Role of Cytological Grading in Breast Cancer Prognosis and its Histo-pathological Correlation

Dr. Ruplekha Mitra Mustaphi[1], Dr. Surupa Chowdhury[2], Dr. Seema Mondal[3], Dr. Sugata Kumar Bhattacharya[4], Dr. Sanjay Sarkar[5], Dr. Tushar Kanti Saha[6]

{[1&2] (Demonstrator, Dept of Pathology) [3](Assistant Professor, Dept of Pathology) Burdwan Medical College & Hospital}, {[4](Assistant Professor, Dept of Physiology), [5](Assistant Professor, Dept of Medicine), [6](Assistant Professor, Dept of Community Medicine) N.R.S. Medical college & Hospital}

Abstract:

Objective: *Breast carcinoma is the most common cause of death in females globally, which should be detected early and treated promptly. This study aims at establishing Fine Needle Aspiration Cytology (FNAC) as an individual parameter in diagnosing & grading carcinoma breast and to correlate cytological grading with the histopathological grading done post-operatively.*

Materials & methods: *We present here, a series of 44 cases, clinically suspected of carcinoma breast, presenting with hard, painful breast lump with or without axillary lymphadenopathy, sent for cytological examination to our department. Aspiration was done, following using 20G needle and smears were stained with Haematoxyline & Eosin, Papanicolau, and May-Grünwald-Giemsa.*

Results: *The stained smear showed highly pleomorphic ductal cells in large number forming dyscohesive sheets & also lying singly. Cells had nuclei with hyperchromasia, irregular nuclear margin, open chromatin & conspicuous nucleoli. The diagnosis of carcinoma breast was offered and cytological grading was done according to Robinson's nuclear grading system in all cases. Urgent biopsy was also however, recommended. The mastectomy specimens of these patients, when grossed & stained with Haematoxyline & Eosin proved the cytological diagnosis conclusive and cytological grading of the tumors concordant in 80% of the cases. Higher cytological grades showed increased nodal metastasis.*

Conclution: *So, early diagnosis & precise grading with the help of FNAC itself can prove to be a very good informative tool & prognostic indicator, leading to commencement of early treatment & can prevent many untimely deaths in future.*

Key Words: *Fine needle aspiration cytology, cytological grading, histological grading.*

I. Introduction

Neoplasm constitutes the most important lesion of the breast. It is the most common cancer in women, worldwide accounting for 22% of all new cancers in females in the year 2003.[1] It is also however, the most common cause of death from carcinoma in females, globally [1] being responsible for 375000 deaths in the year 2005.[2] In India, it is in the 2nd position, incidence wise only to be preceded by cancer cervix; Age standardized incidence being 9 – 28.6 per 100000 women.[3]

Frequently the need arises to distinguish benign from malignant lesions prior to definitive treatment. As a result of early detection and improvement in therapy, mortality due to breast carcinoma is now beginning to fall in the West. This, however, unfortunately not the case for developing countries in which breast cancer mortality is still rising. Breast cancer however, is a disease with a heterogeneous prognosis. Many factors have been identified till date, the most important & commonly used among them being - patient's age, BRCA 1 status, early diagnosis, presence and absence of invasiveness, size of tumor, axillary lymph node status, anatomical quadrant, cytoarchitectural type, microscopic grade, hormone receptor status, type of margins, tumor necrosis, stromal reaction, micro vessel density, elastosis and pattern of lymph node reaction.[4] Among these prognostic factors microscopic grading is one of the very important factors. Histological grading of breast carcinoma was first attempted in 1925 by Greenough [5] by using variations of morphological appearances of tumors.It was shown quite early that survival is related to histological grade [8] and this was confirmed by Bloom [6]. But of late, the evaluation of cytological features of infiltrating ductal carcinoma of breast has been proven valuable & shown to provide ample information regarding intrinsic features of the tumor as well as its prognosis & treatment outcome

Thus ,this study plan to establish FNAC as an individual parameter of grading & staging of breast carcinoma, especially in inoperable cases , facilitating early treatment and final outcome of the disease. Specific objectives of this study being: - 1) grading of breast cancers cytologically, on the FNAC smears according to Robinson's nuclear grading system, at the time of diagnosis. 2) Determining the role of cytological grading, as

an individual parameter in the prognostication of the tumor. 3) Detecting the histopathological grade of the tumors by Bloom-Richardson grading system, on the mastectomy specimens, post operatively 4) establishing any correlation, if present, between these two grading systems.

II. Materials and Methods

The study was performed in the Department of Pathology of Burdwan Medical College & Hospital. In this prospective study total 44 adult females are included. . Age ranges from-28-60 years and they have history of breast lump with or without axillary lymphadenopathy. Study was done from February 2010 to January 2011. Fine needle aspiration cytology was performed on all lesions using a 20 gauge needle. FNAC material was fixed with 95% alcohol and stained with Hematoxyline & Eosin (H &E), May-Grunwald-Giemsa (MGG) and Papanicolaou (PAP) stains.Cytological grading of FNAC smears were done according to grading system described by Robinson et al.This takes into account six parameters- cell dissociation, cell size, uniformity, nucleolus, nuclear margin & nuclear chromatin.A score of 1-3 was given to each of these parameters, & final grading of the tumor was done by adding up the scores.Scores-6-11 were graded as grade-1; scores-12-14 as grade-2; & score 15-18 as grade 3.Histological grading was done on H&E stained, formalin fixed, paraffin embedded sections from mastectomy specime **Method used**: Elston's modified Bloom-Richardson's grading system. Three parameters considered- degree of tubule formation, nuclear pleomorphism & mitotic count. Mitotic figures were scored using a leitz ortholux microscope – field diameter –0.59mm. Statistical analysis was done by calculating concordance rate which shows the degree of correlation between two grading systems. All 44 cases were also evaluated for presence or absence of metastasis to axillary lymph nodes, and percentage of nodal metastasis for each grade was performed.

III. Results

All FNAC smears showed hypercellularity, with cells lying dispersedly as well as in loosely cohesive sheets. The cells show varying degrees of pleomorphism, nuclear hyperchromicity, increased nuclear: cytoplasmic ratio, irregular nuclear margins & prominent nucleoli. There is conspicuous lack of myoepithelial cells in whole smear in most of the cases. Background is haemorrhagic with inflammatory cells lying dispersedly.After doing preoperative cytological grading of the 44 cases, according to nuclear grading system proposed by **Robinson et al.**, the result was tabulated in **table 1**:

Histopathological findings of all 44 resected post mastectomy specimen of breasts, and grading them according to Elston modified Bloom- Richardson's grading system, following results were shown in **table2** . Comparison is done in **table 3** which shows that, concordance rate between grades I tumors in cytology and histology was 62.5%, while for grade II and 3 were 88.9% each.

The overall sensitivity amounted to **80.1%** and specificity was **100%**. Further comparison of the two grading systems, namely Robinson's cytological grading and Elston modified Bloom- Richardson's grading, by applying Z test showed that difference between the cytological and histological grading was insignificant in all three grades ($P > 0.05$). Therefore, it can be sated that cytological grading is comparable to histological grading of tumors to assess the tumor behavior and prognosis,

Table 4 shows assessment of lymph node status data, utilizing chi- square test for the various tumor grades in 27 of 44 cyto-histologically graded tumors. Analysis of this data showed lymph node metastasis in 25% of grade I, 62.9% of grade II, and 88.9% of grade III tumors. Chi- square test between CG1:CG2 shows a value of 6.79 i.e. statistically significant difference in incidence of lymph node metastasis was found between grade I and grade II ($P <0.01$). chi- square value between CG 2 :CG3 was 3.64 i.e. >0.05 and between grade I & III tumors 11.54 i.e. ($P < 0.001$), indicating a significant rise in incidence of lymph node metastasis with increasing cytological grade of the tumor, thus establishing cytological grade itself as an important prognostic marker.

IV. Discussion

On performing Robinson's cytological grading, on all 44 cases, and adding up the parameters, we found that majority of the examined smears , 27 out of 44 , fell under cytological grade II (61.4%), followed by 18.2% of cytological grade I cases (8 out of 44) and 20.4% cytological grade III cases (9 out of 44 cases).– Table No 1.

The optimal number of cell clusters necessary to define an adequate FNA of a palpable breast mass is not clear, although many authors have used six as the definitive number of epithelial cell clusters [7]. A study by Sinha **et al** [8] shows that a better concordance between grading systems may be achieved by examining 8 cell-clusters.

Assessment of lymph node status for the various tumor grades in 27 of 44 cytologically graded tumors, showed lymph node metastasis in 25% of grade I, 62.9% of grade II, and 88.9% of grade III tumors. (TABLE-4). , thus proving the association of higher cytological grades with greater percentage of nodal metastasis, and

reinforcing the validity and utility of cytological grading once again. Further chi- square test done on incidence of lymph node metastasis in all 3 grades , show increasing significance of association between cytologically higher grade tumor and nodal metastasis.- supporting our finding statistically too.

After going through the results of cytological grading of all 44 cases, done preoperatively, and histopathological grading, done after their resection, we tabulated the results as follows: 5 out of 8 patients graded cytologically as grade I, before mastectomy, showed concordance after resection. 24 out of 27 patients in grade II, showed concordance after histological grading, whereas, 8 out of 9 patients showed concordance in grade III. (Table- 3). Concordance rate between grade I tumors in cytology and histology was 62.5%, while for grade II and 3 were 88.9% each. The over all sensitivity amounted to 80.1% and specificity was 100%.

Further comparison of the two grading systems, namely Robinson's cytological grading and Elston modified Bloom- Richardson's grading, by applying Z test showed that difference between the cytological and histological grading was insignificant in all three grades (P > 0.05). A number of studies have confirmed the prognostic value of histological grade in invasive ductal carcinoma breast [9],[10]. Fine- needle aspiration studies have developed a number of scoring systems, with results similar to those obtained from histological sections. [11] [12].thus confirming the value of FNAC for predicting the histological grade of certain tumors preoperatively and therefore its eventual biologic behavior. Robinson's cytological grade is found to correspond well with the established histological grades (Elston's modified Bloom Richardson method) [13]. **Pandit and Parekh** [14] graded 75 breast carcinomas by Robinson's method and showed 64% concordance with Bloom Richardson's' grading on histopathology. They concluded that cytological grade could be used to predict the histological grade as a significant relationship exists. In this study, histological grade correlated well with the cytological grade. Beside its role in early diagnosis, FNA also helps to assess the prognosis, providing information on tumor grading and the lymph node status. It allows the judicious use of neoadjuvant therapy, which can then be monitored by repeating the fine needle aspirate and also gauging the response clinically and mammographically.

V.   Conclusion

Thus, it is concluded that assigning a cytological grade in breast carcinoma aspirates ,done with little effort, much before resection, is reproducible and with rare exceptions, depending on sample limitations, correlates precisely with the histological grade and permits determination of the aggressiveness of a breast carcinoma. It is a useful parameter to be taken into consideration while selecting mode of therapy for carcinoma breast and to predict the tumor behavior and outcome of the patients in future.

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Table No. 1: Cytological grading

Total number of cases	Cytological grade I	Cytological grade II	Cytological grade III
44	8	27	9
Percentage	18.2%	61.4%	20.4%

Table No. 2: Histopathological type & grading (n=44)

HISTOLOGIC TYPE	TOTAL NO OF CASES (44)	GRADE- I		GRADE- II		GRADE- III	
		NO OF CASES (6)	% OF CASE	NO OF CASES (28)	% OF CASE	NO OF CASES (10)	% OF CASE
IDC NST	34	4	11.7	25	73.5	5	14.7
MUCINOUS	2	2	100	0	0	0	0
MEDULLARY	5	0	0	2	40	3	60
ILC	1	0	0	1	100	0	0
METAPLASTIC	1	0	0	0	0	1	100
PAPILLARY	1	0	0	0	0	1	100

Table No. 3: Cytological & Histopathological correlation (CONCORDANCE = APPROXIMATE SENSITIVITY)

Robinson's cytological grade (CG)	Number of cases (cytology)	Histological Grade I.	Histological Grade II	Histological Grade III.	Concordance Rate. (%)
Grade- I.	8	5	3	0	62.5%
Grade –II	27	1	24	2	88.9%
Grade- III.	9	0	1	8	88.9%
Total-	44	6	28	10	80.1%

Table No. 4: correlation of cytological grade with lymph node status

Cytological grade	Metastatic deposit in palpable axillary lymph nodes	Non- palpable lymph nodes with no deposit	Total cases
Cytological grade I	2	6	8
Cytological grade II	17	10	27
Cytological grade III	8	1	9
Total	27	17	44