[8]

This is the retrospective study to evaluate the significance of histopathological factors influencing the recurrences in carcinoma of the breast.

There were two groups of the patients studied.

1. Patients with carcinoma of the breast without recurrence.
2. Patients with carcinoma of the breast with recurrence.

The histopathological factors of the patients with carcinoma of the breast were compared with the histopathological factors of the patients with carcinoma breast with recurrences.

There were 327 patients in this study evaluated. All the patients were women.

The slides of the patients were studied by the two certified pathologist of the Department of Pathology.

Government Medical College, Nagpur. Histopathological factors considered in this study were :-

1. Histological type
2. Histological Grade
3. Tubule formation
4. Intraductal growth pattern
5. Tumor necrosis
6. Nuclear pleomorphism
7. Inflammatory cell reaction
8. Lymphatic invasion
9. Vascular invasion
10. Tumor margin circumscription.

The last factor tumor margin circumscription could not be commented upon in this study because it is retrospective study and the excised tumor material was not available for macroscopic examination followed by microscopic study of the tumor margins.

It is well accepted fact that the histological factors are also responsible for the recurrences.

But different authorities have their opinions on the value of these factors.

In this study most of the patients were presented with their disease after it was fully established and hence the histological type in this study was found to be infiltrating ductal carcinoma in almost all the cases. Thus in 100% of the slides reviewed showed infiltrating ductal carcinoma as the histological type.

The histological type of breast cancer seems to be of prognostic value. The WHO grading system which is based on tubule formation, nuclear pleomorphism and mitotic frequency is of definite prognostic value in the breast cancer.

Histologically, breast cancer is a heterogenous disease and the predictive value of certain histological types is well known. Ductal carcinoma is the most common histological type in breast carcinoma.

In this study tubule formation and intraductal growth pattern revealed indirect relationship with the recurrences.

In present study, as already seen breast cancer presented when the disease was established. It is established fact that tubular pattern is found in early cases of cancer breast and hence have better prognosis. In axillary lymph node negative patient only tubule formation independently predicted the tumor recurrence. This is shown in the study carried out by Aaltomaa S.et.al. and showed its indirect relationship with the tumor recurrence. It has definite value in predicting the recurrence.^[9]

In tumors with extensive tubule formation, no recurrences were detected in long followup.

The present study coincides with the results of the recent observations made by Aaltomaa S and Co-workers.^[10] They have suggested that intraductal carcinomas should be considered as particular subcategory of breast cancer associated with more favourable prognosis. The tumors with predominantly intraductal growth pattern represent an early stage breast cancer in which invasive growth is not invariably present. Even so however these tumors possess the potential to become invasive.

SUMMARY AND CONCLUSION

This study was carried out at Government Medical College and Hospital, Nagpur from July 1992 to July 1994.

Patients of breast cancer are frequently seen in the outpatient departments of surgery and the radiotherapy. As the major killing malignancy in women causing lot of morbidity from the recurrences and the distant metastasis terminal events are very painful and inhuman.

Hence search for the factors responsible for its recurrences are studied by different authorities world wide.

This was the idea behind taking this opportunity to discuss the factors within our scope. India is a developing country with maximum number of illiterate population residing in villages in poverty. Hence the patients most often reaches the hospital after their disease is well advanced. This might be the reason, why all the operated patients had poorly differentiated infiltrating ductal carcinoma of the breast.

This study comprises of 327 operated patients at Government Medical college and Hospital Nagpur in its six teaching surgical units. Most common modalities of treatment in carcinoma breast is radical mastectomy followed by radiotherapy in stage I and II disease. In smaller number of the patients simple mastectomy with axillary clearance is done, it is followed by radiotherapy. It is done in stage 1 disease without axillary nodes.

The patients belonging to these two groups were studied retrospectively. The records were made available from department of radiotherapy as the patients are irradiated in its cobalt unit. The tickets of the patients were scrutinised from the Medical Record section of the Hospital. There were 55 patients with recurrences found out of the 327 patients operated in the institute. The percentage of recurrences comes to be 16.81%.

The slides of the tumor pathology were studied on the lines stated in the proforma by two certified pathologists of the Department of Pathology, Government Medical College, Nagpur.

The patients who have undergone simple mastectomy with axillary clearance had more incidence of recurrences as compared to the patients where radical mastectomy was done. This indicates that it was inadequate removal of the disease.

In this study the factors like axillary lymph node status, tumor size, receptor study could not be undertaken because it was retrospective study.

In this study the comparative study of the histopathological factors responsible for recurrences were studied.

The incidence of the carcinoma breast was found maximum in the perimenopausal years of the women.

The patients who failed to receive their complete radiotherapy had definitely increased incidence of recurrence.

This suggests that still the radiotherapy has definite role in the treatment of carcinoma of the breast.

The recurrences were found maximum during the first 24 months of the surgery. In 70% of the cases had recurrences within 2 years of the surgery.

The original slides of the tumors and the slides of recurrences were studied and analysed retrospectively.

Tubule formation and intraductal growth pattern was found to be in minimal number of cases and established the indirect relationship with the recurrences.

There is relationship between tumor necrosis, inflammatory cell reaction and nuclear pleomorphism which show predictor of the recurrence.

Tumor necrosis was more frequent in large tumors than in smaller ones probably because of their in sufficient blood supply in proportion to their active proliferation, frequent mitoses and rapid growth. Breast carcinomas with abundant necrosis frequently showed an intense inflammatory cell infiltrate.

In this study the slides of original pathologies has similar picture as that of the slides of their recurrences. This suggests that there was no effect of radiation or drugs on the cellular pattern of the histopathology in the patients who received these modality of treatment.

Lymphatic invasion and vascular invasion was seen in almost all the slides where recurrence was noted. This indicates that it is contributory factor in recurrences in the patients with carcinomas of breast.

The result indicates that despite an intense search for a diversity of prognostic factors by increasingly sophisticated technique the relatively simple light microscopic assessment of the mentioned morphological features seems to be still advocated in predicting the disease outcome in female breast cancer.

The patients with these factors present should be regularly follow up and treated properly so as to avoid the recurrences. Financial crisis, lack of relatives to take care, ignorance about consequences of malignancies and poor nutrition are also important factors for delay in treatment and dissemination.

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