Study of impact of assessment of estrogen receptor, progesterone receptor, Her2 neu receptor and Ki-67 at diagnosis in management of breast cancer patient at Birat Medical College Teaching Hospital (BMCTH)

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INTRODUCTION

Worldwide, WHO Globocan 2020 reports breast cancer as the most common cancer in females with estimated number of more than 2.3 million new cases every year and fifth cause of cancer related death.1 In Nepal, according to the data from seven major cancer service hospitals in 2012, breast cancer was the second most common cancer among women, after cancer of the cervix. The WHO Globocan 2020 reported 1973 new breast cancer diagnosed in Nepal in 2020, with an age standardized rate (ASR) of 13.9 new cases per 100,000 women, mortality ASR of 7.6 per 100,000 women.2 Management of breast cancer is very crucial and complete workup is essential before starting treatment.

ABSTRACT

Introduction: Breast cancer is the most common cancer in Nepal. Treatment of breast cancer includes combined therapy based on hormonal receptors within breast tissue and is linked to prognosis and survival.

Objective: To evaluate hormonal factors preoperatively and assess the impact of how it would change the management practices of treating breast cancer in our setup.

Methodology: This descriptive prospective study was conducted from March to October 2023 in the department of surgical oncology BMCTH in patients with breast mass suggestive of carcinoma meeting inclusion criteria and willing for treatment. Patients demographic data, detailed history and clinical examination was done at the time of diagnosis entered in excel sheet and calculation done by SPSS. Ethical clearance was taken from the institutional review committee of BMCTH (Ref: IRC-PA-296/2023).

Results: In 80 female patients with mean age 46.15 years, Left breast cancer (60%) was more common than right side (40%). Most common site of presentation was the upper outer quadrant (UOQ- 47.%). Invasive ductal carcinoma was the commonest type (47.5%) of all histological variants. 67.5% patients had ER positive receptor, 67.5% had PR positive and Her2 neu was present in 28.7%. TNBC reported 18.75% (15 patients out of 80 patients). Ki-67 prognostic value ranged from 10 to 70 with mean 29.91+-20.795%. Among all 36.3% underwent neoadjuvant chemotherapy prior to surgery and 63.7% underwent upfront surgery for breast cancer.

Conclusion: Screening of Triple negative and luminal type B breast cancers preoperatively is essential. Evaluation of hormonal factors ER, PR, Her 2 neu and Ki-67 preoperatively is must as it changes the management practices of treating breast cancer.
Treatment of breast cancer includes combined therapy; surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy. Breast cancer survival is linked to early detection, timely appropriate treatment and genetic predisposition. The average five year survival rate among people with breast cancer is 90 percent.1 Prognosis is related to a variety of clinical, pathologic and molecular features which include classical prognostic factors like histologic type, grade, tumor size and lymph node metastases.4 Clinical examination, radiological evaluation with either ultrasound or mammogram or both and tissue diagnosis with trucut biopsy has been standard of practise in diagnosis breast cancer. Further staging needs to be done either with CT-scan and bone scan .If available PET CT is preferred.5 Immunohistochemistry evaluation of breast tissue on biopsy is essential to determine molecular variants of breast cancer. Molecular variants of breast cancer are further subdivided into cancer that express ER (luminal type A and B) and those that do not express ER (Her 2).6 Luminal type A has been associated with best prognosis as it tends to express higher ER than type B. Her 2 expressing breast cancer are good predictors of response to trastuzumab (Herceptin) but are associated with poor prognosis. Her 2 neu is an independent negative predictor of overall survival and time to relapse in patients with lymph node positive breast cancer. They are associated with poor histological grade, spread to axillary nodes and an increase in number of nodes involved. Tumors who don’t express ER, PR, Her 2 neu are called Triple Negative Breast Cancer( TNBC). TNBC carries the worst prognosis and high recurrence. TNBC has been worrisome for clinicians because of their aggressive nature and lack of targeted treatment options.7 Estrogen receptor (ER) and progesterone receptors (PR) and more recently, HER-2/neu and Ki-67 have increasing importance influencing the management of the breast cancer.8 Testing for hormone receptors on biopsy specimen is essential prior to therapeutic intervention because it establishes positive correlation of hormone receptors ER, PR, Her2 neu with degree of tumor. Ki-67 helps in predicting prognosis. These results help to decide the treatment plan whether this is likely to respond to hormonal therapy or other treatments like neoadjuvant chemotherapy or adjuvant chemotherapy. In the eastern part of Nepal, we have observed the current practice of treating breast cancer based on clinical examination, radiological evaluation, ultrasound and mammography. Additional fine needle aspiration cytology (FNAC) based tissue diagnosis is done and patients are offered modified radical mastectomy (MRM) as surgical management and based on final diagnosis patients are offered adjuvant chemotherapy. This practice has resulted in unfavourable outcomes in terms of overall survival benefits. Breast conserving surgery ( BCS) has not gained popularity. Screening of Triple negative and luminal type B breast cancers preoperatively would change the management plan. We aim to evaluate the importance of evaluation of these hormonal factors ER, PR, Her 2 neu and Ki-67 preoperatively and assess the impact of it would change the management practices of treating breast cancer in our setup.

**METHODOLOGY**

Between March to October 2023, prospective descriptive, cross sectional observational study was conducted in the department of surgical oncology, medical oncology and clinical oncology, Birat Cancer Institute, BMCTH in all patients with breast mass suggesting breast cancer on clinical, radiological imaging studies and histopathological examination. All patients who presented to OPD with breast mass evaluated outside with FNAC proven or suspicious of malignancy were also included in this study. All patients diagnosed with breast cancer and had undergone lumpectomy or mastectomy or breast conservation surgery or recurrence or metastatic at presentation were excluded from study. All patients diagnosed with breast cancer if already had received chemotherapy either neoadjuvant or adjuvant were also excluded from this study.

Patients demographic data, detailed history and clinical examination was done at the time of diagnosis. Patients who consented for the study were included in this study. A convenient sampling method was used. For case enrollment in the study Ethical clearance was taken from the institutional review committee of BMCTH (Ref: IRC-PA-296/2023 ). All patients underwent clinical examination followed by ultrasound evaluation or mammogram imaging or both. Further all patients underwent ultrasound guided trucut core biopsy from breast mass lesion and biopsy report was collected. Histological grading was assessed according to Nottingham modification of the Bloom- Richardson system. Further histopathological slide was subjected for Immunohistochemical(IHC) analysis for ER, PR, Her2 neu, Ki-67 ( breast IHC 4 panel) at department of pathology BMCTH or outsourced ( Dr Lalpath laboratories India, having collection center at Biratnagar). Based on IHC, clinical and radiological reports patients received either neoadjuvant chemotherapy or were subjected to upfront surgery. All data and finding was noted in a predesigned performa.

Data collected were checked thoroughly for completion and error. Data was entered manually in windows excel sheet and coded and recorded digitally using an IBM Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) on Windows version 22.0. The chi-square, Fisher’s exact tests and cross tabulation were used to compare qualitative data. A p value of < 0.05 was considered statistically significant. RESULTS

A total 80 female patients were included in this study. We didn’t encounter any male patients diagnosed with breast cancer during the study period. Mean age of presentation was 46.15 +/- 7.04 years, range (34-65) years. We observed Left breast cancer (60%) was more common than the right side (40%). Most common site of presentation was the upper outer quadrant (UOQ: 47.2%) and least common was the left inner quadrant (LIQ: 2.5%). 55 % of patients were diagnosed suspicious of malignancy based on FNAC. All patients underwent a trucut biopsy at our center. Invasive ductal carcinoma was the most commonest type (47.5%) followed by invasive carcinoma no specific type 26.5%. 67.5% patients had ER positive receptor, 67.5% had PR positive and her2 neu was present in 28.7 %. All three receptors were absent, triple negative
breast cancer in 18.75% (15 patients out of 80 patients). Ki-67 prognostic value ranged from 10 to 70 with mean 29.91±20.795%. Based on clinical, imaging, histopathology and hormonal receptors 36.3% (29 patients out of 80 patients) underwent neoadjuvant chemotherapy prior to surgery due to higher stage, heavy nodal burden or TNBC and 63.7% (51 patients) underwent upfront surgery for breast cancer.

<table>
<thead>
<tr>
<th>Table 1: Pathological variants of breast cancer among study participants</th>
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<tbody>
<tr>
<td><strong>Variant</strong></td>
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<tr>
<td>Invasive ductal carcinoma</td>
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<tr>
<td>Invasive ductal carcinoma with mixed lobular carcinoma</td>
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<tr>
<td>Invasive lobular carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
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<tr>
<td>Mucoepidermoid carcinoma</td>
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<tr>
<td>Papillary carcinoma</td>
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<td>Tubular carcinoma</td>
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Table 2: Hormone receptor positivity status of breast cancer patient

<table>
<thead>
<tr>
<th>Hormone receptor</th>
<th>Positivity Status</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>Positive</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>PR</td>
<td>Positive</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Her 2 neu</td>
<td>Positive</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>42</td>
<td>42</td>
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Table 3: Correlation of ER, PR and Her2 neu receptors among breast cancer patient

<table>
<thead>
<tr>
<th>Hormone receptor positivity status</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER positive, PR positive and Her2neu positive</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>ER positive, PR positive and Her2neu negative</td>
<td>42</td>
<td>52.5</td>
</tr>
<tr>
<td>ER negative, PR negative and Her2neu positive</td>
<td>11</td>
<td>13.75</td>
</tr>
<tr>
<td>ER negative, PR negative and Her2neu negative</td>
<td>15</td>
<td>18.75</td>
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Table 4: Luminal status of breast cancer

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Luminal type A</td>
<td>42</td>
</tr>
<tr>
<td>Luminal Type B</td>
<td>12</td>
</tr>
<tr>
<td>Her 2 positive</td>
<td>11</td>
</tr>
<tr>
<td>TNBC</td>
<td>15</td>
</tr>
</tbody>
</table>

DISCUSSION

Over years management of breast carcinoma has revolutionized with advances in molecular study, radiotherapy and chemotherapy. Surgery has also been customized from radical procedures to breast conservation procedures. With the growing acceptance of sentinel lymph node biopsy even axillary dissection can be prevented. All these advancements are results of various clinical trials and study and have proven efficacy in overall survival and disease free survival. The prognosis of breast cancer depends on several factors including ER/PR/HER 2 status. The mean age of presentation of breast carcinoma in our study was 46.15 years. In a similar study by Ghosh et al in 2011 peak age of presentation was 49 years. Similar study in southeast asian countries showed peak age of presentation between 45-55 years. However, the mean age of presentation in western countries is 60-70 years. This may be due to biological, genetic and environmental factors. In our study left sided breast carcinoma was more common than right (60 % vs 40%). Majority of published literature on breast cancer shows left side is more common than right. National cancer institute’s SEER programme (Surveillance, Epidemiology, and End Results) in 2022 database
of more than 881,000 patients with breast cancer analyzing that 50.8% of breast cancers occurred on the left side, while 49.2% occurred on the right. Hypothetical theories like right hand dominance being able to detect left sided lump earlier, left breast slightly larger than right being more glandular and increase risk of cancer, incomplete breast feeding on left side as unintentional breastfeeding is more on right side, support above finding.

Tumor location in our study varied with highest frequency in upper outer quadrant (UOQ) and lowest frequency in the left inner quadrant (LIQ). This observation is consistent with the majority of published literature in breast cancer. However tumor location is not an independent prognostic factor but they can affect survival results. Tumors in the upper outer quadrant (UOQ) are associated with improved survival compared to other quadrants. Our study is limited to assessment of receptors on management of breast cancer, we couldn’t measure post treatment outcomes on recurrence and survival. In our study, invasive ductal carcinoma was the most commonest type (47.5%) followed by invasive carcinoma of no specific type (26.5%) which is similar to different studies by Dodiya H et al.

Our study showed ER, PR and Her 2 neu positivity of 67, 67.5% and 28.7% respectively. All three receptors were absent, triple negative breast cancer in 18.75% (15 patients out of 80 patients). Ki-67 prognostic value ranged from 10 to 80 with mean 32.03%. IHC was done in all cases. In a similar study by Shukla A et al in India showed ER and PR positivity of 49.1% and 43.5% respectively. Desai et al in a similar study from India documented low ER positivity of 32.6% and PR positivity of 46.1%. Chatterjee K et al in 2019 reported ER and PR positivity of 37.82% respectively. Gaspur et al in their study from the United states showed ER and PR positivity of 44 and 59% respectively. The relevance of predictive markers ER, PR, Her 2 neu and Ki-67 in management of breast cancer has been well established. ER positive tumors are associated with better overall survival compared to ER negative tumors. As per ASCO/CAP 2010 guidelines, nuclear staining of more than or equal to 1% cells is the current standard to interpret the result. Human Epidermal growth factor receptor 2 (HER 2) positivity in our study is 28.7%. This is associated with rapid tumor proliferation, shorter disease free survival and poor overall survival. Approximately 5% of breast cancer shows positivity of Her 2 neu. Similar result were seen in above studies also. Today, neoadjuvant anti-Her 2 therapy is the standard treatment for early and locally advanced Her 2 positive breast cancers. Anti Her 2 therapy should be started as soon as possible preferably without anthracyclines so as not to delay administration of targeted anti-Her 2 therapy. NeoSphere and TRYPHAENA clinical trials have shown that dual blockade of trastuzumab and pertuzumab with chemotherapy in neoadjuvant settings significantly increases the rate of pathological complete response.

Triple negative breast cancer (TNBC) was identified in 18.75% of patients in our study. Majority of literatures have reported approximately 15-20% TNBC of all breast cancer. Sandhu GS et al in 2016 in their systematic review and meta-analysis of 17 studies across India that involved 7,237 patients with breast cancer, overall combined prevalence of TNBC noted was 31% (95% CI, 27% to 35%). The early age of onset of breast cancer; lifestyle factors, such as diet and obesity; reproductive factors, such as multiparity; socioeconomic status; and screening behaviors may be hypothesized as probable etiology. Another important factor could be a potential genetic susceptibility of Indians to TNBC. There is a lack of expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2). These variant of breast cancer are of aggressive nature, poor outcomes primarily due to lack of effective targeted therapies. They usually are associated with earlier recurrence, tendency to visceral metastasis and worse overall survival. The reported 5 year overall survival in TNBC is 72% with average life expectancy of 3.55 years. The mainstay of treatment for early stage TNBC is neoadjuvant chemotherapy, followed by definitive surgery. Response to initial chemotherapy predicts clinical outcomes in breast cancer. Neoadjuvant therapy has become increasingly used for the treatment of tumor ≥2 cm in standard-of-care clinical practice, and pathological response is routinely assessed for the evaluation of overall prognosis. Pathological complete response (pCR) was associated with better prognosis in neoadjuvant TNBC trials and has become a surrogate marker of survival. The prognosis of TNBC is poor, particularly when pCR was not achieved. This indicates the importance of preoperative evaluation of hormone receptors in breast cancer at diagnosis to guide treatment especially in TNBC.

In our study, Ki-67 prognostic value ranged from 10 to 70 with mean 29.91+- 20.795. Singhai R et al in their study of 100 breast cancer patients in India observed Ki-67 proliferation rate of 30%, which is similar to our study. We observed higher values of Ki-67 associated in Her 2 neu positive patients and TNBC. Lukashina et al also observed that high expression of Ki-67 more frequently was associated with positive expression of Her-2/neu. Ki-67 expression is strongly associated with aggressive tumor biology, tumor proliferation and is a known indicator for prognosis and outcome in breast cancer. Ki-67 proliferation indices remain critical in the 2011 St. Gallen Consensus for differentiating Luminal A and Luminal B molecular subtypes. In 2013 St. Gallen consensus statement redefined greater than 20% as the new threshold for substratifying Luminal subtypes based on the work of Prat et al. Baseline levels of Ki-67 expression in TNBC are expected to be higher than in Luminal tumors, and definitions of cut-offs within triple negative disease are diverse and inconsistent, with reported values as high as 35% within TNBC disease.

In our study based on clinical, imaging, histopathology and hormonal receptors 36.3% underwent neoadjuvant chemotherapy prior to surgery and 63.7% underwent upfront surgery for breast cancer. Patients undergoing neoadjuvant chemotherapy were either Her2 neu receptor positive or TNBC. Evaluation of hormone receptors was started for the first time at our centre as a protocol in management of breast cancer and this resulted in detecting variants of breast cancer and accordingly targeted therapy was done. As a result Her2 neu positive and TNBC patients received neoadjuvant chemotherapy. Identification of this group of patients was very crucial for us as it changed the management plan in comparison to existing
CONCLUSION

From our study we conclude that assessment of estrogen receptor, progesterone receptor, HER 2 neu receptor and Ki-67 at diagnosis on biopsy is essential and plays a crucial role in management of breast cancer. This study helped us in identification of a group of patients diagnosed with aggressive variants of breast cancer with early recurrence, treatment and poor survival outcome. Earlier identification of such groups of breast cancer helped us plan specific targeted treatment plans. Our study was able to diagnose 28.7% luminal type B and 18.75% of TNBC preoperatively in whom neoadjuvant chemotherapy was considered first in contrast to routine practise of upfront surgery in operable breast cancer patients followed by adjuvant chemotherapy.

Recommendations We recommend that estrogen receptor, progesterone receptor, HER 2 neu receptor and Ki-67 must be assessed during initial diagnosis on tissue biopsy before initiating any treatment on patients diagnosed with breast cancer. This must be practiced as standard protocol. Based on findings neoadjuvant chemotherapy must be considered especially in Her2 neu positive and triple negative breast cancer.

Limitation of study Sample size is limited and this is single centre observational study.

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Conflict of interests All authors have no conflicts of interest to declare.

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REFERENCES


