Original Article

Study of Cytomorphological Patterns of Neoplastic Breast Lesions along with Robinson's Cytological Grading of Invasive Ductal Carcinoma

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Abstract

Background

Fine Needle Aspiration Cytology (FNAC) plays an important role as it is a simple, minimally invasive, cost-effective, outpatient-based, and rapid diagnostic method. Grading of breast carcinoma is ideal as it helps in the selection of patients for appropriate therapy. The study was undertaken to observe the cytomorphological patterns of neoplastic lesions, assess the grade of invasive ductal carcinoma by Robinson's cytological grading, and to correlate with Modified Bloom Richardson's histopathological grading wherever possible.

Material and Methods

A descriptive cross-sectional study was conducted over a period of 2 years (July 2015-June 2017). FNAC of neoplastic breast lesions was studied. Invasive ductal carcinomas were graded according to Robinson's cytological grading system and compared with Modified Nottingham Bloom-Richardson's histological grading in instances where resected specimens were available.

Results

In the present study, fibroadenoma (31/33; 94.0%) was the most common benign neoplasm and invasive ductal carcinoma (40/41; 97.6%) was the most common malignant neoplasm. According to Robinson's cytological grading done on IDC breast, the majority of the cases were grade II [24 (60.0%)]. Histopathological correlation was done by Modified Bloom Richardson's grading on 13 cases of IDC in which 6 (42.8%) cases were in grade II followed by grade III and I. There was a significant concordance of 71.4% (p=0.015) between Robinson's cytological grading system and Modified Nottingham Bloom Richardson's histopathological grading system.

Conclusion

Robinson's cytological grading on invasive ductal carcinoma of the breast has good concordance with Modified Bloom Richardson's histopathological grading.

Keywords:

IAC Yokohama reporting system; Modified Bloom Richardson's histopathological grading

Introduction

Breast cancer is the second most common cancer among Indian women, next to cervical cancer, and accounts for high morbidity and mortality [1]. Due to the lack of organized breast cancer screening programs and diagnostic modalities, these cancers are often detected at an advanced stage [2]. Over the last decade, cytodiagnosis has become a widely used diagnostic modality. Fine needle

aspiration cytology (FNAC) plays an essential role as it is a simple, minimally invasive, cost-effective, outpatient-based, and rapid diagnostic method for breast lesions. It also permits several ancillary studies, such as hormone receptor analysis, flow cytometry, and molecular diagnostic studies [3]. Reliable FNAC has reduced intraoperative procedures, like frozen section, by around 80% in the diagnosis of breast malignancies [4].

The cytological grading of breast cancer aids in a better understanding of disease biology, predicting disease outcomes, planning specific therapeutic interventions and treatment modalities, and occasionally alleviating patient anxiety [2]. Histopathological grading by the Nottingham Elston Ellis method is the most commonly used and has shown good prognostic correlation [5]. Since FNAC is now the preliminary test for diagnosing carcinoma of the breast, attempts have been made to grade the carcinoma on smears based on various parameters. Among the many cytological grading systems, Robinson's cytological grading employed in invasive ductal carcinomas (IDC) correlates well with histopathological findings [6]. Therefore, this study intends to analyze the cytomorphology of neoplastic breast lesions and carry out Robinson's cytological grading on invasive ductal carcinomas encountered.

Objectives of the Study: Study the cytomorphological patterns of neoplastic breast lesions. Assess the cytological grade in fine needle aspirates of breast carcinoma using Robinson's grading. Correlate Robinson's cytological grading with Nottingham's Modified Bloom Richardson grading wherever possible.

Materials and Methods

A descriptive cross-sectional study was undertaken in the Department of Pathology, SS Institute of Medical Science & Research Centre (SSIMS & RC), Davangere, over two years (July 2015 to June 2017). Patients attending the surgical OPD of SSIMS & RC and other private hospitals with a history of breast lump who were sent to the Department of Pathology were subjected to FNAC after obtaining written informed consent. A detailed history and local examination of the breast lesion were performed. Under aseptic precautions, FNAC was performed using a 22-23 G needle with a 10 ml disposable syringe attached to a Cameco syringe holder. The fixed smears were stained with routine H&E and Pap stain. Air-dried smears were stained with Giemsa.

FNAC smears were classified into five categories based on the International Academy of Cytology (IAC) Yokohama reporting system [7]: C1 – Inadequate, C2 – Benign, C3 – Atypia probably benign, C4 – Suspicious of malignancy, C5 – Malignant. Further, the cytological smears of invasive ductal carcinomas were graded using Robinson's cytological grading, which has six cytological parameters: cell dissociation, cell size, cell uniformity, nucleolus, nuclear margin, and nuclear chromatin. Each parameter was given a score of 1, 2, or 3. The scores were added to get the total scores for grading the carcinomas [8, 9]. All surgically resected cases of ductal carcinoma-not otherwise specified type were graded as per Modified Scarff Bloom Richardson's grading based on three parameters: amount of tubule formation, nuclear pleomorphism, and mitoses. Each parameter was given a score of 1, 2, or 3, and the scores were added to give the final grade [10]. Robinson's cytological grading of invasive ductal carcinomas was correlated with Modified Scarff Bloom Richardson grading wherever possible.

All neoplastic lesions of the breast, irrespective of age and sex, were included, while inflammatory breast lesions, recurrent tumors, and smears with inadequate cellularity were excluded from the study. Ethical approval was obtained with Reference: IERB No: 87-2015.

Statistics: Data obtained were entered into a Microsoft Excel worksheet and analyzed using the Epi Info version 6 software. The results were expressed as numerals and percentages and presented in tables. The 'p' value was calculated wherever required.

Results

A total of 93 cases were included in the study under the categories C2-C5 as per the IAC Yokohama reporting system, with C1 (unsatisfactory due to scant cellularity and hemorrhage) excluded. The age range of patients was 18-60 years, with the majority in the age group of 41-50 years (29%). The mean age of presentation was 44 years. The male to female ratio was 3:1. Bilaterality was noted in 3 (3.2%) cases, with the rest presenting unilateral breast lesions. Most of the breast neoplasms were located in the upper outer quadrant in 45 (48.4%) cases.

Among these cases, 33 (35.5%) were benign neoplasms (C2), 15 (16.1%) cases were atypical probably benign (atypical ductal hyperplasia, C3), 4 (4.3%) cases were suspicious of malignancy (C4), and 41 (44.1%) cases were malignant neoplasms (C5). The ratio of malignant to benign neoplasms of the breast was 1.24:1.

Among the benign breast neoplasms (C2), a total of 31 cases of fibroadenomas were encountered, accounting for 93.9%. The majority of these cases were in the age group of 25-40 years, with a mean age of 25.4 years. Microscopically, fibroadenomas under the C2 category showed cellular smears with benign ductal epithelial cells in cohesive branching clusters bordered by myoepithelial cells. The background showed bare nuclei and fibromyxoid stroma (Figure-1).

Seven cases of ADH (C3) were in the age group of 41-50 years, with a mean age of 51.6 years. The majority of the smears showed atypia in the form of mild to moderate nuclear pleomorphism, focal nuclear overlapping and crowding with prominent nucleoli. Therefore, a cytological diagnosis of atypical ductal hyperplasia (probably benign, C3) was given (Figure-2).

Four cases of suspicious for malignancy (C4) were encountered. Among them, two were in the age group of 26-40 years, and two were >60 years of age, with a mean age of 52 years.

A total of 41 cases of malignant neoplasms under the C5 category were diagnosed on cytology. Among these, 40 (97.2%) were IDC, and 1 (2.8%) was diagnosed as mucinous carcinoma of the breast. All patients presented with a lump in the breast, and 15 (36.6%) patients showed associated skin changes like ulcer, bloody discharge from the nipple, retraction and puckering of the nipple, peau d'orange, and engorged veins over the skin. On palpation, 33 (82.5%) lumps were hard in consistency, and 7 (17.5%) were firm to hard. Regarding mobility, 24 (60%) lumps were immobile, 13 (32.5%) were mobile, and 3 (7.5%) had restricted mobility.

The majority of the cases (16) were in the age group of 41-50 years, followed by 12 (29.3%) cases in the 51-60 years age group, with a mean age of 51 years. The lesions were in the left breast in 23 (58%) cases, in the right breast in 16 (40%) cases, and bilateral in 1 (3%) case. Most of the invasive ductal carcinomas were located in the upper outer quadrant in 22 (55.0%) cases.

In C4 and C5 categories, lesions showed highly cellular smears displaying pleomorphic malignant ductal epithelial cells in loose clusters, sheets, and single forms. These cells showed enlarged hyperchromatic nuclei, increased N:C ratio, moderate to marked nuclear pleomorphism, coarse to granular to clumped chromatin with prominent nucleoli, and irregular nuclear margins. Further, C5 category smears were cytologically graded using Robinson's cytological grading system, shown in Table 1.
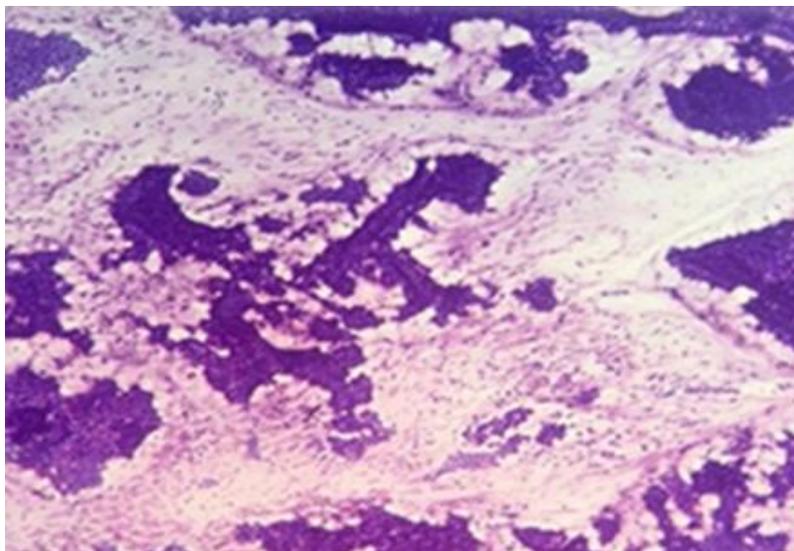
Figure 1: C2 category H & E. low power FNAC of fibroadenoma showing hyper cellularity, monolayered sheets of ductal epithelial cells
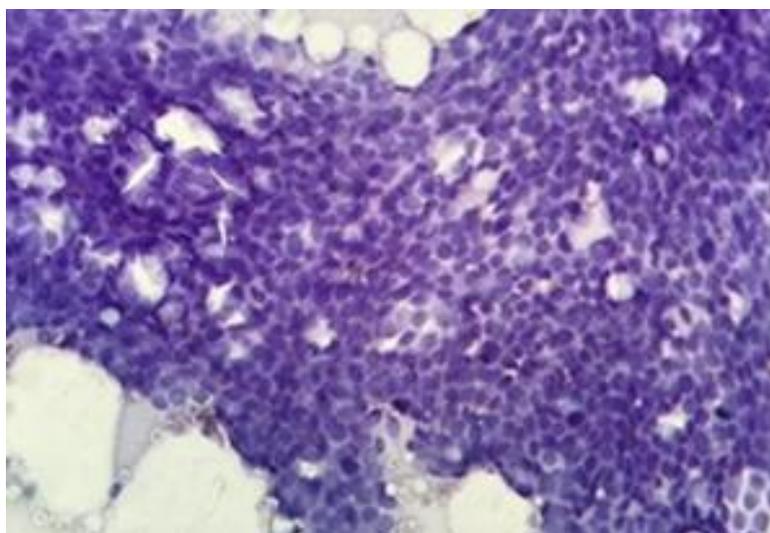

Figure 2: C3 category Atypical ductal hyperplasia. Ductal epithelial cells bordered by myoepithelial cells.

Table 1: Cytology Scoring Distribution according to Robinson's Grading System

Scores	1	2	3
Cell dissociation	3(7.5%)	17(42.5%)	20(50%)
Cell size	4(10%)	26(65%)	10(25%)
Cell uniformity	0	17(42.5%)	23(57.5%)
Nucleoli	5(12.5%)	30(75%)	5(12.5%)
Nuclear margins	14(35%)	16(40%)	10(25%)
Chromatin	10(25%)	25(62.5%)	5(12.5%)

After scoring the IDC aspirates for these parameters, a total score was obtained for each case and graded according to grades I, II, or III, if the total score was between 6-11, 12-14, and 15-18 respectively. In the present study, the majority of the cases were grade II, accounting for 24 (60%) cases, followed by grade III with 9 (22.5%) cases, and 7 (17.5%) were grade I, as depicted in Figures 3.
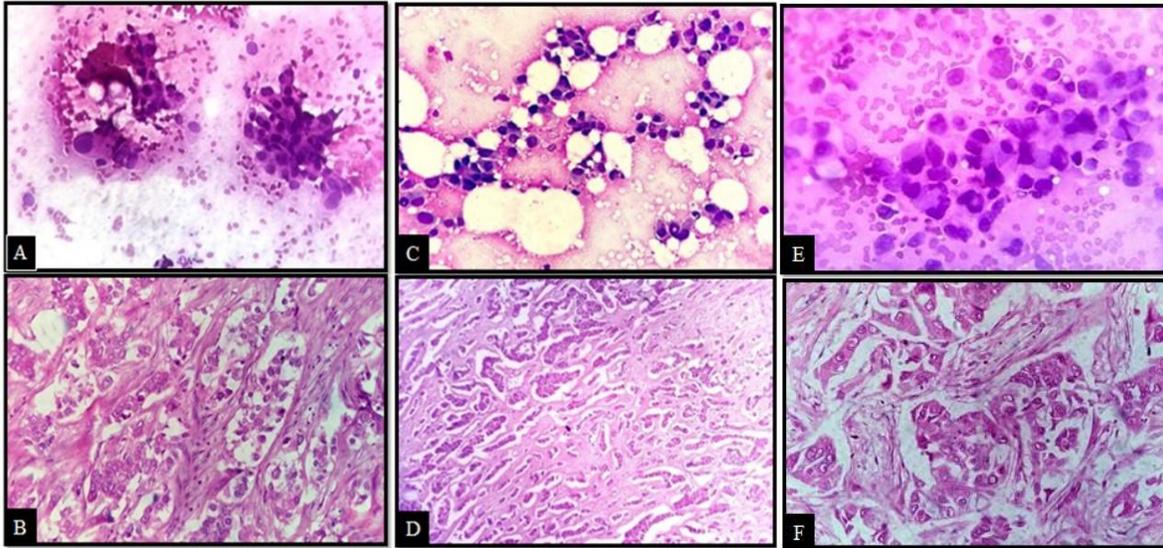
Figure 3: A) Cytological grade I tumor in cohesive clusters of cells with smooth nuclear membranesand inconspicuous nucleoli (HandE stain high power); B.) Histological grade I tumor showing tubule formation more than 75% of the tumor with minimal nuclear pleomorphism (HandE stain high power). C) Cytological grade II tumor in mixture of single cells and clusters, mildly pleomorphic nuclei and noticeable nucleoli (HandE stain high power); D) Histological grade II tumor showing 10% -75% tubule formation and moderate nuclear pleomorphism (HandE stain low power). E) Cytological grade III tumor showing mostly single cells, highly pleomorphic nuclei, and prominent nucleoli (H and E stain high power); F) Histological grade III tumor showing less than 10% tubule formation with marked nuclear pleomorphism (HandE stain high power).

Of these 40 cases of IDC, 14 (35%) patients underwent surgical excision of the neoplasm. The cytological diagnosis of IDC was confirmed histologically in all operated cases, and they were further scored by the MBR scoring system and graded histopathologically, as shown in Table 2. After scoring the IDC cases, they were graded according to grades I, II, or III if the total score was between 3-5, 6-7, and 8-9 respectively, as shown in Table 3. There was a significant concordance of 71.4% (p = 0.015) between Robinson's cytological grading system and Nottingham's Modified Bloom Richardson's Histopathological Grading system, as depicted in Table 4.

Discussion

Fine needle aspiration cytology is not only a diagnostic modality but also helps in providing significant prognostication information by assessing hormone receptor expression in breast carcinoma [11]. Different studies have shown that most lesions are benign and need only reassurance [12]. Early screening and diagnosis of breast lesions and categorization into different groups of breast pathology are important. This can be helpful in the prevention of cancer and in the accurate management of patients. The grading of breast cancer on cytology is very helpful both in prognostication and management of patients. Many grading systems have been introduced, among them nuclear grading is very helpful to plan specific interventions for patients. As the management protocol is different for early, advanced, and inoperable breast cancers, the pre-surgery grading of tumors will help surgeons to plan for neoadjuvant chemoradiotherapy for patients [13]. Studies have also shown that Robinson's cytological grading system is widely accepted as it is more comparable with the Modified Elston Ellis Bloom Richardson grading with a concordance rate of 78-88% [14].

Table 2: Histopathological scoring system- Modified Bloom Richardson Grading System

Scores	1	2	3
Tubule formation	4(31%)	3(23.1%)	6(46.1%)
Nuclear pleomorphism	2(15.4%)	6(46.1%)	5(38.5%)
Mitotic count per 10hpf	2(15.4%)	7(54%)	4(31%)

Table 3: Modified Bloom-Richardson histopathological grading of Invasive ductal carcinoma of breast

Modified Bloom-Richardson histopathological grading	Number of patients	Percentage (%)
Grade I	2	14.3
Grade II	6	42.8
Grade III	5	35.7
Medullary carcinoma	1	7.1
Total	**14**	**100**

Table 4:: Correlation between Robinson's cytological grading and Modified Bloom-Richardson histopathological grading

Robinson's cytological grading of IDC	No. of cases in cytological grading (%)	Nottingham's Modified Bloom-Richardson's Histopathological Grading				P value
		I	II	III	Total	
I	2 (14.3%)	2	0	0	2 (100%)	0.015
II	8 (57.1%)	1	5	1	7 (62.5%)	
III	4 (28.6%)	0	1	3	4 (75.0%)	
Total	14 (100%)	3	6	4	10/14	
		(21.4%)	(42.8%)	(28.6%)	(71.4%)	

The magnitude of breast neoplasms was reported to be higher in females in most of the studies, which was similar to our study. Most studies showed a higher incidence (>50%) of benign breast neoplasms, while Khan et al. [15] and Singh P et al. [16] have reported lower incidence which was consistent with the present study.

C2 Category: Fibroadenoma was the commonest benign neoplasm in the present study, which was concurrent with various studies. They can occur in women of any age, but the peak incidence is during the second and third decades of life [17]. The majority of cases in the present study occurred in the 3rd decade of life, similar to the studies by Singh A et al. [12] and Gupta D et al. [18]. Bilateral breast fibroadenomas were seen in 6.5% of cases; however, Bafakeer S et al. [19] and Vijaykumar A et al. [20] had only 3.1% and 4.3%, respectively, in their studies.

C3 Category: A "gray zone" in breast cytology has long been recognized, in which an unequivocal diagnosis cannot be reached with fine needle aspiration cytology findings. It is due to overlapping features of benign epithelial proliferative lesions, mostly fibroadenoma, and well-differentiated carcinoma, as well as borderline lesions of the breast [21,22]. Diagnosing gray zone pathology as atypical in fine needle aspiration cytology causes no delay in treatment as excision biopsy is recommended for all equivocal cases [22]. This study, like other studies [21,22], also suggested that the diagnosis of atypia was clinically significant because it was associated with an increased likelihood of malignancy and such cases should be evaluated for histology. However, the ultimate management of any of these categories should be based on the result of the triple test. The magnitude of ADH in the present study was 16.1%, which was nearly similar to studies done by Saikia et al., Yusuf et al., and Yeoh and Chan et al. [23,24,25].

C4 Category: There were four cases that were suspicious of malignancy in the present study, which was similar to the study by Singh P et al. [16].

C5 Category: The incidence of breast carcinoma in the present study was 44.1%, while other studies showed 26.6%, 39.4%, and 39% [16,26,27]. Studies done by Shrestha et al. [28], Khan et al. [15], and Singh P et al. [16] have shown that malignant neoplasms of the breast were commonly encountered in the age group of 41-50 years, which was similar to the present study. Invasive ductal carcinoma was the commonest malignant neoplasm in the present study, which was similar to the studies done by Yusufu LMD et al., Likhar et al., Sankaye et al. [29,30,31]. Many studies found that invasive ductal carcinoma occurred in the age group of 41-60 years [12,16,28,38]. The present study showed similar findings as shown in Table-5.

Table 5: Age range of IDC breast in different studies

Studies	Age range in years
Shrestha A et al[28] (2011)	41-60
Singh A et al[12] (2011)	41-60
Chokshi et al[38] (2014)	41-60
Singh P et al[16] (2015)	41-60
Present study	**41-60**

As the grade of breast carcinoma is a known prognostic marker, an attempt to grade these tumors on the FNA sample will provide useful information on tumor behavior prior to tumor excision [2, 5]. The present study showed that most of the IDC (61%) were in Grade II Robinson's cytological grade, which was similar to the results of Bukya et al., Pandya AN et al., Ravikumar et al., and Gupta D et al. [14, 32, 33, 34]. Studies have reported that Grade II was the most common grade, followed by Grades I and II, whereas the present study showed Grade III was more common than Grade I, as depicted in Table-6.

Table 6: Robinson's cytological grading of IDC breast in different studies

Name of the study	Das et al [39] (2003)	Pandya AN et al [32] (2012)	Ravikumar et al [33] (2015)	Gupta D et al [18] (2016)	Present study
Grade I	28.8%	40.68%	22.4%	27.2%	17.1%
Grade II	46.2%	44.07%	62.2%	62.8%	61.0%
Grade III	25%	15.25%	15.3%	12.2%	22.0%

The highest grade of concordance was seen between Robinson's cytological grading and Modified Bloom Richardson's histopathological grading in Grade I tumors (100%), followed by Grade III (75%) and less with Grade II tumors (62.5%), which was comparable with other studies like Rajendran K et al. [35]. None of the high-grade tumors were graded as low-grade or vice versa, which was similar to studies done by Rajendran K et al. [35], Handa et al. [36], and Pal S et al. [37]. Hence, it will be of high clinical significance in planning for the management of patients, as low-grade tumors do not respond to chemotherapy, whereas high-grade tumors respond very well.

In the present study, Robinson's cytological grading system had 71.4% ('p'-0.015) concordance with Modified Bloom Richardson's histopathological grading, which is similar to other studies done by Rajendran K et al., Das et al., Pandya AN et al., and Sinha et al., as shown in Table-7.

Table 7: Comparison of concordance rates reported in different studies

Name of the study	Concordance rate (%)
Robinson et al[8] (1994)	56.9%
Das et al[39] (2003)	71.2%
Sinha et al[5] (2009)	69.5%

Rekha et al[40] (2011)	82.0%
Pandya AN et al[32] (2012)	74.6%
Ravikumar et al[33] (2015)	77.5%
Khan et al[15] (2014)	84.0%
Rajendran K et al[35] (2022)	81.7%
Present study	**71.4%**

Conclusion

To conclude, cytological grading by Robinson's cytological grading should be incorporated in routine FNAC reporting of breast cancer as it shows better concordance with histopathological Bloom Richardson grading. This will guide clinicians in planning management.

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