Original Research Paper

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Radiotherapy

CLINICOPATHOLOGICAL STUDY IN TRIPLE NEGATIVE BREAST CANCER

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ABSTRACT **Background and Objectives: -** Carcinoma Breast is most common malignancy in females in USA and second among cases deaths in females (after lung cancer). There is considerable geographic , ethnic and racial variability in Breast cancer in evidence with about 5 fold variation throughout the world. Triple negative breast cancer is a heterogonous disease diagnosed by Immune Histo Chemistry (IHC).Triple Negative Breast cancer is characterized by tumor that do not express ER or PR and HER2neu . Proto typical Triple Negative Brest cancer is aggressive in nature and associate with poor prognosis. The Objectives of this study is to analyse the clinical and Pathological features of Triple Negative Breast Cancer and compare the result with similar studies in literature. **Methods:-** Fifty cases Triple negative Breast Cancer were included in this study. Clinical and pathological features and treatment were noted. **Result:-** Incidence of Triple Negative Breast Cancer was 35%. The median age of presentation was 45yrs. There were 4% males Triple negative Breast cancer cases out of female patients, most of patients were Pre (or) Perimenopausal(65%). 4% patients had family history of malignantly. Most common stage of presentation was stage III (46%). In Stage IV, Lung and bone metastasis was common. Ten Patients received Neoadjuvant chemo therapy (NACJ) and disease progressed in 4% while on Neoadjuvant chemotherapy, Even though 45 patients had surgery only 34 were eligible to received Adjuvant Radiotherapy. Total of 18% Patients had either progressive disease while on treatment (8%) (or) recurrence 10%. Eighteen percent patients died due to the disease. 33% patients on follow up. There were more Invasive Duct Cell carcinoma (IDCC) cases with medullary differentiations (or) Purse medullary Carcinomas (12%). No deaths Occur in the medullary variants TNBC. Majority of the tumor were high grade margins were negative in most of the cases. **Inclusion:-** Incidence of Triple negative breast cases was higher than western literature but comparable to Indian Studies. The age of Presentation was about 10 years younger than western data. Triple Negative Breast cancer was more common in young, pre (or) perimenopausal women. Small number of patients had family history, majority were state II (or) III. There was high number of progressive disease, recurrence and death while on the study (or) within less than 1 yr of treatment. Triple Negative Breast cancer is very aggressive disease with relatively better prognosis in the medullary variant Triple Negative Breast Cancer.

KEYWORDS : Triple negative breast Carcinoma, Clinicopathological analysis, Pathological types, Pathological grade.

INTRODUCTION

Carcinoma breast is the most common malignancy in females in USA and second among cancer deaths in females (after Lung Cancer). There is considerable geographic, ethnic and racial variability breast cancer incidence with about 5-fold variation throughout the world.

Triple Negative Breast cancer is a heterogeneous disease diagnosed by Immune Histochemistry (IHC).Triple Negative Breast Cancer is characterized by tumors that do not express HER (or) PR and also do not over express HER2neu. Prototypical Triple Negative breast cancer is aggressive in nature and associated with poor prognosis .

Recent advance in genomic technique have lead to the classification of breast cancer into '4' district subtypes; the luminal A , luminal B, HER2 neu positive and basal like subtype. The fourth group is roughly synonymous with Triple negative Breast cancer, featuring absence of ER,PR,HER2neu receptor expression .

AIM & OBJECTIVES

- To analysis the clinical and pathological features of Triple Negative Breast Cancer cases.
- To record all the clinical and pathologies features of Triple Negative Breast cancer cases.
- To stages all cases clinical and record the detail of treatment and response to treatment including chemotherapy surgery and radiotherapy.
- To cancer the clinical pathological features, incidence, response to therapy and behavior of Triple Negative Breast Cancer.

METHODS

The clinicopathogical analysis in Triple Negative Breast cancer. Fifty Breast cancer patients were included in this study. All cases were staged clinically and pathologically and record the details of treatment and response to treatment including chemotherapy, surgery and Radiotherapy.

METHODOLOGY

Fifty cases Triple Negative Breast cases were included in this study, clinical and pathological features and treatment were noted.

Clinical Features

- Age
- Sex
- Menstrual status
- Family history for malignancy, side of breast involved with malignancy
- Tumor size
- Groups of regional lymph nodes involved
- Number of lymph node involved
- sites of metastasizes at presentation
- sites of disease at recurrence suspecting clinically and radiological

Pathological Feature

- Tumor histology in FNAC , biopsy and Histopathological examination (HPE)
- Pathological tumor size
- Number of lymph node involved
- Margin status
- Grade of tumor
- Pathological staging of tumor
- Hormonal receptor status of tumor including ER,PR,HER-2neu at presentation and avid at recurrence of disease.

All cases are staged clinically and pathologically and details of treatment.

Chemotherapy Types:- Neoadjuvant CT , Adjuvant CT, Palliative CT

- Patient received Neoadjuvant CT – 10 Patients (AC, FAC & FEC)
- Patient received Adjuvant CT – 35 Patients (AC, AC-TP, FAC &CMF)
- Patient received Palliative CT – 12 Patients (AC-P, FAC, P, M)

Surgery:-

45 Patients had surgery
MRM – 37 Patients
BCS – 7 Patients
SM – 1 Patient

Radiotherapy

34 Patients undergo adjuvant RT, ,Adjuvant RT to Chest wall, axilla & supraclavicular fossa & Intact Breast.

For all patients received adjuvant RT radiation planning was done by conventional planning. Radiation was delivered to all patients with photon on linear accelerator.

Total dose of 50 Gy/25F/200CCy/day, 5 fractions per week. Patients with intact breast irradiation, radiation boost of 15 Gy to lumpectomy site was delivered with electrons, after completion of 50 Gy dose. Only 1 patient had neoadjuvant RT after completion of chemotherapy followed by surgery.

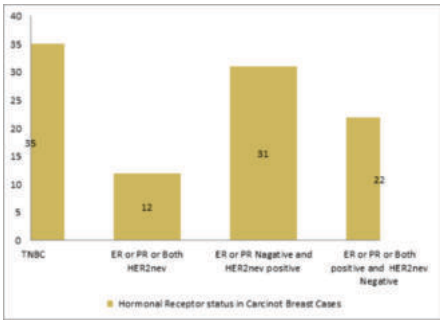
Palliative RT given for 4 patients. Patients was evaluated every week for RT related side effects.

RESULT

Incidence of TNBC was 35% in current study.

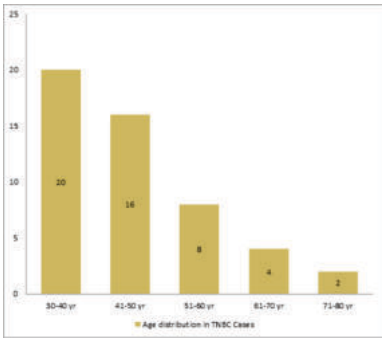
- Patient with ER (or) PR (or) both ER and PR and HER2nev positivity were 12%
- Patient with ER and PR negative and HER2nev positive we 31%
- Patient with ER (or) PR (or) both ER and PR positive and Her2nev negative were 22%

Graph Showing Hormone Receptor Status In Carcinoma Breast Cases



1. Age:- Median age was 45 yrs
   Age of patient is varied from 30-75 yrs
   20 patients from 30-40 yrs
   16 patients from 41-50 yrs
   8 patients from 51-60 yrs
   4 patients from 61-70 yrs
   2 patients from 71-80 yrs

Graph Showing Age Distribution In TNBC Cases



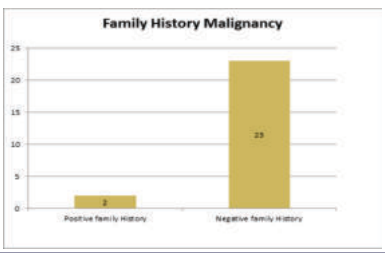
2. Sex:- There were 48 females and only 2 male patients with TNBC out of 50 cases.

Sex Distribution In TNBC Cases

Sex	Number of cases	Percentage of Patients
Female	48	96%
Male	2	4%

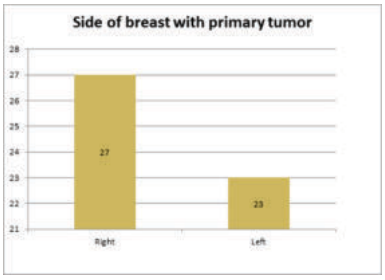
3. Family history of Malignancy- 2 patients site Breast with primary tumor.

Graph Showing Family History Of Malignancy In TNBC Cases



4. Right -27
   Left–23

Graph Showing Side Of The Breast Involve With Disease



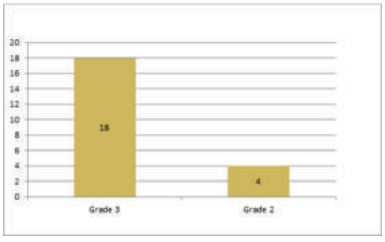
5. State distribution in TNBC cases
   Stage I 2 4%
   Stage II 20 40%
   Stage III 23 46%
   Stage IV 5 10%

Stage Distribution In TNBC Cases

Sl No.	Stage	No of cases	Percentage of Patients
1	I	2	4%
2	II	20	40%
3	III	23%	46%
4	Iv	5%	10%

6. Pathological grade of Tumor
   6(I). G3 – 18(81.8%)
   6(I). G2 – 4(18.82%)

Graph Showing Pathological Grade Of Tumor



Site Of Metastasis And Percentage Of Patients

Sl No.	Site of metastasis at presentation (or) while on treatment	No of Patients	Percentage of Patients
1	Liver	3	60%
2	Lung	2	40%
3	Bone	4	80%
4	Chest Wall	1	20%

Types Of Neoadjuvant CTAnd Percentage Of Patients

Sl No.	Type of NACT	No of Cases	Percentage of Patients
1	AC	6	12%
2	FAC	2	4%
3	FEC	2	4%

AC – Adriamycin + Cyclophosphamide
FAC – 5FU + Adriamycin + Cyclophosphamide
FEC – 5FU + Epirubicin + Cyclophosphamide

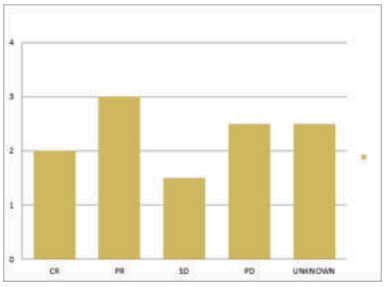
Type Of NACT And Response To NACT

Sl NO	Neoadjvant therapy	Response to Neoadjvant therapy
1	AC	PD after 3 cycles
2	AC	PR 50% after 4 cycles
3	AC	PR 50% after 4 cycles
4	AC	SD after 3 cycles
5	FAC	CR after 3 cycles
6	FAC	PR 60% after 3 cycles
7	FAC	PD after 4 cycles
8	FEC	No data after 3 cycles
9	FEC	No data after 3 cycles
10	4 AC + 50 Gy&T	CR

CR is Complete Response
PR is Partial Response

SD is Stable Disease
PD is Progressive Disease

Graph Showing Response To NACT According To WHO Criteria And Percentage Of Patients Response To Chemotherapy



Type Of Adjuvant Chemotherapy And Percentage Of Patients

Sl No.	Type of Adjuvant chemotherapy	No of patients	Percentage of Patients
1	AC 6 cycles	2	4%
2	Ac / T 4 cycles of AC the 4 cycles of T	25	50%
3	FAC - 6 cycles	7	14%
4	CMF - 6 cycles	1	2%

AC – Adriamycin and Cyclophosphamide
AC/T – Adriamycin and Cyclophosphamide and Taxol (paclitaxel)
FAC – 5 Fheorouracil , Adriamycin , Cyclophosphamide
CMF – Cyclophosphamide, Methotrexate and 5 Fheorouracil

Type Of Palliative CT And Percentage Of Patients

Sl No.	Type of Palliative CT	No of patients	Percentage of Patients
1	AC followed by T	6	12%
2	FAC	3	6%
3	Paclitaxel	2	4%
4	Mitomycin based	1	2%

Type Of Surgery And Percentage Of Patients

Sl No.	Type of surgery	No of patients	Percentage of Patients
1	BCS	7	14%
2	SM	1	2%
3	MRM	37	7%

BCS – Forecast Conservative Surgery
SM – Simple Mastectomy
MRM – Modified Radical Mastectomy

Type Of BCS And Percentage Of Patients

Sl No.	Type of BCS	No of patients	Percentage of Patients
1	Wide local excision with axillary dissection	6	12%
2	Quadrantectomy with axillary dissection	7	2%

Type Of Adjuvant RT , Treatment Areas And Percentage Of Patients

Sl No.	Type of adjuvant Radiotherapy	No of patients	Percentage of Patients
1	Chest wall , axilla including supraclavicular fossa	25	50%
3	Chest wall	2	4%
3	Breast , axilla supra clavicular fossa	5	10%
4	Intact breast	2	4%

Site Of Palliative RT

S. No	Site of palliative RT
1	Chest Wall
2	Shoulder , Pelvis
3	Chest, axilla , sef
4	Spine, femur

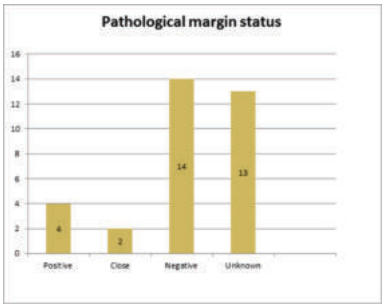
Site Of Recurrence And Progressive Disease

S. No	Site of Recurrence	Site of progression of disease
1	Bone , axilla, lung	Lung, bone
2	Liver	Chest Wall
3	Bone	Chest Wall
4	Liver	Liver
4	Infraclavicular lymph node	

Current Status Of Patient And Percentage Of Patients

S. No	Concurrent status of Patients	No of patients	Percentage of patients
1	Competed treatment on follow up	33	66%
2	Incomplete treatment	8	16%
3	Death due to disease	9	18%

Graph Showing Pathological Margins Of The Tumor After Surgery



Distribution Of TNBC By Stage In Different Countries

Country	Stage I	Stage 2	Stage 3	Stage 4
Canada	27%	54%	16%	2%
USA	29%	58%	13% (Stage 3&4)	13% (Stage 3&4)
India	12%	62%	15%	10%
Current Study	4%	40%	46%	10%

DISCUSSION

Triple Negative Breast Cancer is a heterogenous disease diagnosed by IHC. TNBC is characterized by tumors that do not express ER, PR and do not over express HER2neu prototypical TNBC is aggressive in nature and associate with poor prognosis.

The incidence of TNBC is variable in different ethnic groups. Incidence of TNBC is higher in the Indian studies compared to western literature (Delho12.5%), In the current study the incidence is 35.22%

In Our Study:-

Age:- The TNBC patients had median age of 54,57 (or) 64 yr depending on the race according to US studies.

Current study – median age of 45 yrs (30 - 75 yrs)

Sex:- Incidence of TNBC is very low in males.

Indian studies among TNBC case 50-56% were Pre (or) Perimenopausal presentation

In Current study it was 64%.

Incidence Of Family History:- In Indian studies family history of breast (or) Ovarian Malignancy was positive about 5% of TNBC cases.

In current study – 4%

Stage:- The most common stage of presentation for TNBC was Stage II according to Canada, USA and Indian studies.

In current study - Stage II and III but stage III was relative more common.

Metastasis:- In the current study Visual metastasis and soft tissue metastasis were more Common than bone metastasis (3/50)

Carcinoma Breast is more common in left breast according to western literature.

In some Indian study carcinoma breast is relatively more common on the right side.

In current study IDCC(80%) was the most common pathological type. Medullary and mixed IDce pattern (12%) was the second most

common type of TNBC. It is slightly higher than the other studies. Indian study IDCE 94%, Medullary variant – 4%.

In current study, majority of TNBC cases had a high grade tumour. High grade tumor have an aggressive behaviour compared to low grade tumours.

The high recurrent rate, disease progressive and high mortality rate shows that TNBC is an aggressive disease. Triple Negative Breast Cancer should be included in the prognostic factors of Ca breast and aggressive treatment with surgery, chemotherapy and radiotherapy is mandatory.

Patients who progressive (or) have recurrence should be considered for clinical trial with newer treatment options and targeted therapies like PARP inhibitors , EGFR inhibitors, VEGF inhibitors, TKI, Ixabepilone and androgen receptor targeted therapies.

CONCLUSION

TNBC is a aggressive malignancy with high mortality rate. There are a few studies in India on TNBC, analysing the clinical and pathological features.

The incidence of TNBC varies in different races and ethnic groups. In this study the incidence is is higher than western studies but comparable to Indian studies.

Historically, Immunohistochemistry (IHC) methodologies to detect ER, PR and HER2 status have varied among laboratories and clinical trials.

Inter Observer variability and variation between IHC and FISH (fluorescent in situ hybridization) Testing leading to variable results of ER, PR, Her-2neu testing.

So from this study we concluded that further standardization of hormonal testing to decrease inter observes variability and wider use of FISH testing in addition to IHC are a few things we would consider to further confirm this high rate of TNBC.

TNBC responds poorly to the standard treatment protocols of Ca.breast. Poor understanding on this subtype of Ca.breast and given its aggressive behaviour , further research and studies are needed to identify the prognostic factors, new targets and noel therapies in the treatment of TNBC patients.

The aim of this study was to analyse the cases of TNBC in our community and compare with the literature. We also assessed the behaviour of TNBC and response to treatment.

Historically, IHC methodologies to detect ER, PR and HER2nev status have varies among laboratories and clinical trials.

The reason for the high rate of TNBC cases in our communities need to further analysed.

So from this study we concluded the further standardization of hormonal testing to decrease inter-observer variability and widen use of FISH testing in addition to IHC are few thing we would consider to further confirm this high rate of TNBC.

TNBC respond poorly to standard treatment photocopy Ca.breast poor understanding on this subtype of Ca.breast and given its aggressive behaviour, further research and studies are needed to identify the prognostic factors, new targets and novel therapies in the treatment of TNBC patients.

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