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Clinico-Histopathological Study of Cervical Carcinoma At A Tertiary Care Hospital.

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Abstract
Aims And Objective:*To study various types of cervical carcinoma and correlate histopathological findings with the clinical presentation of the patient.*
Material And Methods:*The present study is a prospective study done over a period of two years, carried out in the department of Pathology in a tertiary care hospital. Our study composed of cervical specimens in the form of biopsies and sections of cervix from hysterectomy specimens received in a tertiary care hospital. Out of 788 cervical specimen 112 (14.2%) were found malignant on histopathology.*
Results:*The maximum number of cases of invasive carcinoma were in 5th and 6th decades. Squamous cell carcinoma (SCC) was the commonest invasive carcinoma observed in this study with 100/112 cases (89.30%). Bleeding in the form of post-menopausal bleeding, post coital bleeding or inter-menstrual bleeding and foul smelling per vaginal discharge were the common presenting symptoms in patients having malignancy.*
Conclusions:*All hysterectomy specimens must be sent for histopathological examination and studied meticulously, regardless of the preoperative diagnosis. As,some unusual findings bearing implications on treatment and prognosis will be revealed regardless of the reason for which cervical biopsy/ hysterectomy is performed. Newer terminologies with their descriptions, given by FIGO and WHO, will help to reduce ambiguity and bring uniformity in future studies.*
Keywords*: cervical,carcinoma,squamous,adenocarcinoma*

I. Introduction

The cervix (term taken from the Latin, meaning neck) is the most inferior portion of the uterus, protruding into the upper vagina. The unique epithelial environment of the cervix renders it highly susceptible to infections with Human Papilloma Virus (HPV), the main cause of cervical cancer. Cervical cancer is the fourth most common cancer among women in the world. Of the 528,000 new cases detected globally in 2012, developing countries accounted to about 85% of its global burden.[1]Cervical cancer is one of the most frequently seen cancer in women in India.

In late 1900, when atypia related with the squamous cervical epithelium (enlarged, hyperchromatic irregular cells with a halo) was linked to infection with human papilloma virus.[2,3] Zur Hausen (1982), has put forth a hypothesis that papilloma virus infection may be the initiating factor for cervical neoplasia.[4]

HPVs play a critical role in the pathogenesis of most cervical cancers and their precursor lesions.Epidemiological studies did demonstrate the association of several risk factorsinclude sexual promiscuity, multiplicity of sexual partners, exposure to sexual intercourse at an early age, number of pregnancies, cigarette smoking, use of oral contraceptives,dietary and Human Papilloma Virus type 16.[5]

Most patients who have a clinically evident carcinoma of cervix will present with abnormal vaginal bleeding viz. bleeding after intercourse or an intermittent spotting or frank haemorrhage. Sometimes the bleeding is associated with an offensive discharge and there may be pain radiating to the sacral region. The advanced cases present with cachexia, weight loss and weakness as well as localized pain and urinary symptoms.[6]

Invasive carcinoma of cervix is classified into different histomorphological patterns according to WHO classification 2014. Squamous cell carcinoma(SCC) is by far the most common tumour of the cervix, accounting for 85-90% of primary neoplasms. SCC can be further classified according to Reagen et aland Broder's grading system.[6]

II. Material And Method

Two years prospective study done from June 2013 to May 2015,carried out in the department of Pathology in a tertiary care hospital. Out of 788 cervical specimens, 112 specimens were malignant, that included cervical biopsies and sections of cervix from hysterectomy specimens received in the histopathology section of department of pathology, were processed according to College of American Pathologists (CAP) guidelines.[7]

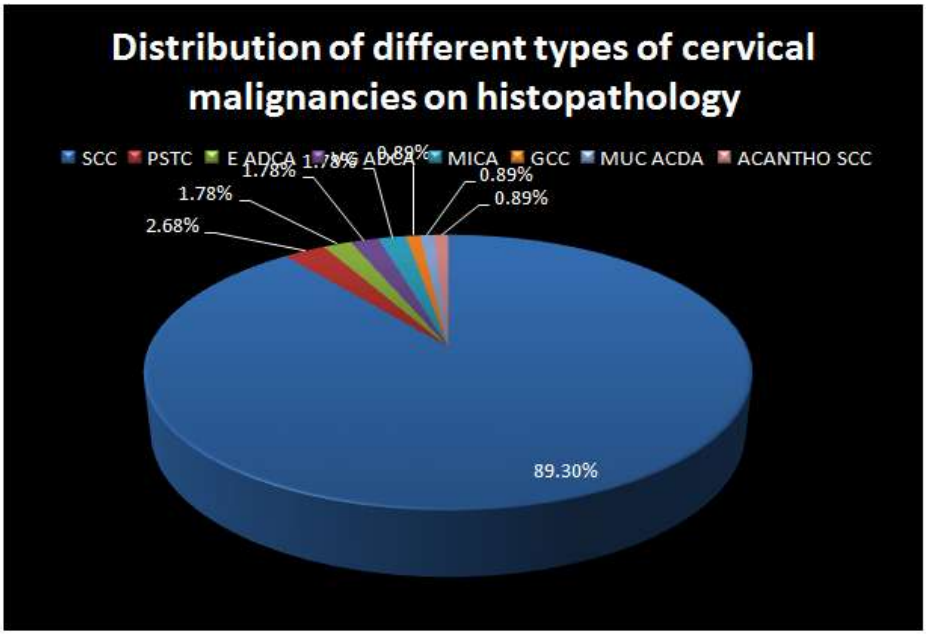
Inclusion Criteria: All the cervical biopsies and cervical sections from hysterectomy specimens received in Department of Pathology, KIMS, Karad ,Maharashtra.
Exclusion Criteria: There was no exclusion criterion in this study.

III. Results

Table No.1:- Distribution of malignant lesions of cervix according to age and histopathological diagnosis.

Histopathological diagnosis of cervical malignancy	**AGE(YRS.)**					**TOTAL**	**%**
	21-30	31-40	41-50	51-60	>60		
Microinvasive squamous cell carcinoma(MICA)	0	0	1	1	0	2	1.78
Squamous cell carcinoma (SCC)	02	05	31	33	29	100	**89.30**
Acantholytic SCC(ACANTHO SCC)	0	0	0	0	1	1	0.89
Papillary squamous cell (transitional) carcinoma(PSTC)	0	1	1	0	1	3	2.68
Glassy cell carcinoma(GCC)	0	1	0	0	0	1	0.89
Endocervical Adenocarcinoma (usual type) (E ADCA)	0	0	0	1	1	2	1.78
Villoglandular adenocarcinoma (VG ADCA)	0	0	1	0	1	2	1.78
Mucinous adenocarcinoma (MUC ADCA)	0	0	1	0	0	1	0.89
TOTAL	2	7	**35**	**35**	33	112	100

Fig no.1:-Pie chart showing distribution of different types of cervical malignancies on histopathology



Above table and figure shows that squamous cell carcinoma (SCC) was the most common cervical malignancy constituting 100/112 cases (89.30%). SCC was seen common in the age group of 51 to 60 years

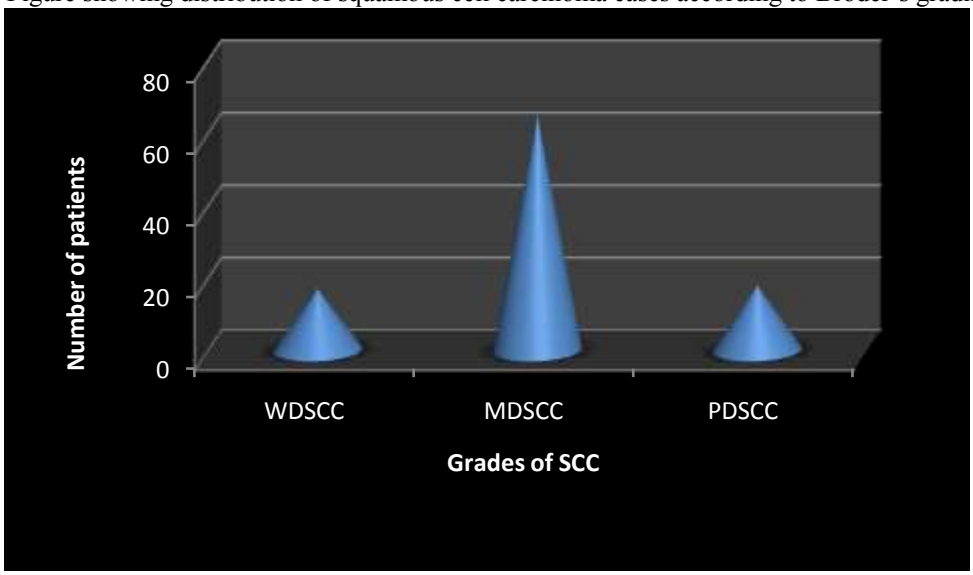
Table No.2:-Correlation between probable clinical and histopathological diagnosis of cervical malignancies

	Clinically growth on cervix		**Clinically suspicious of malignancy**		**Malignancy not suspected clinically**	
Number of cases	83		59		-	
	positive	negative	positive	negative	positive	Negative
Histopathological diagnosis	83	0	27	32	2	0

Table No.3:-Distribution of squamous cell carcinoma (SCC) according to grades of differentiation

Grades Of SCC	**Number Of Cases**	**%**
Well Differentiated (WD)	17	17
Moderately Differentiated(MD)	65	65
Poorly Differentiated (PD)	18	18
Total	100	100

Fig no. 2:-Figure showing distribution of squamous cell carcinoma cases according to Broder's grading system



Above table and figure below shows, squamous cell carcinoma was classified according to Broder's grading system into well, moderate and poorly differentiated grade. Maximum cases were of moderate grade seen in 65/100 (65 %) cases.

Table No.4:-Distribution of various histological types of squamous cell carcinoma.

Histological types of squamous cell carcinoma (SCC)	NUMBER OF CASES	PERCENTAGE
Large cell keratinizing SCC	17	17
Large cell non keratinizing SCC	83	83
TOTAL	100	100

Above table shows that large cell non-keratinizing type was the most common subtype of squamous cell carcinoma seen in 83/100 cases (83%) followed by large cell keratinizing type seen in 17/100 cases (17%). There was no case of small cell non keratinizing type of squamous cell carcinoma in the present study.

Table No.5:-Distribution of malignant lesions according to clinical presentation

Histiopathological Diagnosis Of Cervical Malignancy	**Clinical Presentation Of Patients**					
	GROWTH	PMB	PCB	PVFD	IMB	US
Microinvasive Squamous Cell Carcinoma (MICA)	0	1	1	0	0	0
Squamous Cell Carcinoma(SCC)	88	59	10	21	16	21
Papillary Squamous Cell (Transitional) Carcinoma	1	1	1	0	2	0
Glassy Cell Carcinoma	1	0	0	1	0	0
Acantholytic SCC	1	1	0	0	0	0
Endocervical Adenocarcinoma (Usual Type)	2	0	0	2	0	0
Villoglandular Adenocarcinoma	1	1	0	2	1	0
Mucinous Adenocarcinoma	0	0	1	1	0	0
TOTAL	94	63	13	27	19	21

Above table shows that invasive carcinomas presented with two or more signs or symptoms. Cervical growth (CX GR) was the most common clinical presentation in the patients with squamous cell carcinoma (SCC) followed by bleeding in the form of post coital bleeding (PCB), intermenstrual bleeding (IMB) and urinary symptoms (US). Two cases of microinvasive squamous cell carcinoma (MICA) presented with bleeding

either in the form of post coital bleeding or post- menopausal bleeding (PMB). Three cases of papillary squamous cell (transitional) carcinoma (PSTC) presented with growth and bleeding per vaginum in the form of post-menopausal bleeding, post coital bleeding and intermenstrual bleeding. A case of acantholytic squamous cell carcinoma presented with cervical growth and postmenopausal bleeding. Two cases of endocervical adenocarcinoma (usual type) both presented with growth and foul smelling per vaginal discharge (PVD).Villoglandular adenocarcinoma and mucinous adenocarcinoma presented with bleeding and per vaginal foul smelling discharge. A case of glassy cell carcinoma presented with growth and post menstrual bleeding.

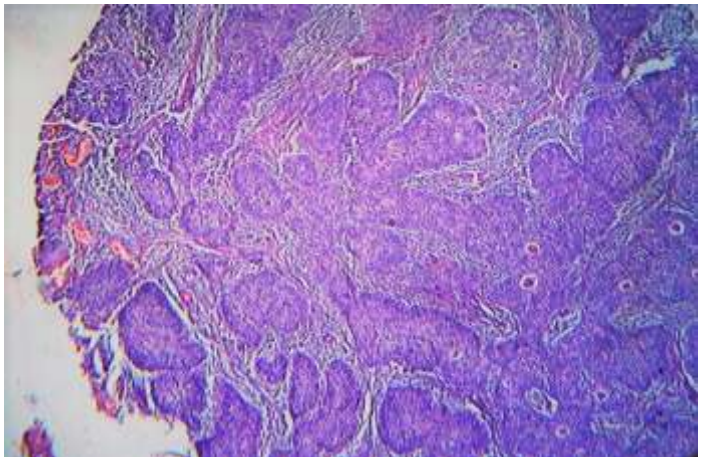


Fig no.3:-Photomicrograph showing microinvasive squamous cell carcinoma (MICA) with tumor infiltrating into the stroma.(400X,H&E)

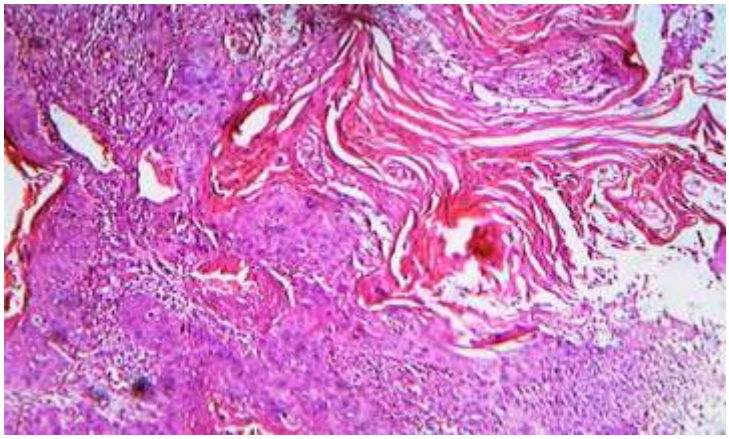


Fig no.4:-Photomicrograph showing well differentiated large cell keratinizing squamous cell carcinoma with keratin pearls (WD LCKC SCC).(400x,H&E)

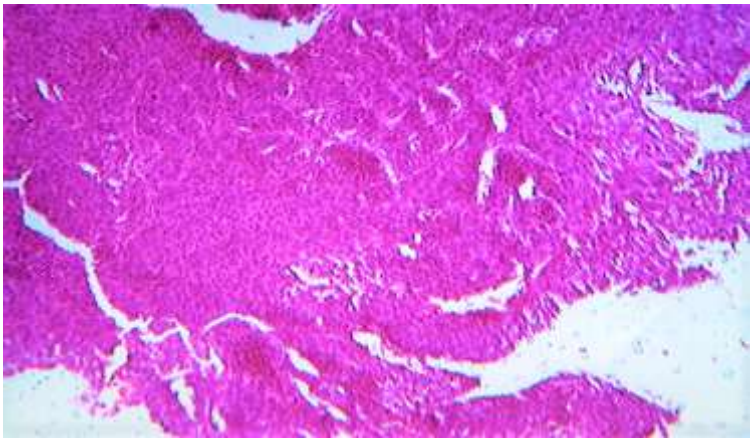


Fig no.5:- Photomicrograph showing moderately differentiated large cell non- keratinizing squamous cell carcinoma (MD LCNK SCC). (100x, inset 400x,H&E)

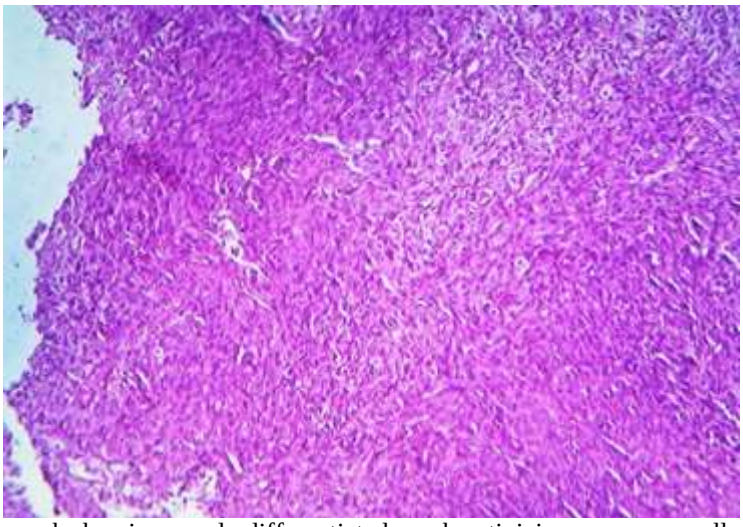


Fig no.6:-Photomicrograph showing poorly differentiated non keratinizing squamous cell carcinoma (PD SCC) (400x, H&E)

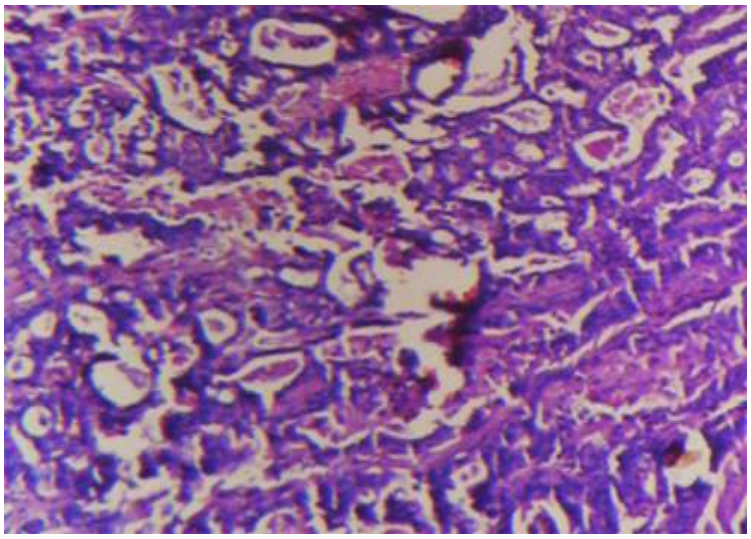


Fig no.7:- Photomicrograph showing adenocarcinoma of cervix,(100x, inset 400x,H&E)

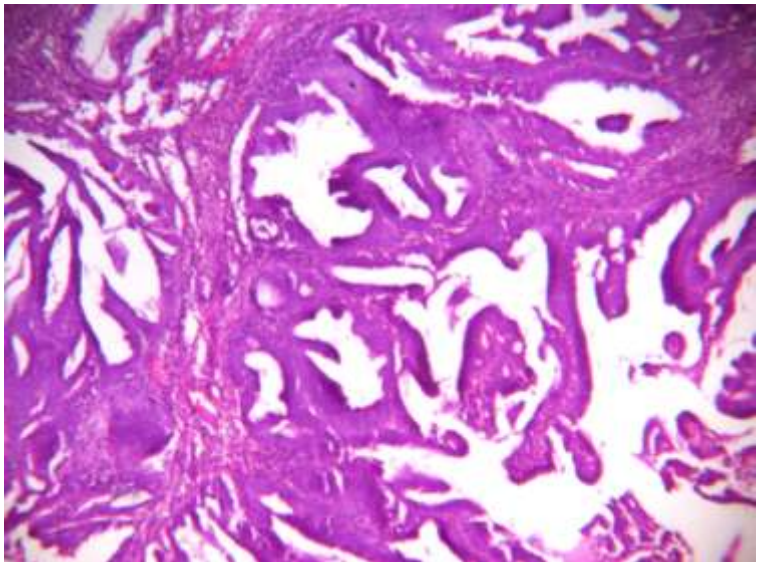


Fig no.8:- Photomicrograph showing villoglandulartype adenocarcinoma of cervix.(400x,H&E).

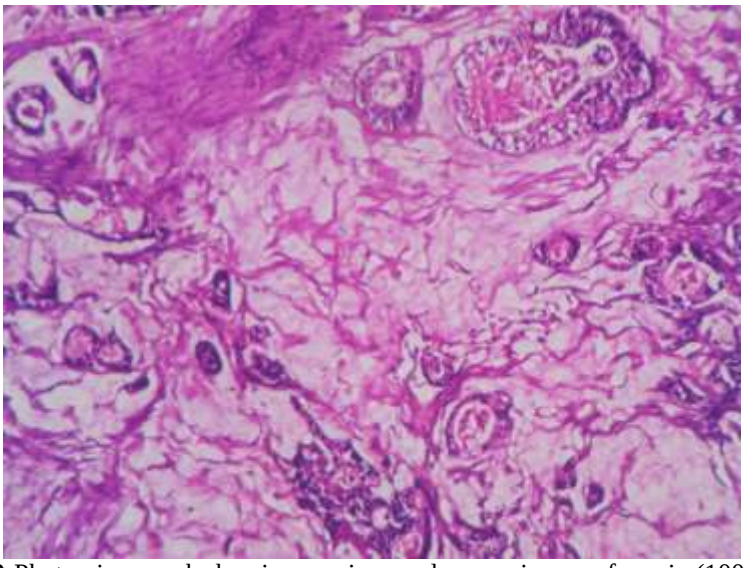


Fig no.9: Photomicrograph showing mucinous adenocarcinoma of cervix.(100x,H&E)

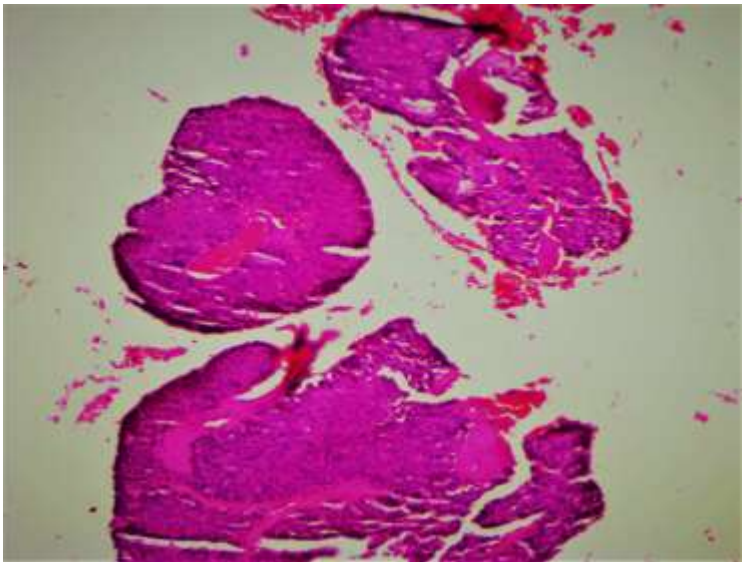


Fig no.10:- Photomicrograph showing papillary squamous cell (transitional) carcinoma with papillary component [A) 100x,H&E]

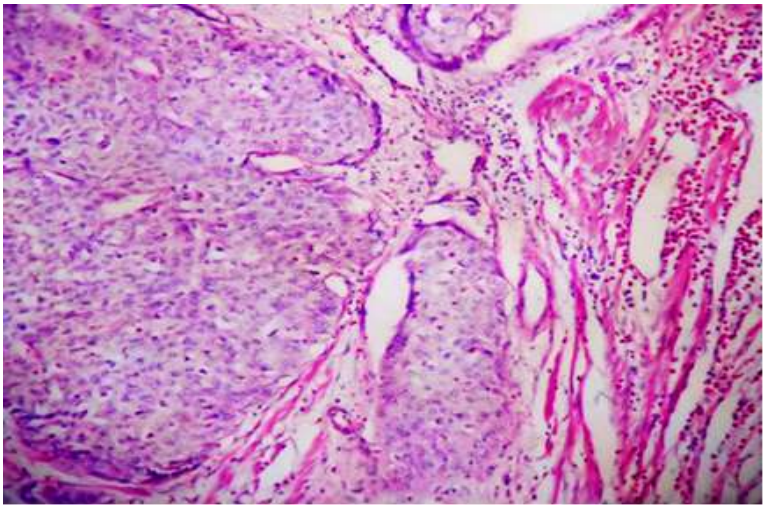


Fig no.11:- Photomicrograph showing glassy cell carcinoma of cervix neoplastic cells with eosinophil infiltration.(400x,H&E)

IV. Discussion

Cervical cancer is the fourth most common cancer among women in the world. Of the 528,000 new cases detected globally in 2012, developing countries accounted to about 85% of its global burden.[1]Cervical malignancy was seen in 112/788 cases. This was a very significant finding. It gave a measure of the risk of malignant transformation in the cervix.In a study by Solapurkar et al [8]1985, occurrence of cervical malignancy was 33.8% (488 out of 1472 cases), which is higher than our study. Whereas, the occurrence in present study correlate well with the study done by Poste et al.[9]In our study, an attempt was made to correlate the clinical diagnosis and the histopathology of malignant tumours of uterine cervix. The cases studied during this period were classified as clinically evident malignancy, clinically suspicious of malignancy and those cases where there was no clinical suspicion of cervical malignancy.All 83 cases with growth on cervix clinically were positive for malignancy on histopathology and not even a single case was found to be negative for malignancy. Thus, the clinicopathological correlation in this category is very good. Out of 59 cases, where malignancy was clinically suspected, 27 cases were positive for malignancy on histopathology, while 32 cases were negative for malignancy.In this group of clinically suspicious for malignancy, the greater proportion of malignancies were diagnosed in the 41 to 50 years age group, the later decades tends to present clinically as growth on cervix. Thus, an unhealthy cervix that needs to be biopsied stands the greatest chance of harbouring a malignancy if the patient belongs to 41-50 years of age group.At the same time, clinical suspicion of malignancy should be followed by a biopsy even in the younger age group, which also showed significant number of cases diagnosed as malignancy. A high index of suspicion would ensure against underdiagnosis of cervical malignancy.Two cases in which malignancy was not suspected turned out to be positive for malignancy. These two cases were Microinvasive Squamous Cell Carcinoma (MICA).According to the modified FIGO staging of carcinoma of cervix, the microinvasive squamous cell carcinoma comprises carcinoma strictly confined to the cervix, the stromal invasion measuring with maximum depth up to 5 mm and no wider than 7 mm .[10,11]Squamous cell carcinoma was the most common invasive cervical carcinoma observed in our study accounted for 89.30% of the total invasive carcinoma. This is comparable with the study done by Solapurkar et al,[8] Jyothi et al [12]and Poste et al.[9]Microscopically, invasive squamous cell carcinoma is characterized by anastomosing tongues or cords of neoplastic epithelium infiltrating the stroma. Characteristically,the contour of the infiltrating nests and clusters is irregular and ragged. Cells in the center of the invading nests frequently becomenecrotic or undergo extensive keratinization cells are generally polygonal or oval with eosinophilic cytoplasm and prominent cellular membranes.[6]Squamous cell carcinomas were graded in this study according to Broder's grading system and Regan et al [13](based on the predominant cell type).

The most commonly used grading system for squamous cell carcinoma is a modification of the original systemproposed by Broder's in 1920. Currently histologic grading divides squamous cell carcinomas into three groups, well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3).[6] In well-differentiated (grade 1) tumors, the most striking feature is abundant keratin, which is deposited as keratin pearls in the center of neoplastic epithelial nests. In moderately differentiated (grade 2) squamous cell carcinomas, the neoplastic cells are more pleomorphic than in grade 1 tumors, have large irregular nuclei, and have less abundant cytoplasm. Poorly differentiated (grade 3) squamous cell carcinomas are generally composed of cells with hyperchromatic oval nuclei and scant indistinct cytoplasm, resembling the malignant cells of high-grade SIL.[6]Solapurkar et al [8]in 1985 observed squamous cell carcinomas to be the highest in 36-65 years of age group. Histologically,the common grade was moderately-differentiated carcinoma. These findings correlate with our study.Keratinizing carcinomas are characterized by the presence of well-differentiated squamous cells that are arranged in nests or cords that vary greatly in size and configuration. The defining feature of keratinizing carcinomasis the presence of keratin pearls within the epithelium, and the presence of a single keratin pearl is sufficient to classify a tumor as a keratinizing carcinoma. Non-keratinizing squamous cell carcinoma is characterized by nests of neoplastic squamous cells that frequently undergo individual cell keratinization but, by definition, do not form keratin pearls. [6]

Large cell non-keratinising type of squamous cell carcinoma was the common type in our study, which correlated with studies done by Misra et al[14], Poste et al[9]and Jyothi et al.[12]There was no case of small cell non-keratinising carcinoma in the present study. Some investigators have reported that this classification has prognostic significance in patients treated with radiotherapy.[13]When the incidence of squamous cell carcinoma in the various age group was studied, the highest incidence of squamous cell carcinoma was seen in 41-60 years of age range and moderately differentiated type being common grade in our study.Gompell and Silverberg[15]reported that out of the 4147 cases of carcinoma cervix studied by them, 88.8% of the cases were in the 31-60 years of age group.N Jeebun et al 2005 [16] documented the occurrence of cervical cancer was common in the age range of 50-59 years. Jyothi V et al[12] 2015 reported that out of 268 cases of carcinoma cervix studied by them 265 cases (98.88%) of squamous cell carcinoma were noted in 40-60 years age group.

In our study, 70/100 (70%) were noted in 41-60 years age group. Poste et al [9] studied that moderatley differentiated squamous cell carcinoma was the predominant histologic type of cervical malignancy constituting

95.73% and the incidence was highest in the age group 41 to 60 years of age.Carcinoma cervix passes through premalignant intraepithelial changes for a variable duration of time ranging from few to many years before turning frankly malignant. Cramer DW [17] has stated that patients with invasive squamous cell carcinoma are 15-23 years older than patient with high-grade SIL (squamous intraepithelial lesion) and 8 years older than patients with microinvasive squamous cell carcinoma. Findings of this study are in accordance to the above fact.Acantholytic squamous cell carcinoma is a variant of squamous cell carcinoma reported in the present study in a 72-year-old female.[18]Papillary squamous cell (transitional) carcinoma reported in the present study, i.e. 3/112 (2.68%) cases compared well with studies done by Odida M [19] and Sinha P et al.[5] Papillary squamous cell carcinoma shows papillary architecture with fibrovascular cores lined by multilayered atypical epithelium.[6]

Endocervical Adenocarcinoma, usual type is the most common histologic type of cervical adenocarcinoma. The cells are columnar with elongated, hyperchromatic nuclei that may show marked atypia with nuclear pleomorphism and coarse chromatin.The cells are often stratified and contain amphophilic or eosinophilic apical cytoplasm.[6]Mucinous adenocarcinomas are composed of cells that have basal nuclei and abundant pale granular cytoplasm, which stains positively with mucicarmine stains. The cells resemble those in the normal endocervical glands but nuclear atypia is significant and mitotic figures are present. Large amounts of mucin may be found in the stroma, forming mucin lakes or pools.[6] Mucinous adenocarcinoma in 1/112 (1.78%) case were observed in the present study. Villoglandular adenocarcinoma were seen in 2/112 (1.78%) cases in the present study. Villoglandular adenocarcinoma is a well-differentiated form of cervical adenocarcinoma that occurs predominantly in young women and has an excellent prognosis.[20, 21] The characteristic features of this tumor are a surface component that is composed of papillae lined by epithelium that has only mild cytologic atypia.Adenocarcinoma and its variants were common in age range of 41-60 years. Christopherson et al[22]1979 documented the mean age of adenocarcinoma range from 41-59 years for advanced invasive carcinoma. Present study correlated well with the above author. It accounted for 5/112 (4.46%) of total invasive lesions, which correlated with the findings of Swan et al.[23]We also reported 1/112 (0.89%) case of glassy cell carcinoma in our study in a 40 years old patient who presented with growth and postmenstrual bleeding. Glassy cell carcinoma comprises <1% of cervical cancers.[24]

In our study, bleeding in the form of post-menopausal bleeding, post coital bleeding or intermenstrual bleeding and foul smelling per vaginal discharge were the common presenting symptoms in patients having malignancy. Nucci M et al[25] stated that the most common clinical presentation of the patients were vaginal bleeding in cervical carcinoma.Histopathological diagnosis affects decisions of clinical management, treatment and followup, this being regarded as a "gold standard".Histological assessment remains the basis for determination of treatment, clinical management and subsequent follow up of patients.[26]

V. Conclusion

Histopathologicalstudy with clinical correlation of cervical carcinoma with different histomorphology, affects treatment and prognosis. All hysterectomy specimens must be sent for histopathological examination and studied meticulously, regardless of the preoperative diagnosis. As,some unusual findings bearing implications on treatment and prognosis will be revealed regardless of the reason for which cervical biopsy/ hysterectomy is performed. Newer terminologies with their descriptions, given by FIGO and WHO, will help to reduce ambiguity and bring uniformity in future studies.

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