



## TO STUDY THE CLINICAL AND PATHOLOGICAL STAGING OF BREAST CANCER AND TO CORRELATE THESE FINDINGS WITH STATUS OF THE TUMOR MARKERS

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**ABSTRACT**

**INTRODUCTION :** The breast cancer markers that are most important in determining therapy are estrogen receptor, progesterone receptor, and HER-2/neu. Clinicians evaluate clinical and pathologic staging and the expression of estrogen receptor, progesterone receptor, and HER-2/neu in the primary tumor to assess prognosis and assign therapy.

**AIMS AND OBJECTIVES:** To study the clinical and pathological staging of breast cancer and to correlate these findings with status of the tumor markers.

**MATERIALS AND METHODS:** 40 breast cancer patients who attended department of general surgery, RIMS srikakulam and king george hospital between october20012 to september 2014 were included in this study. All the patients were submitted to detailed clinical examination and investigations including FNAC to confirm the disease and to find out the clinical stageAll the details/data of 40 patients is analyzed to find out whether there is any correlation between clinical staging, pathological staging and tumor markers. An attempt was made to compare the findings of the study with the available Indian and international studies.

**OBSERVATIONS & RESULTS:** In this study majority of the patients presenting with carcinoma breast belong to 5<sup>th</sup> and 6<sup>th</sup> decade. Our observation regarding the stage of the disease revealed that stage II and stage III disease was equally distributed. Of the 14 patients in the age group 20-40yrs 7 presented with stage II and remaining 7 with stage III, 10 patients in the age group 41-60yrs presented with stage II disease where as 11 presented with stage IIIdisease. Our observation regarding the stage of the disease revealed that 24 were in pathological stagell and 16 were in stagelll. Majority of the patients(15) were in stage IIB. Majority (23 out of 40) of the patients were presented with pN0 status, 10 with pN1, and 7 with pN2 stage. Clinically node negative cases were 19 out of 40. But pathologically node negative cases were 23 out of 40. 90% of patients with clinical stage II and stage IIB were remained in the same stage in pathological staging, where as in stage III A only 50% remained in the same stage. It is observed that change of clinical stage to pathological stage is due to change in nodal status.

**CONCLUSION :** Majority of the patients were triple negative independent of age, nodal status , clinical , pathological stage and histological type. Testing for ER, PR, Her2neu receptor status was recommended in all patients with breast cancer to facilitate neoadjuvant and adjuvant therapy and for the prognostication.

**KEYWORDS**

Infiltrating duct cell carcinoma, hormone receptors.triple negative tumors.

**INTRODUCTION:**

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20 to 59 years. It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer-related deaths in women. Selection of optimal therapy for breast cancer requires both an accurate assessment of prognosis and an accurate prediction of response to therapy. The breast cancer markers that are most important in determining therapy are estrogen receptor, progesterone receptor, and HER-2/neu. Clinicians evaluate clinical and pathologic staging and the expression of estrogen receptor, progesterone receptor, and HER-2/neu in the primary tumor to assess prognosis and assign therapy.Tumors positive for both receptors have response rate of >50%, tumors negative for both receptors have a response rate of <10%, and tumors positive for one receptor only have an intermediate response rate of 33%. When Her2neu is over expressed in breast cancer, Her2neu promotes enhanced growth and proliferation and increases invasive and metastatic capabilities. Testing for Her2neu can be done with immunohistochemical analysis to evaluate the overexpression of the cell surface receptor at the protein level or by using fluorescent in situ hybridization(FISH) to evaluate for gene amplification. Patients whose tumors overexpress Her2neu are candidates for anti-Her2neu therapy. Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody directed against Her2neu. During the last decade significant advances were made in the management of breast cancer with invention of new treatment modalities. So a study based on clinical staging,

pathological staging, hormone receptor status and Her2neu status is important in the appropriate management of the breast cancer patients.

**AIMS AND OBJECTIVES:**

Low incidence of positive hormone receptor status was reported in Indian women. So a study was conducted mainly focusing on the clinical stage, pathological stage and tumor markers status with the following objective:

To study the clinical and pathological staging of breast cancer and to correlate these findings with status of the tumor markers.

**MATERIALS AND METHODS**

40 breast cancer patients who attended department of general surgery, RIIMS SRIKAKULAM and King george hospital Visakhapatnam between October 20012 to september 2014 were included in this study. All the patients were submitted to detailed clinical examination and investigations including FNAC to confirm the disease and to find out the clinical stage.

Investigations included FNAC, X-ray chest and Ultrasound abdomen. Tru cut biopsy for locally advanced malignancies to assess the tumor marker status to facilitate neoadjuvant therapy. All the patients are grouped into early breast cancer, locally advanced breast cancer and treatment is initiated according to the protocols. For early breast cancer modified radical mastectomy followed by adjuvant therapy depending upon the histopathology

report and tumor markers, for locally advanced breast cancers neoadjuvant chemotherapy followed by modified radical mastectomy and adjuvant therapy as indicated. All the specimens after modified radical mastectomy are subjected to histopathological examination including pathological staging, grading and tumor markers (ER, PR and Her2neu ). All the details/ data of 40 patients is analyzed to find out whether there is any correlation between clinical staging, pathological staging and tumor markers.

An attempt was made to compare the findings of the study with the available Indian and international studies.

**OBSERVATIONS & RESULTS**

**Age distribution in the study group**

In this study majority of the patients presenting with carcinoma breast belong to 5<sup>th</sup> and 6<sup>th</sup> decade, which is represented as 21 out of 40 patients. 14 patients belong to 3<sup>rd</sup> and 4<sup>th</sup> decade. Only 5 patients belong to the age group of 61-80yrs. 14 were <40yrs age with a median age of 33 yrs, 26 were >40yrs age with a median age of 54.8yrs. Youngest patient was 23 yrs old. Oldest one was 80yrs aged male patient.

**Clinical staging in the study group**

Our observation regarding the stage of the disease revealed that stage II and stage III disease was equally distributed. We did not encounter any case with stage I and stage IV disease during the period of study.

**Age distribution in clinical stage:**

Of the 14 patients in the age group 20-40yrs 7 presented with stage II and remaining 7 with stage III, 10 patients in the age group 41-60yrs presented with stage II disease where as 11 presented with stage III disease. It has been observed in our study that among the patients in 61-80yrs age group only one presented with stage IIA , 2 each in stage IIB and IIIA. Patients of younger age are presenting with early clinical stage. In this study majority (19) presented with T3 stage, 14 presented with T2 and remaining with T4 stage. No patient with T1 stage was encountered in our study. When studying the nodal status of the disease 19 presented with N0 stage, 17 presented with N1 stage and the rest with N2 disease. 11 out of 14 patients with T2 tumors had N0 status, 11 out of 19 patients with T3 tumors had N1 status and 5 out of 7 patients with T4 tumors had N1 status.

Patients with large tumors are having more advanced lymph node status in our study.

**Pathological staging in the study group :**

Our observation regarding the stage of the disease revealed that 24 were in pathological stageII and 16 were in stageIII. Majority of the patients(15) were in stage IIB. We did not encounter any case with stageI and stage IV disease during the period of study.

Of the 14 patients in the age group 20-40yrs observations were similar to clinical staging. 13 patients in the age group 41-60yrs presented with stageII disease where as 8 presented with stageIII disease. Among the patients in between 61-80yrs age only 4 presented with stageII and remaining 1 in IIIA. Similar to clinical stage patients of younger age are presenting with early pathological stage.

**Distribution of pathological nodal status in study population:**

Majority (23 out of 40) of the patients were presented with pN0 status, 10 with pN1, and 7 with pN2 stage. Clinically node negative cases were 19 out of 40. But pathologically node negative cases were 23 out of 40. Which indicates that 4 patients who were clinically positive for nodes found to be negative on pathological examination. Clinical N1 were 17, but pathological N1 were 10. Clinical N2 were 4, but pathological N2 were 7. The discrepancy with regards to clinical N1 and N2 to pathological N1 and N2 is due to different criteria adopted in staging the nodal status pathologically.

**Correlation between clinical stage and pathologic stage**

In this study when a correlation was made between clinical stage and pathological stage it was observed that out of 11 patients with clinical stage IIA 9 belonged to pathological stageIIA, 1 to IIB and 1 to IIIA. It has been observed that all the 9 patients with clinical stage IIB pathologically also belonged to stage IIB.

Among the 10 patients with clinical stage IIIA, 4 patients pathologically belonged to stage IIB, 5 belonged to IIIA and 1 to stage IIIB.

Among 10 patients of clinical stage IIB, 9 belonged to pathological stage IIB and 1 was grouped under IIB.

90% of patients with clinical stage II and stage IIB were remained in the same stage in pathological staging, where as in stage III A only 50% remained in the same stage .

In stage IIA 1 case was upstaged to pathological stage IIB and another case was upstaged to IIIA. In stage IIB one case was down staged to IIB . In stage IIIA 4 cases were down staged to IIB .This was due to change in nodal status and different criteria adopted in pathological nodal staging. It is observed that change of clinical stage to pathological stage is due to change in nodal status.

**TABLE 1: Showing Receptor status in the study group**

Receptor status	No.of patients
ER+,PR+,HER2neu+	0
Hormone receptor +, HER2neu-	10
Hormone receptor-, HER2neu+	5
ER-,PR-,HER2neu-	25

Hormone receptor positive and Her2neu positive cases are not present in this study.25 cases were triple negative.10 cases were reactive for hormone receptors but negative for Her2neu. 5 cases were non reactive for hormone receptors but positive for Her2neu.

**Relationship of hormone receptor status with age:**

9 out of 14 (64.3%) in 20-40 yrs age group were triple negative . 13 patients in the age group of 41-60yrs were triple negative which accounts to 61.9% .Similar to the above two age groups in 61-80yrs age group triple negative constituted 60% . So in each of the above mentioned age groups triple negative tumors were contributing to nearly 60% . So triple negative cases were almost equally distributed in all the age groups.

**TABLE 2 : Showing Relationship of receptor status to clinical stage**

Clinical stage	Number of patients	Hormone receptor+,HER2neu-	Hormone receptor-HER2neu+	Triple negative tumors
IIA	11	3	1	7
IIB	9	3	1	5
IIIA	10	3	3	4
IIIB	10	1	Nil	9

Triple negative tumors in stage IIA were 63.6% (7 out of 11), in stage IIIA were 40 %(4 out of 10), in stage IIB were55.5% and in stage IIIB were 90%(9 out of 10). As there was no linear relationship found between the clinical stage and triple negative status, definitive correlation between them could not be established.

**TABLE 3: Showing Relationship of receptor status to pathological stage**

Pathological stage	Number of Tumors	Hormone receptor+,HER2neu-	Hormone receptor-,HER2neu+	Triple negative tumors
IIA	9	3	1	5
IIB	15	3	1	11
IIIA	6	3	2	1
IIIB	10	1	1	8

In stage IIA 55.5% (5/9) tumors were triple negative, in stage IIB 73.3% where as in stage IIIA and IIIB tumors 16.7 % (1/6) and 80% (8/10) tumors were triple negative respectively. So definite correlation was not possible between the pathological stage and triple negative status.

#### Relationship of receptor status with T stage of tumor

50% (7/14) of T2 tumors, 63% (12/19) of T3 tumors and 85.7% (6/7) of T4 tumors were triple negative. These observations indicate that there is a linear correlation between the size of tumor and triple negative status.

#### Relationship of receptor status with clinical N stage of tumor

With respect to clinical N status we observed that triple negative were more common among N0 and N1 patients. Though it was not observed much in patients with N2, the number is very low to comment on it.

#### Relationship of receptor status with pathologic pN status of tumor

In pN0 status triple negative cases were 60.9% (14/23) where as Her2neu positive and luminal A were constituting 39.1% (9/23). In pN1 status triple negative cases were 7% (7/10) where as Her2neu positive and luminal A constituting 30% (3/10). Both Her2neu positive and luminal A constituting 42.9% (3/7) of cases in pN2 stage. Triple negative were contributing to 57.1% of the total pN2 cases.

From these observations we can conclude that in each pN status triple negative was more common than the other two groups.

**TABLE 4 : Showing Correlation of receptor status with histological type of tumor**

Type of tumor	Number of tumors	Hormone receptors+, her2neu-	Hormone receptors-, her2neu+	Er,pr, Her2neu-
Infiltrating duct cell ca NOS	32	9	3	20
Medullary ca	3	Nil	2	1
Invasive lobular ca	1	Nil	Nil	1
Tubular ca	2	1	Nil	1
Metaplastic ca	2	Nil	Nil	2

62.5% of Infiltrating duct cell carcinoma NOS are triple negative .28.1% belong to luminal A type and the remaining 9.3% belong to Her2neu positive type. In the Invasive lobular carcinoma and metaplastic carcinoma most triple negative cases were observed.

#### Relationship of tumor grade with receptor status

64.5% (20/31) of the grade1 tumors were triple negative. In grade 2 tumors 57.1% (4/7) were triple negative. 50% (1/2) of the grade 3 tumors were triple negative. Correlation cannot be established with these observations. Grading of tumor did not had any influence on triple negative status in my study. Because of small sample size it was not possible to come to a conclusion.

#### DISCUSSION

ER,PR and Her2neu receptors are the useful prognostic and predictive markers to know the response to various modalities of treatment including chemotherapy, hormone therapy and biotherapy. These receptors are the first to be targeted for good response and outcome of therapy.

Basing on receptors status the carcinoma breast is divided into Luminal A, Luminal B, Her2neu positive and triple negative. In this study we have done an immunohistochemical analysis of hormone receptor status and Her2neu status in 40 patients suffering from breast cancer. In this study all the patients were evaluated through proper history and complete physical examination including various biochemical, pathological and radiological investigations. Following the evaluation, diagnosis was confirmed and patients

were operated and specimens sent for histopathological examination and assessment of tumor markers. The information obtained from the pathological studies is utilized to identify the pathological staging. An attempt was made to correlate clinical staging and pathological staging with tumor markers.

In this study the mean age of breast cancer patient was 47.9yrs, which is much lower than the mean age of 56yrs reported in a similar study<sup>1,2</sup> done on 55 breast cancer patients at Indira Gandhi medical college, Shimla, Himachalpradesh, India.

The incidence of carcinoma breast in India is rising in younger population. Patients with younger age are presenting with early clinical stage and early pathological stage. This may be probably due to increased awareness among these people. In pre operative staging both stage II and stage III were equally distributed in the population. But in pathological staging more number of patients are in stage II.

In this study clinical node negative cases were 47.5% and node positive cases were 52.5%, whereas Navani et al<sup>3</sup> reported 52.8% of node negative cases and 47.2% of node positive cases.

Of the 40 cases majority 19(47.5%) of the patients in this study were presented with T3 tumors, 14(35%) presented with T2 tumors and 7(17.5%) presented with T4 tumors. Tata memorial cancer hospital registry reported majority (60%) of patients with T2 lesions, S.B.Desai et al<sup>4,5,6</sup> also reported the same (57%). But in my study majority of the lesions were T3 tumors.

90% of the patients with clinical stage II and stage IIB were remained in the same stage in the pathological stage, whereas 50% of stage IIIA tumors remained pathologically also in the same stage. Correlation between clinical staging and pathological staging was observed in majority of the patients in this study.

In this study stage II and stage III tumors were equally distributed with each contributing to 50%. Tata memorial cancer hospital registry was showing patients presenting with stage II as 57.4% and stage III as 28.9%. Compared to Tata memorial cancer hospital registry, in my study patients presenting with stage II disease were less in number and those with stage III disease were more in number. In Tata memorial cancer hospital registry 7.8% cases were in stage I and 5.9% cases were in stage IV. But in my study period stage I and stage IV tumors were not encountered.

In this study hormone receptor positivity with Her2neu positivity was not encountered. 25 out of 40 (62.5%) presented as triple negative cases, whereas Her2neu positive cases were only 5(12.5%). Majority of the triple negatives were seen in the age group 41-60yrs. Triple negative cases were more common in patients with clinical stage III and pathological stage III. When comparing this data with Adedayo et al<sup>5</sup> which was done on 1134 carcinoma breast patients with a median age of 62.7yrs in Marshfield clinic/ St. Josephs hospital reporting ER/PR+Her2neu+ as 10.2%, ER/PR+, Her2neu- as 68.9%, ER/PR-Her2neu+ as 7.5% and triple negative as 13.4%, my study showed more number of triple negative cases and less number of Her2neu positive cases. This may be explained by small sample size and more number of younger patients in this study. Breast cancer cases seen by me are a decade younger as compared to those seen in the west. Young patients have high circulating levels of estrogen and correspondingly low expression of steroid receptors which is reflected in their tumors.

Triple negative tumors were common in patients presenting at an advanced clinical stage or pathological stage and with large tumors. In each N stage and pN stage and T stage triple negative cases were more common than other two types. Node negative cases were showing 10.5% of Her2neu positive tumors and Node positive tumors showing 14.3% of Her2neu positive tumors. When comparing this data with Navani et al<sup>5</sup> study done in Breach candy hospital, Mumbai on 48 cases of breast cancer patients which had reported 90% of Her2neu positive tumors in node

negative cases and 83.3% Her2neu positive tumors in node positive cases. Her2neu positive cases were very less among both node negative and node positive cases in my study. When compared to Navani et al study high proportion of Her2neu negative cases in my study were probably due to the younger age of our patients.

7Adedayo et al study published in clinical medicine and research volume7 reported 31.5% ER/PR+,Her2neu negative cases, 43.5% Her2neu positive cases and 43.4% triple negative cases in stage II. But in this study among stage II cases 30% were ER/PR+,Her2neu-, 10% were Her2neu positive tumors and 60% were triple negative tumors. When comparing with Adedayo et al study this study reporting more number of triple negative tumors and less number of Her2neu positive tumors with almost equal number of ER/PR+ with Her2neu – tumors(luminal B).

In stage III cases Adedayo et al reported 5% ER/PR+,Her2neu negative cases 22.4% Her2neu positive cases and 11.2% triple negative cases. But in my study among stage III cases 20% were ER/PR+,Her2neu-, 30% were Her2neu positive tumors and 13% were triple negative tumors. When comparing with Adedayo et al study my study reported more number of ER/PR+ with Her2neu-tumors, triple negative tumors and Her2neu positive tumors. Interestingly both the studies reported similar values for triple negative cases in stage III. Percentage of triple negative cases and Her2neu positive cases in this study were more when comparisons made with Adedayo et al study.

8,9 With advanced stage of tumor Her2neu positive cases were increased in this study. The same observation was reported in the study done in 40 breast cancer cases by Lifespan Academic Medical centre cytogenetics laboratory, Rhode island Hospital, USA, which showed 0% Her2neu positive cases in stage II and 10% Her2neu positive case in stage III. In this study Her2neu positive cases were 10% and 30% in stage II and stage III respectively. These values were much higher when compared to the above study. Some linear correlation was observed in both studies between advanced stage of the disease and Her2neu overexpression.

Infiltrating duct cell carcinoma NOS was the common histological variant and is found in 80% Of study population. Out of them 62.5% were triple negative. Badwe R.A.et al8reported >80% of cancers as infiltrating duct cell carcinomas in different religious communities of India.

In this study 77.5% cases are grade1, 17.5% are grade 2 and only 5% are grade3. Badwe R.A.et reported 6% of cases in both grade1 and grade2, 86% of cases in grade3. Eventhough 80% of cases in both of the studies were histologically belong to infiltrating duct cell carcinoma similarity was not found in grading. In my study no correlation was found between Grade of the tumor with tumor markers.

**CONCLUSION:** Carcinoma breast is essentially a disease of 5th and 6th decades, however there is rising incidence in the younger population. The commonest stages of presentation were stage II and stage III in both clinical staging and pathological staging. There is a good linear correlation between clinical stage and pathological stage. Majority of the cases were Infiltrating duct cell carcinoma NOS type, out of them majority were triple negative. Majority of the patients were triple negative independent of age, nodal status, clinical, pathological stage and histological type. Testing for ER, PR, Her2neu receptor status was recommended in all patients with breast cancer to facilitate neoadjuvant and adjuvant therapy and for the prognostication.

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