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Comparative evaluation of Robinson's cytological grading with Scarff Bloom Richardson's histologic grading for Carcinoma breast

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ABSTRACT

Breast carcinoma is one of the most common cancers in women. The important preoperative diagnostic modalities include ultrasonography and cytology. Prior to operation cytological grading of breast carcinomas would be desirable for the selection of patients for neoadjuvant therapy. This study has been carried with the aim to evaluate and correlate Robinson's cytological grading with modified Bloom Richardson histological grading system for infiltrating ductal carcinoma. The period of study was one year (January 2015- December 2015), comprising of 56 female patients attending both outpatient departments (OPD) as well as admitted in ward. Fine needle aspiration cytology (FNAC) smears of invasive breast carcinoma, were graded according to the Robinson's grading system. The corresponding histological sections were graded according to Elston and Ellis' Nottingham modification of Bloom Richardson method. Out of **56** cases, **15 (27%)** cases were graded as grade I, **31 (55%)** grade II, and **10 (18%)** grade III on cytology, whereas **16 (29%), 32 (57%)** and **8 (14%)** cases were graded as grade I, II and III on histology. The concordance rate between cytology and histology grades were **73.3%, 81%** and **70%** for grade I, II and III tumor respectively. Absolute concordance rate was **76.78%.** Apart from being simple and non-invasive investigation, cytologic grading method could be comparable with histologic grading system and a useful parameter for selecting neoadjuvant chemotherapy in patients of breast carcinoma.

Keywords: breast cancer, FNAC, Robinson's cytology grading, Elston and Ellis's Nottingham modification of Bloom-Richardson method.

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INTRODUCTION

Breast carcinoma is the most common non skin malignancy among females.[1] It is the leading cause of death in women, with more than 1,000,000 cases occurring annually. The prognosis of breast carcinoma depends on many factors, such as tumor type, histological grading (HG), hormone receptor status, DNA ploidy, cell proliferation markers and expression of different oncogenes.[2]

Elston-Ellis modification of Scarff-Bloom-Richardson (SBR) grading system for histological grading of carcinoma breast is the most widely used grading system and also have prognostic value.[3]

As aspiration cytology has been found to be minimally invasive compared to core biopsies, attempts are being made to grade carcinoma on cytological ground that may prove to be beneficial for surgeons such as administration of preoperative neoadjuvant chemotherapy to the patient. It can also provide information about the aggressiveness and lymph node metastasis.[4] Assigning a grade to breast cancer cases provides significant prognostic information and a guide for favourable therapy.[5] Therefore it is desirable to grade the tumor before surgery for the judicious use of chemotherapy especially in indian setup where patients usually come with advanced disease requiring preoperative chemotherapy and/or radiotherapy.

Of the different cytological grading (CG) methods corresponding to Elston-Ellis modified SBR HG, the method described by Robinson *et al* [6] was found to be useful in grading breast carcinoma in fine needle aspiration (FNA). The present study was done with the objective to find the concordance between cytological grading of breast carcinoma using Robinson method with histological grading using Elston-Ellis modified SBR method.

MATERIALS AND METHOD

The present study was carried out at Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh, for a period of one year from January 2015 to December 2015. It comprised of 56 female patients, diagnosed as breast carcinoma on FNAC and later on confirmed by histopathology following mastectomy, in the department of pathology. The inclusion criteria was that all female patients, irrespective of age diagnosed as breast carcinoma cytologically and confirmed by histopathology were included in the study. The exclusion criteria were: (i) uncooperative patients (ii) patients with recurrence of breast carcinoma after mastectomy (iii) patients with history of chemo or radiotherapy prior to mastectomy (iv) patients who lost followup for management and (v) male patients. Informed consent was obtained from every patient in the study. Fine needle aspiration cytology was done using 22G needle, fixed to a 10 ml syringe. The aspirated materials were deposited on

the slides and minimum 3-4 slides were made using a flat pressure by another slide with a smooth edge. Slides were immediately placed in 95% ethanol for fixation. Alcohol fixed smears were stained using routine Papanicolaou (Pap) and hematoxylin and eosin (H&E) method. Pap stained smears were used to grade breast carcinoma using the criteria described by Robinson *et al* [6] **(Table 1)**

Histological grading of breast carcinoma was performed on formalin-fixed paraffin-embedded sections stained with H&E using Elston-Ellis modification of SBR grading system[3] **(Table 2)**

The results of cytological grading were compared with gold standard modified SBR histological grading. In each grade concordance percentage between cytological and histopatholgical grades were calculated separately and then absolute value of concordance was derived among all three corresponding grades. Finally Kappa (κ) coefficient was estimated according to Landis and Koch classification, for each grade to compare the degree of agreement[7].

Table 1: Robinson's cytological grading system for breast cancer

Cytological features	Score 1	Score 2	Score 3
Cell dissociation	Mostly in clusters	Mixture of single & cell clusters	Cells mostly single
Cell size	1-2x RBC size	3-4x RBC size	>5x RBC size
Cell uniformity	monomorphic	Mildly pleomorphic	Pleomorphic
Nucleoli	Indistinct	noticeable	Prominent
Nuclear margin	smooth	Folds	Buds/cleft
chromatin	vesicular	Granular	Clumped and cleared
Grade I score 6-11, Grade II score 12-14, Grade III score 15-18			

Table 2: Elston and Ellis modified Bloom-Richardson grading system

Parameters	Score1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Small, regular	Moderately pleomorphic	Marked pleomorphism
Mitosis per 10hpf in 0.65 mm field diameter	0-5	6-10	>/=11
Histological grade: Grade I well differentiated (score 3-5), Grade II moderately differentiated (score 6-7), Grade III poorly differentiated (score 8-9)			

RESULTS AND DISCUSSION

In the present study, a total number of 56 cases of breast carcinomas were included. Ages of the patient's ranges from 27 to 73 years with a maximum number of patients in the age group of 40-49years.

All the cases were grouped based on Robinson's cytological grading and modified bloom Richardson histological grading and then, comparison between both the grading systems was done as depicted in table 3. In our study, cytologically, 15 (27%), 31 (55%) and 10 (18%)

cases were found to fall in grade I, II and III respectively. In grade I (figure 1a) ductal cells are smaller in size, found to form clusters and have smooth nuclear membrane. In grade II (figure 1b), ductal cells are found in clusters as well as singly scattered showing some degree of pleomorphism. whereas grade III (figure 1c) cells are larger in size showing marked pleomorphism with coarse and clumped nuclear chromatin and have prominent nucleoli.

If we look distribution of cases on histological ground, 16 (29%), 32 (57%) and 8 (14%) cases were seen in grade I, II and III respectively. In grade I (fig 2a) section shows cords and tubules of uniform tumor cells. In grade II (figure 2b), ill defined tubules and cords of moderately pleomorphic cells are seen. In grade III (figure 2c) shows highly pleomorphic malignant cells with hyperchromatic nuclei and prominent nucleoli.

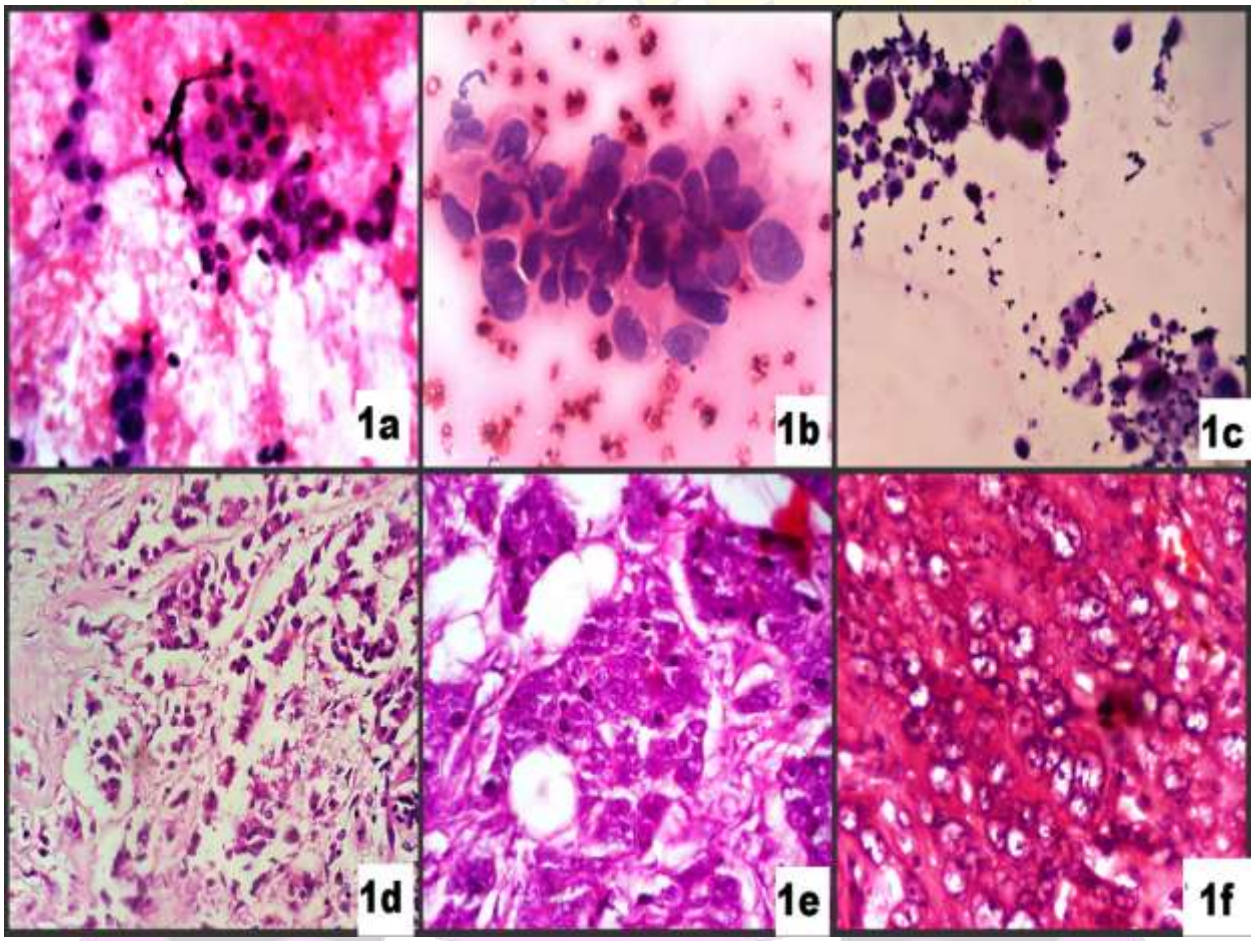

Figure 1a- Grade I carcinoma breast, smear shows ductal cells with mild nuclear atypia forming ill defined tubules, Score-7 (H&E, x400)

Figure1b- Grade II carcinoma breast, smear shows malignant cells in loose clusters with moderate nuclear pleomorphism. Score- 13 (H&E, x400)

Figure 1c- Grade III carcinoma breast, smear shows loosly cohesive cells with pleomorphic nuclei and prominent nucleoli. Score- 16 (H&E, x400)

Figure 1d- Grade I, Section of carcinoma breast showing cords and tubules of uniform tumor cells (H&E, x400)

Figure 1e- Grade II, Section of breast carcinoma showing ill defined tubules and cords of moderately pleomorphic cells (H&E, x400)

Figure1f- Grade III, Section of carcinoma breast showing highly pleomorphic malignant cells with hyperchromatic nuclei and prominent nucleoli (H&E, x400)

Table 3: Concordance of Robinson's cytological grading with histological grading in carcinoma breast (concordance rate=Approximate sensitivity)

Cytological grade (CG) of tumor	No. of cases diagnosed in cytological grading (%)	No. of cases diagnosed in histological grading			Concordance rate (%)
		Grade I	Grade II	Grade III	
I	15 (27)	**11**	4	0	73.3
II	31 (55)	5	**25**	1	81
III	10 (18)	0	3	**7**	70
Total	56	16 (29)	32 (57)	8 (14)	
Absolute concordance					**43/56 (76.78%)**

Thus the extent of concordance between cytological and histological findings for grade I tumor was 73.3% , for grade II tumors, was81% and for grade III tumors was 70%.The absolute concordance rate came out to be 76.78% (43/56) between all three corresponding grades.

Table 4 shows degree of concordance between cytological and histological grading by using kappa statistics. Value of Kappa for grade I and grade II tumors are 0.59 and 0.52 respectively indicating a moderate agreement between cytological and histological grading systems. For grade III tumor Kappa coefficient was 0.736, indicating a good agreement between cytological and histological grading systems.

Table 4: Comparative evaluation of cytological and histological grades using kappa coefficient

Grade of tumor	No. of cases diagnosed cytologically	No. of cases diagnosed histologically	Kappa value (95% CI) for agreement	Standard error value	Strength of agreement
I	15	16	0.599 (0.363 to 0.834)	0.120	moderate
II	31	32	0.528 (0.305 to 0.752)	0.114	moderate
III	10	08	0.736 (0.492 to 0.980)	0.124	Good

Breast carcinoma is the second most prevalent cancer (after cervical carcinoma) in women and is one of the most common cause of death in middle-aged females among developed countries.[8] Therefore it is crucial for accurate pathological diagnosis, aiding further in treatment and management. Diagnostic accuracy is based on agreement of triple test result, which is a combination of clinical examination, radiological details (mammography), and

aspiration cytology. If all these three investigations findings are in accordance, diagnostic accuracy is over 99%[9]. Thus the cytological diagnosis even without histological confirmation forms the basis of definitive treatment, unless there is disagreement between the three parameters of triple tests[9]

Various cytological grading systems for breast carcinoma are presently in use. Robinson's grading system is found to be preferred in various studies because of its simplicity, specificity and reproducibility.[10,11,12] . It uses six different cytological parameters namely; cell dissociation, cell size, cell uniformity, nucleolus, nuclear margin and nuclear chromatin. Robinson's grading system has a concordance with the histological grading ranging from 56.9% to 89.1% in different studies.[13] Histological concordance provides the cytopathologist with a positive feedback and indirectly helps in increasing the efficiency of work.

In the present study, out of total 56 cases, 15 (27%) cases were cytologically in grade I, 31 (55%) in grade II and 10 (18%) cases were in grade III. Hence majority of cases were grade II which is comparable with other previous studies. Robinson *et al* did a study on 608 patients of breast carcinoma. They had 38.3% in grade I, 38.5% in grade II and 23.2% in grade III.[6] Similarly Das et al graded breast carcinomas by similar method and found 28.8%, 46.2% and 25.0% cases in grade I, II and III respectively.[14] The result of the present study showed similar concordance with these studies..

Regarding concordance of cytology with histological grading, the present study showed overall concordance of **76.78%** which is comparable with other published studies **(Table 5)**

The parameters included in histological grading are tubule formation, mitosis and nuclear pleomorphism. The probable causes of discordance between cytological and histological grading systems might be due to difficulty in accessing the tubule formation and mitotic index on cytology.

Table 5: Comparison of concordance rate between cytohistological grading among different studies

Authors	Concordance (%)
Robinson et al (1994) (6)	56.9
Das et al (2003)13	71.2
Chabbra et al (2005)14	65.0
SK Sinha (2009) (15)	69.5
Nazoor Khan et al (2009)3	89.1
TS Rekha et al (2011)16	82.0
Present study (2015-2016)	76.78

Many studies has established the fact that histologic grading system is an important prognostic parameter for breast carcinoma.[2] Thus, FNAC is indirectly helpful in predicting

the histological grade, the biological behavior of the tumor and useful parameter in selecting neoadjuvant therapy.

High cytological score is associated with higher propensity for lymph node metastasis.[15] Many studies have been done that show association of tumor grade with ER/PR status .[16] A positive ER and PR status is associated with low cytological score whereas expression of her2/neu, ki67 and p53 is associated with positive high score [17].

Importantly cytological grading is found to be beneficial in detecting the fast growing high grade tumors which show good respond to chemotherapy than low grade/slow growing tumors. Additionally neoadjuvant therapy can be applied as preoperative chemotherapy which is becoming common in management of breast carcinoma patients. Hence, it is desirable to grade tumor before surgery so that appropriate modality of treatment can be selected.[18]

The current study shows the absolute concordance value of 76.78% (43/56 cases) between all three corresponding grades. Whereas the total discordance was 23.22% seen in 13 cases out of 56 cases (four cases in grade I, six cases in grade II, and three cases in grade III). Table 5 shows strength of agreement between Robinson's cytological grading and histologic grading in different studies based on kappa statistical analysis. Kappa values were calculated according to Landis and Koch classification,

As clearly seen in table 4, Kappa values for grade I, II and III tumors were 0.59, 0.52 and 0.73 respectively.

Thus indicating a moderate degree of agreement for grade I and II tumors. Whereas Kappa value in case of grade III tumors indicate good agreement between cytological and histological grading systems. Strongest correlation was noted for grade II tumors than grade I and lastly grade III tumors.

CONCLUSION

So to be concise, fine needle aspiration cytology besides being noninvasive, rapidly diagnostic, having minimal complications, usage from multiple lesions, easy repeatability, high accuracy, is comparable with histological grading and is also useful in assessing the tumor behavior and prognosis with additional assistance for neo adjuvant chemotherapy.

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