

Patterns of Failure in Breast Cancer Patients of Kashmir Valley

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ABSTRACT

Background: Breast cancer is the most frequent cancer among women and also the leading cause of cancer related deaths in women. The patterns of failures in carcinoma breast seem to differ by cell type, pathological stage and by the treatment modality instituted. Breast cancers can recur locally, regionally and distantly. Survival rates decrease progressively as the stage of the disease increases. **Aims & Objectives:** To evaluate the patterns of failure in patients with Breast Carcinoma after definitive treatment modalities. **Methods:** We conducted an analytical, non-randomized, cross-sectional study on the Patterns of Failure in 1238 patients with primary breast cancer who reported to our Regional Cancer Centre from 2002 to 2010. **Results:** A total of 1238 patients with 1189 females and 49 males were evaluated. Most of the patients were above fifty years of age with breast lump being the most common presentation. Infiltrating ductal carcinoma was the most common histology and stage II being the commonest stage of presentation. Most of the patients were hormone receptor positive and Her 2 neu receptor negative. Overall local failure was 3.9%, regional failure 2.7% and distant failure 22.5%. Overall 5 year disease free survival was 78.4%. **Conclusion:** The most common form of local failure is chest wall recurrence, regional failure is supraclavicular lymphadenopathy and distant failure is bone metastasis. The 5 year disease free survival is lower for all the stages when compared to world scenario. This may be attributed to more aggressive disease behaviour in our patients.

Keywords: Patterns of failure, Breast cancer, Kashmir valley.

INTRODUCTION

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women (25% of all cancers).^[1] It is also the leading cause of cancer related deaths in women (14% of all cancer related deaths).^[2] In India, it is the second most common cancer among women after cancer cervix.^[3] In Kashmir, it is the commonest malignancy in females and constitutes approximately 17% of all cancers.^[4]

Breast cancer is strongly related to age, with only 7% of all breast cancers occurring in women under 40 years of age.^[5] Male breast cancer is an uncommon entity and represents less than 1% of all breast cancers and the median age is between 55 to 60 years.^[6] Ductal carcinoma is the most common invasive histology accounting for 70% to 80% of all

cases. Lobular carcinoma constitutes 10% to 15% whereas other types like papillary, tubular, mucinous, pure medullary carcinomas etc. comprise around 10% of all cases.^[7]

Management of invasive breast cancer is based on the clinical extent, pathological characteristics of tumor and age of the patient. The treatment of breast cancer includes a multidisciplinary approach comprising of local therapy (surgery and radiotherapy) and systemic treatment (chemotherapy, hormonal therapy, immunotherapy). The usual sequence of treatment is surgery followed by chemotherapy ± immunotherapy followed by radiotherapy and hormonal therapy.^[8] Surgical procedures include breast conserving surgery (BCS), modified radical mastectomy (MRM) and radical mastectomy (RM).^[9] Breast Conserving Therapy (BCT) comprises of breast conserving surgery (BCS) and Radiotherapy.^[10] Radiotherapy includes Post BCS RT (i.e. BCT) and post mastectomy radiotherapy (PMRT). Systemic therapies comprise of different chemotherapy regimens, hormonal agents and immunotherapy.^[11]

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Understanding breast cancer pathophysiology has historically evolved from being a local disease in earlier times to a systemic disease in the present day setting. Relapses in breast cancer have primarily been systemic, as evident in the past literature & present day studies.^[12] Various trials aimed at improving breast cancer relapse using systemic modalities include the landmark Milan trial.^[13] Subsequently various trials were undertaken with newer chemotherapeutic drugs using various schedules & sequencing for improved survival and favourable toxicity profile.

Radiotherapy as an adjuvant treatment in breast cancer was used as early as 1940's, with initial results showing a decrease in local relapse rate, however recent studies have depicted a favourable impact on mortality trends also.^[14] Modifications in radiation delivery systems & precision have greatly affected the toxicity profile of radiotherapy, following which dose escalation with minimal treatment related morbidity have been possible.

Tamoxifen was explored as the first targeted therapy in breast cancer patients in early 1970's. The idea of targeting estrogen receptors (in receptor positive patients) with a competitive antagonist like tamoxifen resulted in it being used as a chemopreventive drug in high risk women.^[15] Continued research on the pharmacology of tamoxifen facilitated its ubiquitous use for the targeted treatment of breast cancer, chemoprevention and pioneered the exploration of selective oestrogen receptor modulators (SERMs).^[16]

Amplification of the HER-2 neu gene is a significant predictor of both overall survival and time to relapse in patients with breast cancer.^[17] Role of trastuzumab, a humanized monoclonal antibody is well established in advanced breast cancer, its recent role in the adjuvant setting has been shown to reduce the disease recurrence by about 50% & mortality by about 35%.^[18]

The majority of breast cancer recurrences occur within the first five years of diagnosis. Various determinants affecting relapse include primary tumor size, nodal status, histological grade, resection margin status, lymphovascular & perineural invasion and receptors status.^[19] It is widely accepted that the appropriate use of adjuvant treatment improves the disease free and overall survival in breast cancer. It is therefore, standard clinical practice to give adjuvant treatment to breast cancer patients as per their stage of disease.^[20]

Breast cancers can recur locally after BCT and mastectomy. In patients who undergo mastectomy, recurrence is usually within the first 3 years of surgery and postmastectomy radiotherapy (PMRT) reduces the risk of locoregional recurrence (LRR) by about 60%–70% which in-turn impacts overall survival (OS).^[21] Locoregional recurrence rates are higher in women undergoing BCT without adjuvant RT, having positive margins, high grade tumor

and presence of lymphovascular invasion.^[22] Additional dose of radiation to the site of removed cancer reduces local recurrence by nearly 50% among women with stage I or II breast cancer.^[23] The chances of local recurrence after surgery appear to be very low, with a mean hazard of recurrence between years 5 to 12 post-surgery being 4.3% per year.^[24] Patients with ≥ 4 involved axillary lymph nodes, $>20\%$ involved axillary nodes, or gross extranodal extension are at increased risk of regional failure in the supraclavicular fossa & axilla.^[25] Predictors of distant failure include T stage, number of involved lymph nodes & HER-2 positivity.^[26] For stage I, stage II and stage III, 5 and 10 year breast cancer specific survival rates are 97.1% & 94.0%, 88.0% & 79.4% and 70.1% & 46.3% respectively.^[27]

Aims and Objectives:

To evaluate the patterns of failure in patients with Breast Carcinoma after definitive treatment modalities in terms of :

1. Local failure.
2. Regional failure.
3. Distant failure.
4. 5 year Disease free survival.

MATERIAL AND METHODS

This study was carried out in the Department of Radiotherapy, SKIMS, Soura, Srinagar. Patients with histologically confirmed Invasive Breast Carcinoma registered at RCC SKIMS from year 2002 to year 2010 were enrolled in the study. It was a retrospective study in which patients clinico-demographic characteristics such as sex, age, residence, site of tumor, stage at presentation, histopathological details, treatment prescribed and treatment received in each case were studied in detail. Follow-up details were thoroughly studied with regards to local failure, regional failure, distant failure and disease free survival. Patients who had completed the prescribed treatment with a follow up of more than five years were included in the study. Patients with Stage IV disease were excluded. The more advanced relapse was taken into consideration while evaluation of patients (distant failure > regional failure > local failure). A proper informed consent was taken from all the patients and the study was approved by the institute ethical committee.

RESULTS

A total of 1238 patients with 1189 females and 49 males were evaluated. The male to female ratio was 1:24. Seven hundred sixty eight patients (62%) were above fifty years of age and 757 patients (61%) belonged to rural background. Breast lump was the commonest presentation in 1104 patients (89%) with

majority of the patients having left sided lesions (51%). Commonest location of the tumor was upper outer quadrant (622 patients-50%) followed by central area (290 patients -23%). Ninety patients (7%) had family history of breast cancer. Infiltrating duct carcinoma was the commonest histology in 1110 patients (90%). One hundred four (8%) patients had Stage I, 645 patients (53%) Stage II and 480 patients (39%) had stage III disease. Hormonal receptor status was positive in 788 patients (64%) and Her 2 neu was positive in 247 patients (20%). [Table 1]

MRM was the commonest surgical procedure done in 993 patients (80%) followed by BCS in 101 patients (8%). FEC/FAC was the most commonly administered chemotherapy regimen in 1074 patients (87%). Radiotherapy was received by all the patients to appropriate sites at recommended doses. Tamoxifen was the most common hormonal agent prescribed in 450 patients (36%). Trastuzumab was received by only 37 patients (3%). [Table 2]

Table 1: Patient Characteristics.

Parameter	Stage I	Stage II	Stage III
Sex			
Male	0(0%)	12(0.9%)	37(2.9%)
Female	104 (8.5%)	642 (51.9%)	443 (35.8%)
Age			
<50 Years	91 (7.3%)	235 (18.9%)	144 (11.7%)
≥50 Years	13 (1.1%)	419 (33.8%)	336 (27.2%)
Residence			
Rural	91 (7.3%)	390 (31.5%)	0 (0%)
Urban	13(1.1%)	264 (21.4%)	480 (38.7%)
Clinical Presentation			
Lump	104 (8.5%)	604 (48.8%)	396 (31.9%)
Nipple Discharge	0(0%)	25 (2%)	36 (2.9%)
Others	0(0%)	25 (2%)	48 (3.9%)
Laterality			
Right	52(4.2%)	314(25.4%)	228(18.5%)
Left	52(4.2%)	340(27.4%)	240(19.4%)
Bilateral	0(0%)	0(0%)	12(0.9%)
Site			
Upper Outer Quadrant	52(4.2%)	402(32.5%)	168(13.6%)
Upper Inner Quadrant	0(0%)	26(2.1%)	156(12.7%)
Lower Outer Quadrant	0(0%)	0(0%)	96(7.7%)
Lower Inner Quadrant	0(0%)	0(0%)	48(3.8%)
Central Area	52(4.2%)	226(18.3%)	12(0.9%)
Family history			
Positive	23(1.9%)	32(2.5%)	45(3.5%)
Negative	81(6.4%)	622(50.3%)	435(35.2%)
Histopathology			
Infiltrating Duct Carcinoma	90(7.3%)	600(48.5%)	420(33.8%)
Infiltrating Lobular Carcinoma	6(0.4%)	40(3.3%)	50(4%)
Others	8(0.6%)	14(1.1%)	10(0.8%)
Hormonal receptor status			
Er/Pr Positive	44(3.5%)	475(38.4%)	269(21.7%)
Er/Pr Negative	50(4%)	49(4%)	154(12.5%)
Unknown	10(0.8%)	130(10.5%)	57(4.6%)
Her 2 neu Receptor status			

Positive	4(0.3%)	122(9.9%)	121(9.8%)
Negative	66(5.3%)	356(28.8%)	259(20.9%)
Unknown	34(2.7%)	176(14.2%)	100(8.1%)

Table 2: Treatment Modalities

Treatment	Stage I	Stage II	Stage III
Surgery			
Breast Conserving Surgery	91(7.3%)	10(0.8%)	0(0%)
Modified Radical Mastectomy	13(1.1%)	644(52%)	384(31.1%)
Radical Mastectomy	0(0%)	0(0%)	96(7.7%)
Chemotherapy			
FEC/FAC	100(8.1%)	634(51.2%)	340(27.4%)
AC FOLLOWED BY TAXANES	4(0.3%)	20(1.6%)	104(8.5%)
CMF	0(0%)	0(0%)	36(2.9%)
Radiotherapy			
Received	104(8.5%)	654(52.8%)	480(38.7%)
Not Recieved	0(0%)	0(0%)	0(0%)
Hormonal therapy			
Tamoxifen	44(3.6%)	370(29.9%)	36(2.9%)
Letrozole	0(0%)	180(14.6%)	230(18.6%)
Tamoxifen Followed By Letrozole	10(0.8%)	20(1.6%)	30(2.4%)
Exemestane	0(0%)	35(2.8%)	30(2.4%)
No Hormonal Therapy	50(4%)	49(4%)	154(12.4%)
Targetted therapy (trastuzumab)			
Received	0(0%)	25(2%)	12(0.9%)
Not Recieved	104(8.5%)	629(50.8%)	468(37.9%)

Table 3: Patterns of Failure

Outcome	Stage I	Stage II	Stage III
No Failure	102 (8.3%)	576 (46.6%)	196 (15.9%)
Local Failure			
Chest Wall	0 (0%)	15 (1.2%)	31 (2.5%)
Post Bct Scar	2 (0.1%)	1 (0.1%)	0 (0%)
Regional failure			
Supralavicular Fossa	0(0%)	12(0.9%)	12(0.9%)
Axilla	0(0%)	0(0%)	12(0.9%)
Distant failure			
Bones	0(0%)	25(2%)	109(8.8%)
Lungs	0(0%)	13(1.1%)	48(3.9%)
Liver	0(0%)	12(0.9%)	36(2.9%)
Brain	0(0%)	0(0%)	36(2.9%)

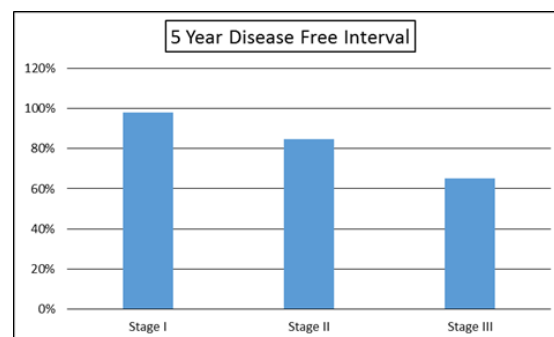


Figure 1: Stage wise 5 Year Disease Free Survival

Overall local failure was 3.9%. Post-BCT scar recurrence constituted 0.2% and chest wall failure was 3.7%. The post BCT scar recurrence was 1.9% in Stage I, 0.1% in stage II and was 0%

for stage III. Chest wall failure was 0.0% in stage I, 2.3% in stage II and 6.5% in stage III. Overall regional failure was 2.7%. Among regional failures, supraclavicular constituted 1.8% and axilla 0.9%. Supraclavicular failure was 0.0% in stage I, 1.8% in stage II and 2.5% in stage III. Axillary failure in stage I & stage II was 0.0% and 2.5% in stage III. Overall distant failure was 22.5%. The first site of distant failure was taken into account while evaluating patients. Bone was the most common site of distant metastasis in 10.2% followed by lung (5%), liver (3.8%) and brain (2.9%). Distant failure in stage I was 0.0%, 7.6% in stage II and 47.7% in stage III. Bone as site of distant failure for stage II constituted 3.8%, lung constituted 1.9% and liver constituted 1.8%. For stage III, skeletal metastasis constituted 22.7%, lung 10%, liver 7.5% and brain 7.5%. [Table 3]

Overall 5 year disease free survival was 78.4% (970/1238). For stage I it was 98.1% (102/104), for stage II it was 84.5% (555/654) and for stage III it was 65.2% (313/480). [Figure 1]

DISCUSSION

Breast cancer is amongst the commonest female malignancies in Kashmir, corroborating world statistics, but differs with the Indian data, where cancer cervix is the number one malignancy among females.^[28] This may be attributed to difference in lifestyle and religious practices between the two populations. As per literature, sex being the highest risk factor for breast cancer, over 95% of all breast cancers are seen in females.^[29] In our study 96% of patients were females and 4% were males. Male breast cancer being an uncommon disease, represents less than 1% of all breast cancers.^[30] The incidence of breast cancer increases steadily with age. As per international data, about 75% of breast cancers are diagnosed in post-menopausal women.^[31] In our study, around 65% patients were post-menopausal.

Breast cancer is seen to be more prevalent among women of higher socio-economic background.^[32] In our study around 50% patients belonged to a higher socio-economic status.

Left sided breast cancer was slightly higher than right sided breast cancer (51% vs 49.1%) in our patients which is in accordance with world literature.^[33] As per literature, bilateral breast cancer constitutes about 1-2% of all patients and it was 0.9% in our study.^[34]

Breast lump was the commonest presentation in our patients in 89.2% cases followed by nipple discharge in 4.9% patients. Other presentations like axillary LAP, skin changes etc. were present in 5.9% patients. Globally, breast lump is the most common presentation in breast cancer patients.^[35]

In our study, tumor was located in upper outer quadrant in 50.3% patients and in lower inner quadrant in 3.8% patients. Thus, the most common

location of tumor was upper outer quadrant and the least one was lower inner quadrant. As per international data also, the most common site of breast tumor is upper outer quadrant and the least one is lower inner quadrant.^[36]

In our study 7.9% patients had a positive family history of breast cancer which is comparable with world literature.^[37]

The most common histology in our patients was invasive ductal carcinoma in 89.6% cases. According to world literature also invasive ductal carcinoma is the most common histology in 70% to 80% patients followed by invasive lobular carcinoma in 10% to 15% patients.^[38]

Majority of patients in our study were ER/PR positive (63.6%) and Her 2 neu negative (55%). Nearing sixteen percent (15.9%) patients had unknown ER/PR status and 25% patients had unknown Her 2 neu status. Close to fifteen percent (14.7%) patients were triple negative. As per literature 10.2% patients are ER/PR+, Her2+; 68.9% are ER/PR+, Her2-; 7.5% are ER/PR-, Her2+, and the remaining 13.4% are classified as triple negative.^[39]

In our study, 83.2% patients underwent MRM, which is the most common surgical procedure done for the management of carcinoma breast.^[40]

Adjuvant FEC /FAC based chemotherapy for a total of six cycles was received by 86.7% patients. As per literature, Adriamycin based chemotherapy is the most common chemotherapy prescribed for breast cancer patients as adjuvant treatment.^[41]

In our study, patients were treated with EBRT to appropriate sites at adequate doses. Patients who had undergone MRM/RM received EBRT to chest wall and drainage sites to a dose of 45 Gy in 20 fractions, 5 fractions/week over 4 weeks. Patients who underwent BCS received EBRT to intact breast to a dose of 50 Gy in 25 fractions, 5 fractions per week over 5 weeks followed by a boost of 15 Gy in 7 fractions to tumor bed. 75 patients (6%) received boost to tumor bed. Twenty five percent of patients who underwent BCS did not receive boost to tumor bed. The schedule of EBRT given to our patients is in accordance with global practice for the same.^[42]

In our study, 36.4% patients received Tamoxifen, 33.2% patients received Letrozole and 4.8% patients received Tamoxifen followed by Letrozole. The administration of hormonal therapy was as per international guidelines.^[43]

Only 3% patients received Trastuzumab for one year with each cycle being administered three weekly. Most of the Her 2 neu positive patients could not afford Trastuzumab due to financial constraints. Wherever administered, it was given according to standard practices.^[44]

The locoregional recurrence rate for stage I breast cancer is approximately 5-10%, for stage II, it is about 10-25% and for stage III it is about 50-45%. The overall risk of LRR, including

the chest wall and nodal sites, is influenced by tumor size, tumor grade, the presence or absence of lymphovascular space invasion, surgical margin status, involvement of the fascia or skin, the number of involved nodes and the percentage of nodal involvement⁴⁶. The frequency of locoregional recurrence is 30% among patients who do not receive adjuvant treatment and 5% for patients who receive adjuvant treatment.⁴⁷ In our study, the overall locoregional failure was 6.6% with local failure comprising 3.9% and regional failure 2.7%. In stage I locoregional failure was 0.1%, in stage II 2.2% and stage III 4.3%.

Post-BCT scar recurrence was 1.9% for stage I, 0.1% for stage II and 0% for stage III. Chest wall failure for stage I was 0%, 2.3% for stage II and 6.4% for stage III. All 3 cases of post BCT scar recurrence were seen in patients who did not receive boost to tumor bed. As per international literature, boost to tumor bed decreases the risk of local failure.⁴⁸

Seventeen percent of patients who had chest wall failure had positive resection margins which is considered a strong risk factor for the same.⁴⁹

Among regional failure, supraclavicular failure for stage I was 0%, 1.8% for stage II and 2.5% for stage III. Axillary failure for stage I was 0%, it was also 0% for stage II and 2.5% for stage III. Thirty two percent patients among regional failures had inadequate nodal dissection and eleven percent had perinodal extension. Most of the studies have shown that SCF was the most common site followed by axilla among regional failures.⁵⁰

Approximately 10–15% of patients with breast cancer have an aggressive disease and develop distant metastases within 3 years after the initial detection of the primary tumor. However, the manifestation of metastases at distant sites 10 years or more after the initial diagnosis is also not unusual. The risk of metastasis development increases with the presence of lymph-node metastasis, a larger-sized primary tumour and loss of histopathological differentiation (grade).⁵¹ In our study, distant failure was 0% in stage I, 4% in stage II and 18.5% in stage III. The 4 most common anatomic sites of distant metastases as the first exclusive event after treatment for breast cancer are bone (41.1%), lung (22.4%), liver (7.3%), and brain (7.3%).⁵² With respect to site wise distant failure in our patients, bone constituted 48% of distant failure, lungs 21.8%, liver 17.2% and brain 13%.

Five year disease free survival rates are influenced by tumor size, nodal status, receptor status and age of the patient. Relative survival rates for women diagnosed with breast cancer are 89% at 5 years after diagnosis, 83% after 10 years and 78% after 15 years⁵³. Five-year relative survival is lower among women with a more advanced stage at diagnosis. The 5-year relative survival is 99% for

localized disease, 84% for regional disease, and 24% for distant-stage disease. Larger tumor size at diagnosis is also associated with decreased survival. Among women with regional disease, the 5-year relative survival is 95% for tumors less than or equal to 2.0 cm, 83% for tumors 2.1-5.0 cm, and 65% for tumors greater than 5.0 cm.⁵⁴ As per National Cancer Institute SEER data-base, the 5-year disease free survival rates for stage I, stage II and stage III are 100%, 93% and 72% respectively⁵⁵. In our study 5-year DFS for stage I was 98.1%, for stage II 84.5% and stage III 65.2%. Overall 5 year DFS was 78.4%.

CONCLUSION

Breast cancer is the most common malignancy among females in our population. Most of the patients had histology of invasive ductal carcinoma with stage II being the commonest presenting stage. Most of the clinico-demographic parameters had a similar pattern of distribution when compared with rest of the world. The treatment protocol administered in our patients were in accordance with international guidelines. Chest wall recurrence was the most common form of local failure while supraclavicular lymphadenopathy, the commonest form of regional failure. Bone was the most common site of distant metastasis and stage III patients were the most predisposed for the same. The 5 year disease free survival was lower for all the stages when compared to world scenario. This may be attributed to more aggressive disease behaviour in our patients. However, further studies are needed so that exact cause for the same is ascertained.

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