



Original Article

Cytological grading of breast carcinoma and its correlation with histopathological grading

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ABSTRACT

Background: Diagnosis of breast cancer is made in most of the cases near accurately by fine needle aspiration cytology. With the advent of neoadjuvant chemotherapy, the need for identification of aggressiveness of the tumor has become essential. So cytological grading may be of prime importance for the patient, who may undergo neoadjuvant therapy prior to surgical resection.

Objective of this study was to grade the breast carcinoma on FNAC using Robinson's and Mouriquand's grading systems and to assess the concordance of both cytological grading (CG) systems with histological grading using modified Scarff-Bloom-Richardson grading system.

Materials and Methods: This study was done between 2016 and 2018 in subjects with breast carcinoma undergoing FNAC. Cytological grading of the samples were done by Robinson's and Mouriquand's method. Subsequent Histological grading was done on subsequent specimens according Modified Bloom Richardson grading system. Obtained histological grades were correlated with the cytological grades.

Results: Robinson's grading system showed significant association with modified Bloom Richardson grading system ($p < 0.01$), with a specificity of 71.4% (43/60) whereas there was no significant association in the case of Mouriquand's grading system.

Conclusions: Cytological grading of invasive breast cancer corresponds well with the histological grade. In our study we found that grading a tumor by the Robinson's method was more specific and elementary compared to Mouriquand's system of grading.

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INTRODUCTION

Breast cancer is the commonest cancer in women worldwide, with a widely variable incidence between countries and regions. The developed countries, even though with a small proportion of the world population, account for almost 50% of breast cancers diagnosed worldwide.¹ Accurate diagnosis of breast cancer is made in most of the cases by the combination of clinical examination, mammography and simple, noninvasive, cost-effective outpatient department procedure, fine-needle aspiration cytology (FNAC). Technique of FNAC has been widely used since long time. With the advent of neoadjuvant chemotherapy, the need for

giving an idea of the aggressiveness of the tumor by FNAC has further more increased applicability and utility for the tumors which are easily palpable on external examination.^{2,4} Cytological grading may be of prime importance for the patient, who may undergo neoadjuvant chemotherapy prior to surgical resection.

MATERIALS AND METHODS

The present study was a prospective study which included patients being referred for FNAC with suspected breast carcinoma from outpatient clinic of a tertiary medical care hospital in South Karnataka, over a period of eighteen months. Institutional Ethical Committee gave approval for the study. A total of 60 patients with carcinoma breast belonging to the age-group of 35 years and older constituted the study population. These cases were followed up and mastectomy and lumpectomy specimens sent to Department

of Pathology, Mysore Medical College and Research Institute were collected and histopathological examination was done. Those cases which were reported as benign in FNAC, which were not operated in this institution, and the ones which underwent neoadjuvant therapy were excluded from the study. FNAC was done by non-aspiration technique. The aspirated material was expressed on slide, smeared and fixed with 95% alcohol for 20 minutes. These wet fixed slides were stained with Papanicolaou method and H&E.

The stained smears were evaluated and diagnosed as invasive carcinoma of breast when there is definite features of malignancy like cellular dissociation, nuclear pleomorphism, nuclear abnormalities, absence of bare nuclei. Any special variants of invasive carcinoma were also included. These slides were graded based on grading system proposed by Robinson and Mouriquand. ([Table 1](#) and [2](#))

Table 1: Robinson's cytological grading system

	SCORE 1	SCORE 2	SCORE 3
Cell dissociation	Mostly in clusters	Single cells and clusters	Mostly in single cells
Nuclear size	1-2 times the size of RBC	3-4 times the size of RBC	>5 times the size of RBC
Cell uniformity	Monomorphic	Mildly pleomorphic	Pleomorphic
Nucleoli	Indistinct/small	Noticeable	Prominent
Nuclear margin	Smooth	Slightly irregular /folds/grooves	Buds and clefts
Chromatin pattern	Vesicular	Granular	Clumping and clearing

The value between 1 and 3 was given for every factor analyzed. Total score was obtained by adding the individual scores which ranged between 6 and 18, according to which grading was done ([fig.1-3](#)).

Grade 1: Score 6- 11; **Grade 2:** Score 12-14; **Grade 3:** Score 15-18

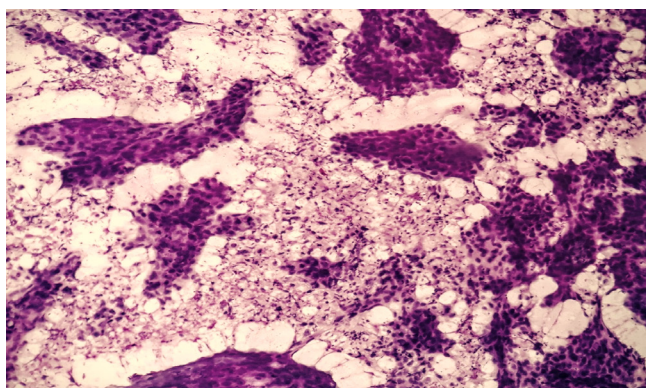


Figure 1: IC-NST-Robinson's grade 1, Pleomorphic cells in clusters, mild nuclear pleomorphism, indistinct nucleoli and vesicular chromatin, (HE stain, 40X).

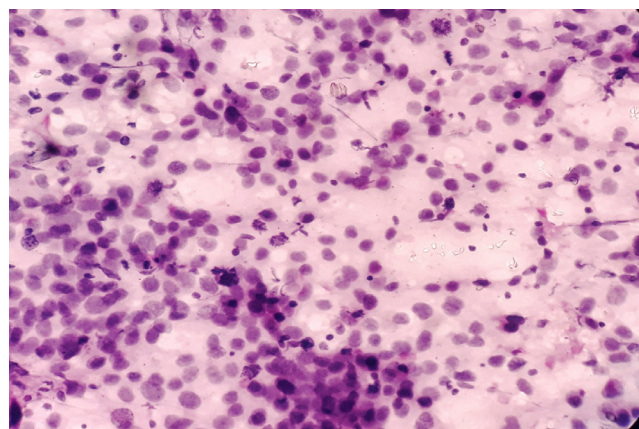


Figure 2: IC-NST-Robinson's grade 2, Pleomorphic cells in clusters and in singles, moderate nuclear pleomorphism, noticeable nucleoli and granular chromatin (HE stain, 40X).

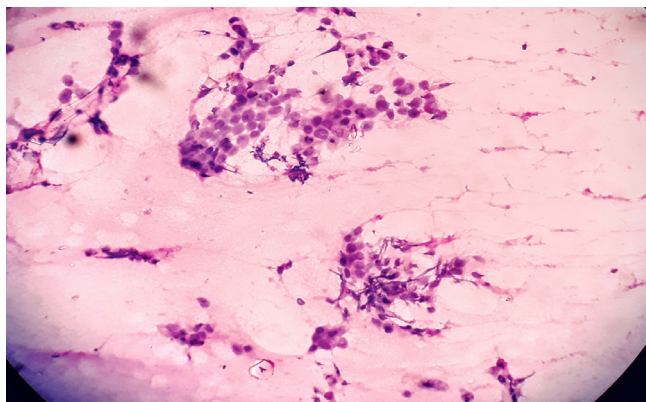


Figure 3: IC-NST-Robinson's grade 3, Pleomorphic cells in singles, nucleus- prominent nucleoli, irregular nuclear margin, clumped up chromatin (HE stain, 40X).

Table 2: Mouriquand's Grading system

Feature	Score
Cells:	
Isolated	3
In clusters	0
Nuclear features:	
Large cell size	3
Anisokaryosis	2
Nuclei:	
Naked	3
Budding	2
Hypochromasia	3
Hyperchromasia	2
Enlarged Nucleoli	
Red	3
Blue	2
Mitosis	
>3/slide	1
>6/slide	3
Grade 1: <5	
Grade 2: 5-9	
Grade 3: >10	

Mastectomy specimens were received in 10% formalin. The tumor size and the tumor location were assessed in the gross specimens. Paraffin embedded sections obtained by routine procedures were cut at thickness of 3 microns using Leica microtome. These slides were routinely stained with H&E stain. The slides were evaluated and the diagnosis of invasive carcinoma was confirmed. Special types of ductal carcinoma other than classical invasive carcinoma NST were also included in this study. Histological grading was done using Nottingham modification of Scarff Bloom Richardson method. This system considers three parameters. They include tubule formation, nuclear pleomorphism and mitotic rate. (Table 3)

Table 3: Modified Bloom Richardson Histologic grading

	1	2	3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Small regular uniform cells	Moderate increase in size and variability	Marked variation
Mitotic count	<7	8-14	>15

Each parameter was assigned a score of 1 -3. Scores were added to give a total score of 3- 9. In the present study mitotic count was done in 0.50 mm field diameter Olympus microscope 20 mm eyepiece with a 40x objective gives a field diameter of $20 \div 40 = 0.50$ mm. Number of mitosis were counted per 10 high power field. Final grade was based on total score obtained:

Grade 1: Score 3-5; **Grade 2:** Score 6-7; **Grade 3:** Score 8-9.

Data was entered in Excel spreadsheet. Descriptive statistics like frequency and proportions were calculated. The grades were compared using Crammer's rule.

RESULTS

Total of 60 subjects who fulfilled the criteria were included. Histopathological subtyping of breast cancer was done according to the WHO classification (5th ed).¹² Out of 60 breast carcinoma, 55 were invasive carcinoma (NST), two cases of invasive lobular carcinoma, one case each of mucinous, medullary and metaplastic carcinoma.

According to Robinson's grading system, the cytological samples were graded based on the scores obtained into three groups. Majority were grade 2 (32/60), followed by grade 1 (15/60) and grade 3 (13/60). Few special types were also reported. Mucinous carcinoma and lobular carcinoma which was graded as grade 2, Medullary carcinoma which was graded as grade 3 and a case of Metaplastic carcinoma which was graded as grade 1.

According to Mouriquand's grading system, the cytological samples were again graded into three groups. Majority of the cases were grade 2 (33/60), followed by grade 3 (15/60) and grade 1 (12/60). Cases of mucinous carcinoma, medullary and two cases of lobular carcinoma which was graded as grade 2, Metaplastic carcinoma which was graded as grade 1.

Histological grading was done according to Elston's modification of Scarff Bloom Richardson grading, and were categorized under three categories. Of the sixty cases, majority were graded to grade 2 (30/60), followed by grade 3 (16 /60) and grade 3 (14/60). The Robinson's grade of the tumor was correlated to the histologic grade to assess the concordance between the two grading systems. (Table 4)

Table 4: Correlation of Robinson's grade with histologic grade

	1	MBR GRADE			TOTAL
		2	3		
ROBINSON'S GRADE	1	10 (71.4%)	4 (13.3%)	1 (6.2%)	15 (25%)
	2	4 (28.6%)	25 (83.3%)	3 (18.8%)	32 (53.3%)
	3	0 (0.0%)	1 (3.3%)	12 (75.0%)	13 (21.7%)

In this study of sixty cases, forty seven cases (78%) showed concordance between cytologic and histologic grading systems. Rest of the thirteen cases (22%) showed discrepancy. Among the 15 grade 1 tumors, ten cases (71.4%) showed concordance with the histological grade whereas five cases were discordant. All these five cases were upgraded. Four cases were upgraded to grade 2 and one to grade 3. Among the thirty-two grade 2 tumors, seven cases did not correlate, three were upgraded to grade 3 and the four were downgraded to grade 1. Twenty-five grade 2 tumors showed good concordance (83.3%). Grade 3 tumors showed good concordance with twelve cases (75%). Only one of the grade 3 tumor was downgraded to grade 2.

The Mouriquand's grade of the tumor was correlated to the histologic grade to assess the concordance between the two grading systems (Table 5). In this study Mouriquand's grading system did not show significant association (Phi-0.325, Crammer's V-0.230) with histological grade ($p > 0.05$).

Table 5: Correlation of Mouriquand's grade with histologic grade

	1	MBR GRADE			TOTAL
		2	3		
MOURIQUAND'S GRADE	1	5 (35.5%)	5 (16.7%)	2 (12.5%)	12 (20.0%)
	2	7 (50.0%)	19 (63.3%)	7 (43.8%)	33 (55.0%)
	3	2 (14.3%)	6 (20.0%)	7 (43.8%)	15 (25.0%)

In this study of sixty cases, thirty one cases (51.6%) showed concordance between cytologic and histologic grading systems. The twenty nine cases (48.3%) show discrepancy. Among the twelve grade 1 tumors, five cases (35.5%) show concordance with the histological grade, whereas seven cases were discordant. Five cases were upgraded to grade 2 and two to grade 3. Among the thirty three grade 2 tumors, fourteen cases did not correlate, seven were upgraded to grade 3 and the seven were downgraded to grade 1. Nineteen cases with grade 2 tumors show good concordance (63.3%). Grade 3 tumors showed good concordance with seven cases (43.8%). Eight grade 3 tumors were downgraded, six (20.0%) to grade 2 and two (14.3%).

The grade I cases were considered as 'low grade' and both grades II and III cases were clubbed together as 'high grade' in both cytological as well as the histological grading methods. These two categories in cytological grading were then separately compared with the corresponding histological grading. (Table 6). For Robinson's grading system, the sensitivity was 89.1% and specificity was 71.4%. For Robinson's grading system the diagnostic accuracy was 85%, sensitivity 89.1% and specificity 71.4%.

Table 6: Comparison of statistical parameters of both the cytological grading systems with histological grading

Statistical parameter	Robinson's grading	Mouriquand's grading
Sensitivity	89.1%	84.7
Specificity	71.4%	35.7
Positive predictive value	93.1%	81.2
Negative predictive value	66.6%	91.66
Diagnostic accuracy	85%	73.3%

DISCUSSION

Breast carcinomas are now on an increasing trend and are being easily diagnosed on initial

Investigation on FNA. As the tumor grade is a known prognostic marker to assess the severity of the disease, an attempt was made to grade these tumors on cytology. Various grading systems to grade on cytology have been used by many studies and have also attempted to compare them with the MBR grading system. Robinson's and Mouriquand's grading systems were found to be more comparable than other grading systems when MBR as considered as the gold standard.⁷ Grade on cytology when done by Robinson's grading system has good association with MBR which is in concordance with our study.

Cytological grading of breast carcinoma

In the present study, distribution of the cases according to Robinson's grading showed 25 per cent cases graded as cytological grade I, 53 per cent as grade II and 22 per cent as grade III. Robinson et al in their study of 608 cases had the distribution of cases as 38.3, 38.5 and 23.2 per cent in cytological grades I, II and III, respectively.⁷ Pandit and Parekh graded 75 breast carcinomas by Robinson's method with 34.7 per cent each in grades I and grade II, and 30.6 per cent in grade III. Thirteen cases (22%) showed discordance which was comparable with Pandit and Parekh's study.⁸

The rate of discordance in the study by Robinson et al⁷ was relatively higher (39.5%), however, majority of the cases had only one grade discordance with histological grading. Percentage of cases showing two grade differences were very less in our study as in these studies. The distribution of cases by the Mouriquand's grading system showed a predominant grouping of cases into grade 2 and grade 3. Comparison of the present results with that of Das et al and

other studies show similarity.⁸⁻¹¹

Of the 15 grade I cases by Robinson's method, 8 were graded as grade 1, whereas 6 cases were over graded as grade 2 and 1 case as grade 3 by Mouriquand's method. Of the 13 grade III cases by Robinson's method, 8 cases were graded as grade III by Mouriquand's method, and 4 cases were under graded as grade II and one case as grade 1. Out of 32 grade II tumors by Robinson's method, 23 were grade II by Mouriquand's method of which 6 were over graded as grade 3 and 3 were undergraded as grade 1.

Some degree of discordance between the two grading methods was observed in all the grades with the majority of the discordant cases observed in grade I tumors. The reason for the over-grading of the tumors by the Mouriquand's method appears to be the presence of mitosis in most of the discordant cases. Mitosis is one of the parameters used for grading by Mouriquand's method, whereas mitosis is not taken into consideration in Robinson's method.

In our study Robinson's grading system showed significant association with MBR grading system ($p < 0.01$) where as there was no significant association in the case of Mouriquand's grading system ($p > 0.05$).

These findings suggested that Robinson's method of cytological grading was a reasonably reliable method of grading breast carcinoma in FNA smears. The overall concordance of Robinson's grading with histological grading in the present study was 78% per cent and this is comparable with other published data.⁸⁻¹⁰ Discordant cytological grading in 15 cases (28.8%) with one grade difference in 13 was comparable with Pandit and Parekh's study.⁸ Histological grading was based on degree of tubule formation, mitosis and nuclear pleomorphism. Tubule formation was difficult to assess in FNA smears, though some authors believed that cell clustering or dissociation reflected the tubule formation.⁷ This could be responsible for the discordance observed between the cytological and histological grading systems. For cases with both well differentiated and poorly differentiated areas like metaplastic carcinoma, the area of the tumor where FNAC is being taken also matters. Another cause of discordance could be due to time gap in surgery which resulted in increase in the histopathological grade.

In the present study sensitivity (89.1% and 84.7%) and diagnostic accuracy (85% and 73.3%) of both Robinson's and Mouriquand's methods was similar. However, the specificity by the Mouriquand's method was quite low, which was comparable with study by Das et al and Pandey et al.^{9,10}

The Robinson's method of cytological grading was more specific when Elston and Ellis's method of histological grading was considered as gold standard. It was also found that the criteria for grading a tumor by the Robinson's method were simpler and easier to apply as compared

to the Mouriquand's method. Robinson's cytological grading correlated better than Mouriquand's cytological grading with histological grading system. This is probably because Robinson's grading method has two more criteria, cell dissociation and uniformity which is not present in Mouriquand's cytological grading system. This results in a tendency to over grade in Mouriquand's grading system. The criteria for grading a tumor by the Robinson cytological method were simple as compared to the Mouriquand's method.

CONCLUSIONS

Our study reemphasizes that it is possible to grade invasive breast cancer on cytological aspirates and that the cytological grade corresponds well with the histological grade. Moreover, the system used is simple, less tedious and the information obtained is of prognostic value especially when combined with mammographic findings. As neoadjuvant therapy is becoming increasingly common for the treatment of early breast cancer, it is desirable to grade the tumor preoperatively on FNAC so that the most appropriate medical regimen could be selected. It could be said in confidence that this grading system will be useful in prognostication for better management of patient of malignant breast lesions in the near future. And in our study we found that the criteria for grading a tumor by the Robinson's method was more specific and elementary compared to Mouriquand's system of grading.

Conflict of Interest: None

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