Section: Pathology

Original Research Article

CYTOHISTOPATHOLOGICAL STUDY OF PRECANCEROUS AND CANCEROUS LESIONS OF UTERINE CERVIX

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ABSTRACT

Background: The histogenesis and progression of cervical carcinoma is well documented. It is possible to prevent the development of invasive carcinoma by identifying and treating pre invasive lesions. This study was a prospective study conducted from 01 July 2014 to 01 July 2016. The objectives of the study were to evaluate and interpret the cases of precancerous and cancerous lesions according to The 2001 Bethesda System and to correlate cytology diagnosis with histopathology diagnosis.

Materials and Methods: Pap Smears were received along with their corresponding cervical biopsies or hysterectomy specimens in the Department of Pathology, Raja Rajeswari Medical College and Hospital, Bangalore. The Pap smears were stained with Papanicolaou stain and the corresponding biopsies or hysterectomy sections were stained with H & E stain and examined for microscopic details.

Results: The cytological evaluation of 200 pap smears was done and 61.5% of lesions were reported as Negative for intraepithelial lesion or malignancy, 15% as ASCUS, 11% as LSIL, 5.5% each as HSIL and SCC and the remaining 1.5% as positive for malignancy. Majority of the women were from the age group of 41-50 years and the commonest presenting complaint was white discharge per vaginum. Of 200 specimens received for histopathology, 137 (68.5%) were reported as Benign, 37 (18.5%) as Premalignant and 26 (13%) as Malignant. Amongst the 37(18.5%) premalignant lesions encountered on histopathology, 11% cases were reported as koilocytic atypia, 43% cases as CIN 1, 27% cases as CIN 2, 16% cases as CIN 3 and 3% cases as CIS. The total number of malignant lesions were 26 (13%) in number. Out of these, 92% were reported as Squamous cell carcinoma and 4% cases each of microinvasive SCC and Adenocarcinoma. Of these 24 cases of SCC, 58% cases were moderately differentiated SCC, 33% were well differentiated SCC and 9% cases were diagnosed as poorly differentiated SCC.

Conclusion: The regular screening of population by Pap smear and reporting as per The 2001 Bethesda System is a cost-effective method for early detection of premalignant and malignant cervical lesions. The procedure is simple, inexpensive and can be performed in the outpatient department which is useful in a country like ours. It also has an important role in the diagnosis of inflammatory lesions including the identification of causative organism and atrophic changes and helps in the definitive management of patients. All lesions on Pap smears should be followed by repeat Pap smear examination and cervical biopsies hysterectomy which will improve the diagnostic accuracy and help in staging of malignant lesions.

Keywords: The 2001 Bethesda System, Papanicolaou stain, cervical biopsy.

INTRODUCTION

Worldwide, invasive cervical cancer is the second most common female malignancy after breast cancer and the fifth most deadly cancer in women. It affects about 16 per 1,00,000 women per year and kills about 9 per 1,00,000 per year.[1]

Carcinoma of cervix is the most common cancer in Indian women and accounts for 20% of all malignant tumours in the females. It is the most common malignancy in women in developing countries.[1]

It is possible to prevent the development of invasive carcinoma by identifying and treating pre invasive lesions. The efficacy of cervical smear study was established by George N Papanicolaou.[2]

Since cytology is the examination utilized for the screening of cervical cancer, it is important to determine its correlation with histologic examination, the gold standard in the diagnosis of cervical disease.[3]

Hence the goal of this study is to study cervical smears and grade them according The Bethesda system 2001 and subsequently formulate a cytological and histopathological correlation.

MATERIALS AND METHODS

The present study was undertaken to assess the reliability of 200 cervical smears in diagnosing various precancerous and cancerous lesions of cervix in correlation with histopathological examination.

For this purpose Pap Smears were received along with their corresponding cervical biopsies or hysterectomy specimens in the Department of Pathology, Rajarajeswari Medical College and Hospital, Bangalore. Detailed clinical data was obtained which included age of presentation, presenting complaints, obstetrical and menstrual history and other relevant details from the patient and noted on a structured proforma. The study was conducted for a period of 2 years from July 2014 to July 2016.

Cervical smear was taken after obtaining consent of the patient. Cervix of the patient was exposed adequately with a speculum. The squamocolumnar junction was visualized, with the hooked end of Ayre's spatula, squamocolumnar junction was scraped gently throughout its circumference and material was transferred to glass slides.

Two such smears were fixed with 95% alcohol immediately and stained by Papanicolaou stain. The diagnosis of these smears was done using The 2001 Bethesda System of Reporting Cervical Cytology.

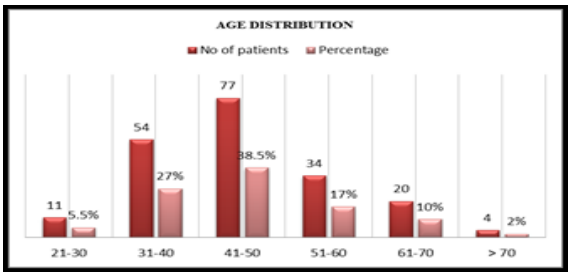
Biopsy and hysterectomy specimens were received in 10% formalin, processed and embedded in paraffin blocks. 4 µ thick sections were taken and stained with haematoxylin and eosin (H & E). The slides were then examined.

The histological findings were then correlated with cytology finding.

RESULTS

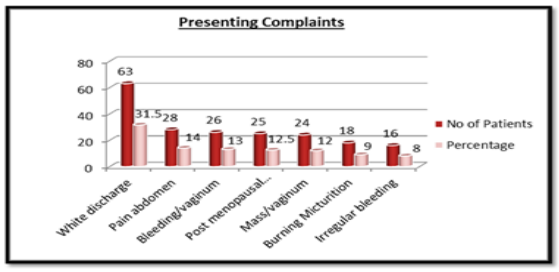
The present study was done on 200 cervical smears using The 2001 Bethesda System of reporting cervical cytology in the Department of Pathology, Raja Rajeswari Medical College and Hospital, Bangalore. These smears were then correlated with histopathology (cervical biopsy or hysterectomy specimens).

The study period was from July 2014- July 2016. The following results were obtained.



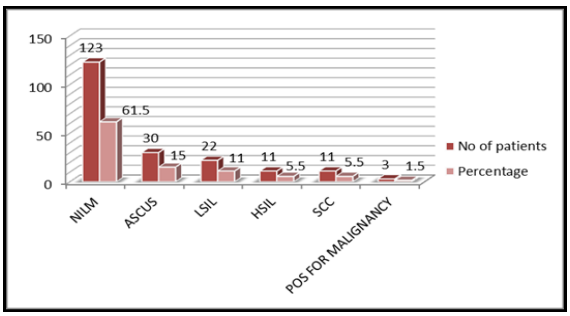
Graph 1: Age Distribution

Out of the 200 patients, 38.5 % patients were from age group 41-50years, 27% were of the age group of 31- 40 years, 17 % from 51 – 60 years, 5.5% from 21 -30 years, 10 % from 61-70 years and only 2% were from age group greater than 70 years. The maximum number of patients were from age group of 41-50 years i.e. 38.5%. The mean age was 47 years. **(Graph 1)**



Graph 2: Presenting Complaints

The patients presented with a wide spectrum of complaints. The predominant presenting complaint was white discharge per vaginum which was seen in about 63 patients (31.5%), followed by pain abdomen in 28 women (14%), bleeding per vaginum was seen in 26 women (13%). The other symptoms included postmenopausal bleeding, mass per vaginum, burning micturition and irregular bleeding. **(Graph 2)**



Graph 3: Cytological Diagnosis Of 200 Cases Using Bethesda System 2001

Out of a total of 200 cases, 123 (61.5%) cases were diagnosed as Negative for intraepithelial lesion or malignancy (NILM), 30 (15%) cases as ASCUS, 22(11%) as LSIL, 11(5.5 %) cases as HSIL, another 11 (5.5 %) cases as SCC. 3 (1.5%) cases showed pap smear which was positive for malignant cells **(Graph 3)**

Table 1: Distribution of lesions on pap smear examination.

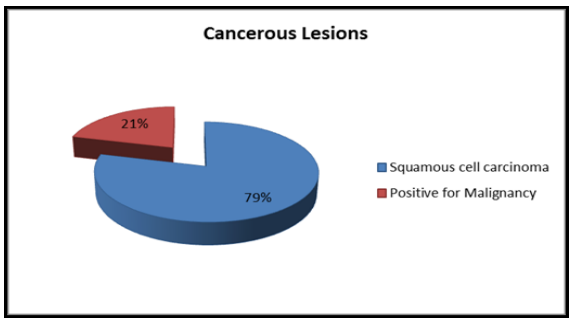
Sl. No.	Lesion	No. of Cases	Percentage
1	Non-neoplastic	123	61.5%
2	Precancerous Lesions	63	31.5%
3	Cancerous Lesions	14	7%
4	Total	200	100%

Of the 200 pap smears examined, 123 cases (61.5%) were non neoplastic, 63 (31.5%) cases were precancerous lesions and 14 cases (7%) were cancerous lesions **(Table 1).**

Table 2: Distribution Of Precancerous Lesions On Cytology (N=63)

Sl. No.	Lesion	No. of Cases	Percentage
1	ASCUS	30	48%
2	LSIL	22	35%
3	HSIL	11	17%
4	Total	63	100%

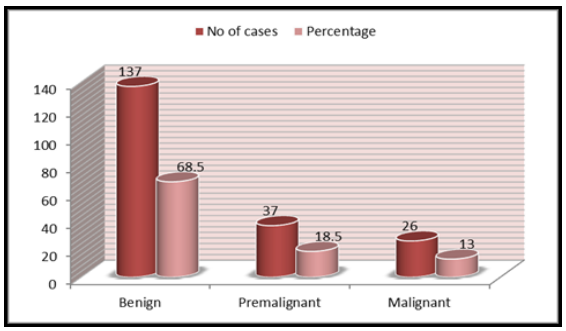
Of the total 63 precancerous lesions diagnosed on 200 Pap smears, 30 (48%) cases were of ASCUS, followed by 22 (35%) cases of LSIL and 11 (17%) cases of HSIL **(Table 2).**



Graph 4: distribution of cancerous lesions on cytology (n=14)

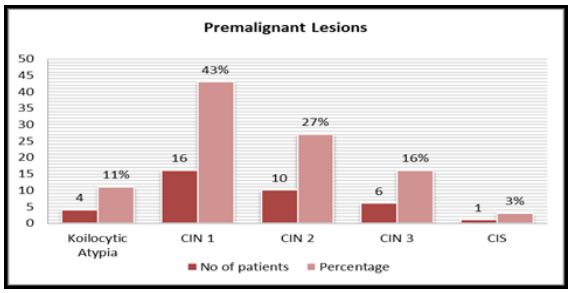
14 cases were diagnosed on Pap smear examination as cancerous lesions. Of these 11 cases (79%) were diagnosed as squamous cell carcinoma (SCC) and 3 cases (21%) were showing cytologic features positive for malignancy **(Graph 4).**

Of the 200 histopathological specimens sent, 122 (61%) were cervical biopsies and 78 (39%) were hysterectomies.



Graph 5: diagnosis of lesions on histopathology (n=200)

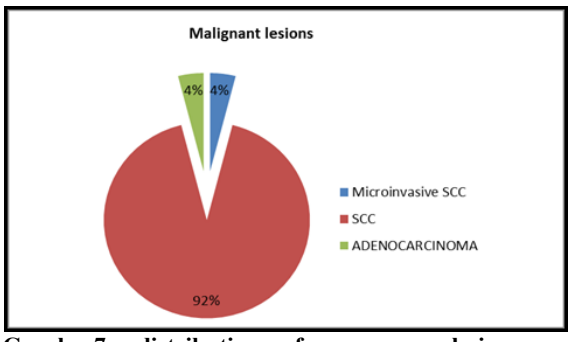
Of all the 200 specimens sent for histopathological examination, 137 (68.5%) cases were diagnosed as benign/non neoplastic, 37(18.5%) cases as premalignant, 26 (13%) as malignant. **(Graph 5)**



Graph 6: distribution of precancerous lesions on histopathology (n=37)

A total of 37 precancerous/ premalignant lesions were diagnosed on histopathological examination. Of these 16 (43%) cases were CIN 1 followed by 10

cases (27%) of CIN 2 and 6 cases (16%) of CIN 3. Also 4 cases (11%) were showing koilocytic atypia and only 1 case (3%) of carcinoma in situ was diagnosed. **(Graph 6)**



Graph 7: distribution of cancerous lesions on histopathology (n=26)

Of the total 26 cancerous/malignant lesions diagnosed on histopathology, 24 (92%) were Invasive Squamous cell carcinoma (SCC) and 1 case each (4% each) of Microinvasive squamous cell carcinoma and Adenocarcinoma were diagnosed. **(Graph 7)**

A total of 24 lesions were diagnosed as Squamous cell carcinoma on histopathological examination. Of these 8 (33%) cases were reported as well differentiated squamous cell carcinoma which showed predominantly mature squamous cells with abundant keratin pearls, occasional well-developed intercellular bridges, minimal pleomorphism and minimal mitotic activity.

14 cases (58%) were diagnosed as moderately differentiated squamous cell carcinoma which showed less distinct cell borders and relatively greater nuclear pleomorphism.

2 cases (9%) were diagnosed as poorly differentiated squamous cell carcinoma which had highly pleomorphic cells with hyperchromatic nuclei and scant cytoplasm and more numerous mitotic figures. No keratin pearls seen.

Table 3: comparison of cytology diagnosis with histopathological diagnosis

Pap Smear	**Histopathology diagnosis**							
	BENIGN			**Pre cancerous**			**Cancerous**	
Precancerous /cancerous lesions	CNSC	Polypoidal Endocervicitis	Procidential Changes	CIN 1	CIN 2	CIN 3	SCC	Adenocarcinoma
ASCUS (30)	15	1	-	11	3	-	-	-
LSIL (22)	6	-	1	3	5	4	3	-
HSIL (11)	-	-	-	-	2	2	7	-
MALIGNANT (14)	-	-	-	-	-	-	13	1

In the present study, the concordance rate for precancerous and cancerous lesions was 70 percent while discordant cases accounted to be 30 percent.

Out of the total 77 cases diagnosed as precancerous and cancerous, 54 were concordant and 23 were discordant on histopathology.

Of the 30 cases of ASCUS diagnosed on pap smear examination, 14 were concordant on histopathology. Of these 14 cases, 11 were confirmed as CIN 1 and 3 cases as CIN 2. Of the 16 discordant cases, 15 were diagnosed as chronic non-specific cervicitis and 1 as polypoidal endocervicitis.

On Pap smear examination 22 cases were reported as LSIL. Of these 15 cases were concordant on histopathology in terms of being neoplastic. Of these 15 concordant cases, 3 were reported as CIN 1, 5 as CIN 2, 4 as CIN 3 and 3 as SCC **(Table 3).**

Out of the remaining 7 discordant cases, 1 case was reported as chronic non-specific cervicitis and 1 case as having procidential changes on histopathology.

Similarly of the 11 cases reported as HSIL on cytology, 2 were diagnosed as CIN 2, 2 as CIN3 and 7 as SCC.

14 cases were diagnosed as malignant on pap smear examination of which 11 cases were reported as squamous cell carcinoma and 3 cases were having cytologic features positive for malignancy. Of the 3 cases that were positive for malignancy on cytology, 2 cases showed features of poorly differentiated SCC and 1 case was diagnosed as Adenocarcinoma cervix. All 14 cases were concordant on histopathology.

Similarly, a total of 37 cases were diagnosed as precancerous on histopathology. Of these 30 cases correlated well with cytological diagnosis. Of the remaining 7 cases ,4 were diagnosed as koilocytic atypia, 2 as CIN 1 and 1 as insitu carcinoma. All 4 cases of koilocytic atypia showed inflammatory pap smears. Out of 2 cases of CIN 1, 1 was reported as inflammatory pap smear and the other was diagnosed as atrophic pap smear. 1 case of In situ carcinoma also had shown features of inflammatory smear on previous pap smear examination.

A total of 26 cases were reported as malignant on histopathology. Of these 24 cases correlated well with cytology diagnosis. The rest 2 cases had shown inflammatory smear on previous pap smear examination.

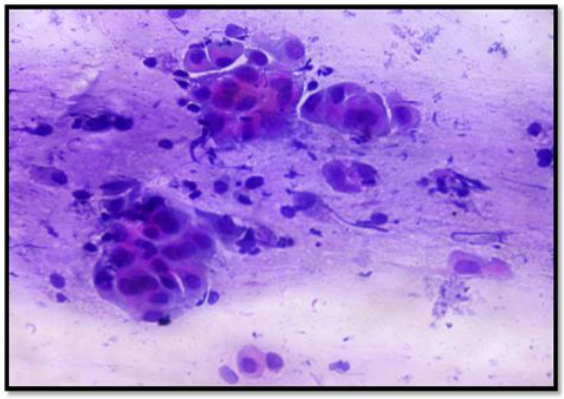


Figure 1: Microphotograph of Pap smear showing squamous cells arranged in clusters with high nuclear cytoplasmic ratio, hyperchromatic nuclei with irregular nuclear contours- HSIL (PAP;40X)

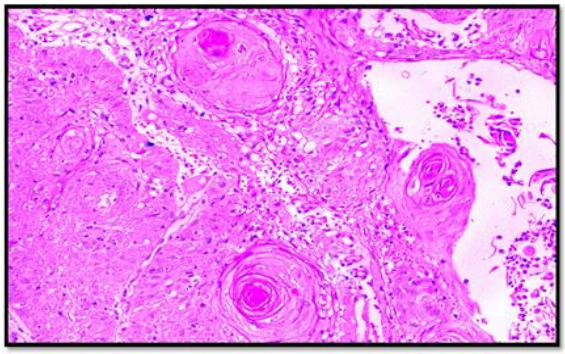


Figure 2: Microphotograph showing features of well differentiated squamous cell carcinoma- cervix (H&E;20X)

DISCUSSION

200 cervical smears were studied and graded according to The Bethesda System 2001 and the results were correlated with the histopathological findings.

The results of the present study and their comparison with the results obtained by different workers have been discussed.

The mean age in the present study was 47 years which was comparable with the study of Autier P et al,[4] and Robyr R. et al,[5] which had the mean ages of 46 years and 43.7 years respectively.

Our study showed varied symptoms, of which discharge per vaginum was commonest presenting complaint with 31.5% cases presenting with this which correlated well with the studies of Shrivastava M. et al,[6] and Bhojani KR et al,[7] Also second most common symptom in our study was pain abdomen (28%) which was in close proximity with the study done by Shrivastava M et al.

In the present study, 61.5% lesions diagnosed on Pap smear examination were non neoplastic lesions which correlated well with the studies done by Bodal VK et al,[8] and Saha R et al,[9] in which the benign lesions were 59% and 51.1% respectively. The premalignant lesions on cytology were 31.5% which was in close proximity with Bodal VK et al,[8] in which premalignant lesions were 27 %. The study done by Saha R et al,[9] showed a relatively higher percentage of premalignant lesions (41.9%). However, both the studies showed similar incidence of malignancy with our study.

In the present study the prevalence of premalignant lesions was high as compared to malignant lesions. The percentage of premalignant lesions in our study was 82%. The study done by Comanescu et al,[10] also showed a higher percentage of Premalignant lesions over malignant lesion with premalignant lesions around 95%. Both the studies showed similar patterns of cytological diagnosis. However, the percentage of HSIL was lower in our study. This ambiguity can be attributed to presence of only a few abnormal cells representative of high grade lesion on smear and the confounding effects of excessive inflammation and obscuring blood in undercalled cases.

In our study the proportion of benign lesions/non neoplastic lesions was more as compared to premalignant and malignant lesions on histopathological examination. Our study showed 68.5% of benign lesions/non neoplastic lesions followed by 18.5% of premalignant lesions and 13% of malignant lesions. This trend was similar to the study done by Abali R. et al,[11] in his study which showed about 56.9 % benign lesions/non neoplastic lesions followed 43.1 % premalignant lesions and 7.4 % malignant lesions. However, the percentage of premalignant lesions was quite high in his study (43.1%) in comparison to our study (18.5%). This variation can be attributed to the different selection criteria of both the studies.

In our study, out of 30 cases of ASCUS diagnosed on Pap smear, 14 (7%) cases were diagnosed as premalignant lesions on histopathological examination. The concordance rate for ASCUS was 47% in our study.

In the study conducted by Choudhary RD et al,[12] out of 17 cases of ASCUS diagnosed on Pap smear, 12 (6%) cases were diagnosed as Premalignant and 1 (0.5%) case was diagnosed as malignant on histopathology. The concordance rate for ASCUS was 76% which was high as compared to our study.

22 LSIL cases were diagnosed on Pap smear examination in our study. Of these 12 (6%) cases were diagnosed as Premalignant and 3 (1.5%) as malignant on histopathology. The concordance rate was 68%.

In the study by Choudhary RD et al,[12] out of 10 LSIL cases on cytology, 3 (1.5%) cases were diagnosed as premalignant and 7 (3.5%) cases as malignant on histopathology. The concordance rate was 100% which was higher than that of our study.

In our study, 11 cases were diagnosed as HSIL on Pap smear examination. Of these, 4 (2%) cases were diagnosed as Premalignant and 7 (3.5%) cases diagnosed as malignant with a concordance rate of 100%.

In the study done by Choudhary RD et al,[12] of the 5 HSIL cases diagnosed on pap smear examination, 3 (1.5%) cases were reported as premalignant and 1

(0.5%) case as malignant on histopathology. The concordance rate was 80% which was lower than that of our study.

Our study showed 14 cases as malignant on Pap smear examination, of which all 14 were confirmed as malignant on histopathology with a concordance rate of 100%.

In the study done by Chaudhary RD et al,[12] of the 2 cases diagnosed as malignant on cytology, 1 case was confirmed to be malignant on histopathology. The concordance rate was 50% for malignancy which was lower than that of our study.

The concordance rate was 70% in the present study which correlated well with the study done by Saha R et al,[9] which had a concordance rate of 76% for neoplastic lesions on cytology while that done by Pradhan B et al,[13] depicted a concordance rate of 88% respectively.

The sensitivity in the present study was 92% which was comparable to the study by Yeoh GP et al,[14] and was high as compared to the other studies. Also the positive predictive value in the present study was 70% which was in close vicinity to the value calculated by Saha R et al.[19] However, the specificity of the our study was 84% which was low in comparison to the studies done by Tengli MB et al,[15] and Saha R et al.[19] The negative predictive value of our study was 95 % which was comparable to the study done by Tengli MB et al.[15]

CONCLUSION

The regular screening of population by Pap smear and reporting as per The 2001 Bethesda System is a cost-effective method for early detection of premalignant and malignant cervical lesions. The procedure is simple, inexpensive and can be performed in the outpatient department which is useful in a country like ours. It also has an important role in the diagnosis of inflammatory lesions including the identification of causative organism and atrophic changes and helps in the definitive management of patients. All lesions on Pap smears should be followed by repeat Pap smear examination and cervical biopsies/ hysterectomy which will improve the diagnostic accuracy and helps in staging of malignant lesions.

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