UTILITY OF NOTTINGHAM’S MODIFICATION OF BLOOM-RICHARDSON’S GRADING AS A TIME BOUND PREDICTIVE PROGNOSTIC TOOL IN DIAGNOSIS OF BREAST CANCER

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ABSTRACT

BACKGROUND
The breast cancer among women both in the developed and developing world is rampant, the assessment of grading system of carcinoma breast and its utility for better time-bound prognostification can significantly improve in predicting aggressive tendency of the breast cancer and also further help develop a therapeutic protocol.

The aim of the study is to compare between the histopathological tumour grade with prognostic factors like age (based on menstrual status), tumour size, lymph node status and to establish histopathological grading (modified Bloom-Richardson’s) as a time-bound prognostic indicator.

MATERIALS AND METHODS
The present work was carried out in the histopathology and immunohistochemistry section of Department of Pathology, Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, Sawangi (M), Wardha, from January 2013 to July 2016. It was a prospective analytical study. A total of 114 female patients presenting in the Outpatient Department of Surgery with lump in breast were included in the present study. All patients underwent modified radical mastectomy for tumour resection. Tumour masses and lymph nodes were subjected to routine H and E staining, then examined by a senior pathologist. Comparisons were made between histopathology grades with patient age, tumour size and lymph node status.

RESULTS
The study found that the breast carcinoma having an excellent correlation between the histopathologic grades and the well-established prognostic tools, i.e. tumour size, lymph node status, though age-based on menstrual status was insignificant statistically. The ‘p’ value was significant when correlation between histopathological grade, tumour size and lymph node status was done respectively, P=0.0001, S=0.0006, S, whereas the ‘p’ value was insignificant, i.e. P=0.18, NS when correlation between the histopathology grade and age was done.

CONCLUSION
Nottingham’s modification of Bloom-Richardson histopathological grade being an excellent predictive prognostic tool should be continued for assessing the grades in breast cancer patients as well as be incorporated at the clinical level with the tumour size, nodal involvement, metastasis (TNM) staging of breast cancers.

KEYWORDS
Histopathology, Bloom-Richardson’s Tumour Grade, Lymph Node, Carcinoma, TNM.


BACKGROUND
An estimated 22.9% of invasive cancers in women arise from the breast1 and breast cancer comprises of 16% of all cancers occurring in females.2 Carcinoma of breast tends to present in an extremely heterogeneous manner as far as the gross and histomorphological features of the breast tumour are concerned. Robust clinical and pathological prognostic and predictive factors to support clinical and patient decision making for carcinoma breast are available through extensive clinical advances in understanding of the pathology of breast cancer.

Since the advent of the 19th century, there have been certain prognostic factors, which have been well documented for playing a major role in breast cancers occurring in females. These include patient age, axillary lymph node status, tumour size and histological features (especially histological grade and lymphovascular invasion).
These factors since then have majorly aided in prognostication and helped categorise patients with breast cancer for decision making as far as the therapeutic protocols are concerned. Despite these risk categories being useful for assessing prognosis, the role for developing a treatment protocol has been nonspecific and patients have been put on more or less a generalised non-individual based treatment strategy.

Clinical history, exams, cancer stage together with pathological grades in combination are of superior clinical value than utilising any of the clinical and pathological parameters in isolation. Blending the histopathologic grades with the TNM staging in breast cancer tissue has been assessed as one of the best combinations for prognosticification and deciding treatment protocol in these patients.

Treatment algorithms rely on breast cancer classification to define specific subgroups that are each treated according to the best evidence available. Classification and categorisation aspects must be carefully tested and validated, such that confounding effects are minimised, making them true prognostic factors. The present study focused on the utility of Nottingham’s modification of Bloom-Richardson’s grading system for breast cancers as a significant prognostic factor and emphasising its time-bound predictive accuracy in comparison to other significant prognostic factors like tumour size and lymph node metastatic status.

**Aim and Objectives**

To establish histopathological grading (modified Bloom-Richardson’s) as a time-bound prognostic indicator.

1. To determine the diagnosis and histological grade (modified Bloom-Richardson’s) of the breast carcinomas.
2. To compare between the histopathological tumour grade with prognostic factors like age (based on menstrual status), tumour size and lymph node status.

**MATERIALS AND METHODS**

The present work was carried out in the histopathology section of Department of Pathology, Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, Sawangi (M), Wardha, from January 2013 to July 2016. It was a prospective analytical study. A total of 114 female patients (N=114) presenting in the outpatient department of surgery with lump in breast were included in the present study.

These patients were examined and suspected patients for carcinoma breast underwent fine-needle aspiration cytology or core needle excisional biopsy. The patients diagnosed with carcinoma breast on fine-needle aspiration cytology or core needle excisional biopsy were admitted as IPD (inpatient department) patients of Department of Surgery. All patients underwent modified radical mastectomy for tumour resection. All these resected specimens were grossed as per standard protocol. Multiple sectioning from tumour mass was done. A minimum of 10 lymph nodes were resected from the specimen. Formalin-fixed, paraffin embedded blocks of tumour masses and lymph nodes were subjected to routine H and E staining, then examined by senior pathologist.

**Inclusion Criteria**

All cases reported to the surgical OPD with breast lump and subsequently diagnosed as breast carcinoma on FNAC/core needle biopsies, histopathology and operated by modified radical mastectomy are included in the present study.

**Exclusion Criteria**

- Patients with previous lumpectomy.
- Patients who underwent neoadjuvant chemotherapy.
- Patients with non-carcinomatous breast malignancy.
- Patients with recurrence.
- Patients with coexisting malignancy.
- Patients on chemotherapy/radiotherapy.
- Patients not compliant for the study.

**Approach and Methodology in the Present Study**

At first, 114 patients were divided based upon their menstrual status into three age groups, which were premenopausal (<48 years), menopausal (48-55 years) and postmenopausal (>55 years).

The second parameter was size of the tumour mass. On gross examination, the tumour mass was categorised into three groups based on the dimensions of tumour mass in greatest dimension, which were group I (<2 cm), group II (2-5 cm) and group III (>5 cm). Tumour sizes were categorised according to the TNM staging protocol.

The histopathological examination of the sections from this tumour mass was done and the tumour was divided into three grades as per the Nottingham’s Modified Bloom-Richardson Histopathological Grading based on histopathological parameters like tubule formation, nuclear pleomorphism and mitosis. This applied system is known as the grades were divided as per score as grade I (3–5), grade II (6–7) and grade III (8–9).

A minimum of 10 lymph nodes were resected from each specimen. The resected lymph nodes were looked for the evidence of metastasis and reactive lymphadenitis by microscopic examination. The sample size in the present study was distributed into two categories based upon the positivity for infiltration by malignant epithelial cells and reactive lymphadenitis. The lymph node status of all the 114 patients were distributed percentage wise and later was correlated with the BR grade and molecular subtype.

The histopathological grade was compared and assessed with three most significant prognostic factors, i.e. age (menstrual status based), tumour size (as per TNM criteria) and lymph node status of patients with breast carcinoma.

Statistical analysis of this correlation was carried out and ‘p’ value was obtained using ‘Chi-square test’ to conclude the final statistical interpretation. Statistical analysis was done by using descriptive and inferential statistics using Chi-square test and software used in the analysis were SPSS 22.0 version, GraphPad Prism 5.0 version and Epi-Info 6.0.
version and p <0.05 is considered as level of significance (p <0.05).

**OBSERVATION AND RESULTS**

Present study encompassed a total of 114 female patients (N=114) diagnosed with carcinoma breast. Tumour mass was examined and diagnosed on histopathology and graded on the basis of Nottingham’s modification of Scarff’s Bloom-Richardson grading system. Lymph nodes were also examined on histopathology for evidence of metastasis.

**Modified Radical Mastectomy Specimen**

**Tumour Size Categorisation**

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**Figure 1.** Cut Surface from Mastectomy Specimen Shows Greyish White Infiltrative Growth with Irregular Peripheral Edges, Size of Tumour <2 cm

**Figure 2.** Cut Surface from Mastectomy Specimen shows Greyish White Infiltrative Growth with Irregular Peripheral Edges, Size of Tumour 2 cm - 5 cm

**Figure 3.** Mastectomy Specimen Showing Greyish White Nodular Infiltrative as well as Ulcerative Growth, Size of Tumour Growth >5 cm

**Nottingham’s Modification of Bloom-Richardson Grading System for Breast Carcinoma**

**Figure 4.** Haematoxylin and Eosin (H and E) Stained Section (10 x view) from Tumour Mass of Breast shows Histopathological Features of Infiltrating Ductal Carcinoma (NOS Type), Bloom-Richardson Grade I

**Figure 5.** Haematoxylin and Eosin (H and E) Stained Section (40 x View) from Tumour Mass of Breast shows Histopathological Features of Infiltrating Ductal Carcinoma (NOS Type), Bloom-Richardson Grade I

**Figure 6.** Haematoxylin and Eosin (H and E) Stained Section (10 x View) from Tumour Mass of Breast shows Histopathological Features of Infiltrating Ductal Carcinoma (NOS Type), Bloom-Richardson Grade II
**Microscopic Findings of Axillary Lymph Nodes in Carcinoma Breast**

**Figure 7. Haematoxylin and Eosin (H and E) Stained Section (40 x View) from Tumour Mass of Breast shows Histopathological Features of Infiltrating Ductal Carcinoma (NOS type), Bloom-Richardson Grade II**

**Figure 8. Haematoxylin and Eosin (H and E) Stained Section (10 x View) from Tumour Mass of Breast shows Histopathological Features of Infiltrating Ductal Carcinoma (NOS Type), Bloom-Richardson Grade III**

**Figure 9. Haematoxylin and Eosin (H and E) Stained Section (10 x View) from Tumour Mass of Breast shows Histopathological Features of Infiltrating Ductal Carcinoma (NOS Type), Bloom-Richardson Grade III**

**Graph 1. Correlation between Histopathological BR Grading and Age (Based on Menstrual Status) in Carcinoma Breast Patients**
Table 1. Correlation between Histopathological BR Grading and Age (Based on Menstrual Status) in Carcinoma Breast Patients (N=114)

<table>
<thead>
<tr>
<th>Histopathological Grade</th>
<th>Premenopausal (&lt;48)</th>
<th>Menopausal (48-55)</th>
<th>Postmenopausal (&gt;55)</th>
<th>x²-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>12 (46.15%)</td>
<td>7 (26.92%)</td>
<td>7 (26.92%)</td>
<td>6.19; P=0.18, NS</td>
</tr>
<tr>
<td>Grade II</td>
<td>25 (60.97%)</td>
<td>3 (7.31%)</td>
<td>13 (31.70%)</td>
<td>41</td>
</tr>
<tr>
<td>Grade III</td>
<td>21 (44.68%)</td>
<td>12 (25.53%)</td>
<td>14 (29.78%)</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>58 (50.87%)</td>
<td>22 (19.29%)</td>
<td>34 (29.82%)</td>
<td>114</td>
</tr>
</tbody>
</table>

Table 2. Correlation between Histopathological BR Grading and Tumour Size in Carcinoma Breast Patients (N=114)

<table>
<thead>
<tr>
<th>Histopathological Grade</th>
<th>T1 (less than 2 cm)</th>
<th>T2 (2-5 cm)</th>
<th>T3 (more than 5 cm)</th>
<th>x²-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>2 (7.6%)</td>
<td>22 (84.61%)</td>
<td>2 (7.6%)</td>
<td>26</td>
</tr>
<tr>
<td>Grade II</td>
<td>1 (2.43%)</td>
<td>33 (80.48%)</td>
<td>7 (17.07%)</td>
<td>41</td>
</tr>
<tr>
<td>Grade III</td>
<td>0 (0%)</td>
<td>15 (31.91%)</td>
<td>32 (68.08%)</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>3 (2.63%)</td>
<td>70 (61.40%)</td>
<td>41 (35.96%)</td>
<td>114</td>
</tr>
</tbody>
</table>

Table 3. Correlation Between Histopathological BR Grading and Lymph Node Status in Carcinoma Breast Patients (N=114)

<table>
<thead>
<tr>
<th>Histopathological Grade</th>
<th>Reactive Lymphadenopathy</th>
<th>Lymph Nodes Positive for Metastasis</th>
<th>Total</th>
<th>x²-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>23 (88.46%)</td>
<td>3 (11.53%)</td>
<td>26</td>
<td>14.70; P=0.0006, S</td>
</tr>
<tr>
<td>Grade II</td>
<td>25 (60.97%)</td>
<td>16 (39.02)</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>20 (42.55%)</td>
<td>27 (57.44%)</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>68 (59.64%)</td>
<td>46 (40.35%)</td>
<td>114</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

The number of breast carcinoma cases worldwide has significantly increased since the 1970s. A phenomenon partly attributed to the modern lifestyles. Breast cancer has become one of the most common type of malignancy in women in the present day world statistics. The cancer surpassing most of the other cancers amongst women both in the developed and the developing world.

Since the turn of the 19th century, breast cancer has been under research and there has been extensive findings emanating from these researches, which have established certain important markers to predict the prognosis amongst breast cancer patients. For many years, the cancer of breast...
has been scaled with respect to prognostic factors like the reproductive age of the patient, the tumour size as well as the lymph node metastatic status. The well-established Bloom-Richardson’s grading (modified) has been used for histopathological grading of breast cancers, though it is incorporated in Nottingham prognostification index, yet the grading is not utilised as part of the TNM staging system. Recommendations have been made to have judicious use of grading system.

Patients presenting with cancer of breast initially were subjected to more or less similar surgical as well as chemotherapy protocol. During the last 50 years, the observation that patients with the same type of cancer show varied forms of different morphological types in histopathology, these tumours also show varying prognosis. This sort of heterogenous as well as unpredictable behaviour in terms of aggressiveness of breast cancer detected by pathologists has led to manifold changes in our medical and scientific understanding of these cancers.

The surgeons as well as the pathologists are standing at the crossroads between the conventional and modern approach to breast cancers. There are many unanswered questions, which add to the dilemma of the pathologist and the surgeons. Foremost amongst them is the relevance of the grading of breast cancers and the typing of breast cancers. The present study was undertaken to analyse and assess the relationship between BR grading system and certain time-bound prognostic factors like age, tumour size as well as nodal status. This study finds an important need to establish whether the conventional BR grading through histopathology still finds itself sufficient and significant within the conventional histopathological reporting protocol and also to stress on the fact that it should be aptly included along with the TNM staging of the breast cancers for predictive prognostification of the same.

The histopathological grading of breast carcinoma were subsequently correlated with all three major prognostic markers considered in the present study individually that is age (based on menstrual status), tumour size and lymph node status in the patients.

Overall Distribution of Carcinoma Breast Cases

<table>
<thead>
<tr>
<th>BR Grade</th>
<th>Age</th>
<th>Tumour Size</th>
<th>Lymph Node Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premenopausal (&lt;48)</td>
<td>Menopausal (48-55)</td>
<td>Postmenopausal (&gt;55)</td>
</tr>
<tr>
<td>Grade I</td>
<td>12</td>
<td>7</td>
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</tr>
<tr>
<td>Grade II</td>
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<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Grade III</td>
<td>21</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

Significance: 6.19, P=0.18, NS

<table>
<thead>
<tr>
<th>Tumour Size</th>
<th>Lymph Node Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 cm</td>
<td>&lt;2 cm</td>
</tr>
<tr>
<td>2-5 cm</td>
<td>Reactive</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>Metastasis</td>
</tr>
</tbody>
</table>

Table 4. Correlation of Histopathological Grade vs. Age (Based on Menstrual Status), Tumour Size and Lymph Node Status in the Patients (N=114)

Comment- Table showing complete correlation between BR grade of breast cancer, i.e. grade 1, grade 2, grade 3 with three important prognostic indices that is menstrual age group, tumour size and the lymph node status.

Interpretation- The correlation between the BR grade and the menstrual-based age groups was found to be nonsignificant, however, the correlation between the BR grade and the tumour size as well as the lymph node status was found to be significant.

Present Study in Comparison with Other Studies

Histopathological grades in breast cancer in comparison to patient age, tumour size and lymph node status.

In our study, histopathological grading of breast carcinoma was done by Bloom-Richardson methodology. These grades were compared and correlated with the age (based menstrual status) of the carcinoma breast patients. The distribution of cases based on their age (based on menstrual status), in each grade was as follows- Grade I patients were categorised as follows 12 cases (46.15%) premenopausal, 7 cases (26.92%) menopausal and 7 cases (26.92%) postmenopausal. Grade II patients were categorised as follows- 25 cases (60.97%) premenopausal, 3 cases (7.31%) menopausal and 13 cases (31.70%) postmenopausal. Grade III patients were categorised as follows- 21 cases (44.68%) premenopausal, 12 cases (25.53%) menopausal and 14 cases (29.78%) postmenopausal.

When grades were compared and correlated with the age-based menstrual status of the carcinoma breast patients, the present study showed maximum patients from all three grades were present in the premenopausal age group 58 cases (50.87%) out of 114 cases and also most cases of grade III tumour were also present in premenopausal age group, i.e. 21 cases (44.68%) out of a total of 47 (grade III cases). These findings were consistent with study of Partridge et al suggesting the fact that higher grade cases were seen in young patients. However, when patient distribution in all the age groups was statistically analysed, the patients diagnosed with Grade II and Grade I did not have a very clear-cut distribution of cases. These cases were also found in young patients below (48 yrs. of age), also grade III cases were seen in postmenopausal patients (>55 yrs.), hence the present study found no significant relationship between histopathological grading and age of presentation of breast carcinoma. The correlation was found to be statistically insignificant unlike the findings stated by Partridge et al.8
In our study, we found patients with lymph nodes positive for metastasis- 46 (40.35%) and patients with reactive lymphadenitis- 68 (59.65%). The study observed that in grade I tumours, there were 23 cases (88.46%) of reactive lymphadenitis and 3 cases (11.53%) of lymph node positive for metastasis. In grade II category, there were 25 cases (60.97%) were of reactive lymphadenitis and 16 cases (39.02%) were of metastatic lymph nodes. In grade III tumours, 20 cases (42.55%) were of reactive lymphadenitis and 27 cases (57.44%) were of metastatic lymph nodes. When correlation was done between histopathological grading in 114 patients of breast carcinoma, the status of axillary lymph node pathology, the study observed that maximum cases of lymph node metastasis were found in grade III that is of 47 cases with grade III tumour, 27 cases (57.44%) patients had metastatic lymph nodes, contrastingly out of a total of 26 cases diagnosed with grade I tumour, 88.46% that is 23 cases presented with reactive lymphadenitis. The findings obviously suggest that as the histopathological grade increases, the percentage of metastasis in the lymph node increases, and at lower histopathological grade, the percentage of reactive lymphadenitis diagnosed on histopathology is more.

In our study, the tumour size was compared with modified Bloom-Richardson grading of breast cancer. The distribution of tumour size in each grade was as follows- Grade I patients were categorised as follows- tumour size <2 cm - 2 patients (7.6%), tumour size 2-5 cm - 22 cases (84.61%) and tumour size >5 cm - 2 cases (7.6%); Grade II patients were categorised as follows- Tumour size <2 cm - 1 patients (2.43%), tumour size 2-5 cm - 33 patients (80.48%) and tumour size >5 cm - 7 cases (17.07%); Grade III patients were categorised as follows tumour size <2 cm - 0 patients (0%), tumour size 2-5 cm - 15 patients (31.91%) and tumour size >5 cm - 32 cases (68.08%). Most of the large size tumours, which fell in the category of T3, i.e. >5 cm were seen to occur in the histopathological grade III of breast carcinoma, whereas no case belonging to category grade III was seen in category of size <2 cm. In case of grade I tumours, 92.21% of grade I tumours fell in the category of T2 (2-5 cm) or T1 (<2 cm). Similarly, 82.91% of grade II tumours fell in the category of T2 (2-5 cm) or T1 (<2 cm). The ‘p’ value interpretations were found to be significant when histopathological grade was compared with tumour size, ultimately indicating the fact that histopathological grade correlates with tumour size in carcinoma breast patients, higher the grade larger is the presentation of tumour size.

The tumour size and lymph node status are major prognostic factors to predict tumour aggressiveness and govern treatment outcome. The present study also stress on histopathological grade as an important prognostic tool independent of other prognostic factors like age, tumour size and lymph node status. The study also points to the fact, grading of breast carcinoma can be definitely used as a should be incorporated at a clinical level with the TNM staging of breast cancers.
REFERENCES


