DOI: 10.7860/NJLM/2018/32340:2276

Original Article

Pathology Section

Histopathological Spectrum of Premalignant and Malignant Lesions of Uterine Cervix

MAMTA GUPTA, PK BASAVARAJ

ABSTRACT

Introduction: Cervical cancer is the most common cancer in Indian women and arises after many years from morphologically defined precancerous lesions. There is a considerable variation in diagnostic criteria for intraepithelial neoplasia and microinvasion also, in cases of frank malignancy histomorphological study helps in typing lesion, establishing stages of development and extent of involvement which is critical for prognostication and clinical management.

Aim: To study the histomorphological features of premalignant and malignant lesions of the uterine cervix and categorise them into various types based on microscopy.

Materials and Methods: The study included all histologically proven premalignant and malignant lesions of the uterine cervix. They were categorised into different types based on the World Health Organisation classification and associated morphological features were studied.

Results: There were 36 premalignant and 74 malignant lesions of the uterine cervix. Cervical Intraepithelial Neoplasia (CIN) 1 was diagnosed in 36.1% patients, followed by CIN 2 (33.3%) and CIN 3 (30.6%). Amongst the malignant lesions, squamous cell carcinoma was the most common lesion encountered in 85.1% cases. There was a progressive increase in mean age of diagnosis from CIN 1 to invasive carcinoma. Other malignant lesions encountered were adenocarcinoma (8.1%), adenosquamous carcinoma (1.3%) and neuroendocrine carcinoma (5.4%).

Conclusion: Cervical cancer continues to be the most common cancer of females in developing countries. Histopathological examination is considered gold standard for diagnosis of intraepithelial neoplasia and cervical carcinoma and should be attempted at an early stage to provide better prognosis, treatment and protection against invasive cervical carcinoma.

Keywords: Adenocarcinoma, Cervical intraepithelial neoplasia, Malignancy grading score Neuroendocrine carcinoma, Squamous cell carcinoma

INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide. Almost 2,50,000 women die each year as a consequence of this disease. In India, the incidence of carcinoma of cervix is estimated to be 1,30,000 new cases every year and accounts for 86-90% of all genital cancers [1].

The transformation zone of the cervix, specifically that associated with squamo-columnar junction, is vulnerable to Human papillomavirus. A persistent infection with high risk human papillomavirus is a necessary causal factor in cervical carcinogenesis. However, it is not sufficient and a variety of cofactors influence development of cervical carcinoma [2,3]. Specific host target epithelial cells in transformation zone play an important part in development of cervical neoplasia [4].

The accurate and reliable diagnosis of cervical intraepithelial neoplasia is critical to cervical cancer prevention; however, their histologic diagnosis can be difficult to reproduce [5]. Grading cervical intraepithelial lesions on whether basaloid proliferation occupies less or more than half of the epithelium may be easier, reproducible and of greater biological value [6].

Invasive cervical carcinomas may portray squamous, columnar and neuroendocrine differentiation. A variety of other patterns, including adenosquamous, glassy cell, sarcomatoid, lymphoepithelial like, transitional and undifferentiated, have been described. This spectrum of neoplastic differentiation reflects either specific cell types infected by Human papillomavirus or pathways of differentiation selected after neoplastic cell transformation [2].

Pathologic indices like extent of invasion, margin status and presence of lymphovascular invasion are critical for appropriate management of patients [7].

This study was undertaken to study the spectrum of cervical carcinomas and its precursor lesions, to classify them according to the WHO classification, observe associated morphological changes and grade these lesions.

MATERIALS AND METHODS

A retrospective and prospective histomorphological study of premalignant and malignant lesions of uterine cervix received consecutively was conducted over a period of two years (2007-

2009) in the Department of Pathology, JJM Medical College, Davangere, Karnataka, India. Institutional ethic review board approval was taken prior to the study. The study comprised of a total of 110 samples which included 59 cervical biopsies and 51 hysterectomies.

All histologically proved premalignant and primary malignant lesions of the uterine cervix were included in the study. Non neoplastic lesions, benign tumours and secondary tumours involving the cervix were excluded.

Cervical biopsies and hysterectomy specimens, received, were initially fixed in 10% formalin. Gross findings were recorded and specimen was processed.

1) Cervical biopsies were embedded in toto.

2) In cervix, with no gross abnormality sections were taken from anterior and posterior portion including the squamo-columnar junction.

3) In hysterectomy specimens with a history of cervical smear positive for intraepithelial neoplasia or a current diagnosis of cervical intraepithelial neoplasia, multiple sections were taken along the endocervical canal, in such a way that epithelium including squamo-columnar junction is present in each section.

4) In hysterectomy done for carcinoma of the cervix, the cervix was cut into transverse slices along the endocervical canal and was submitted along with paracervical tissue. Full transverse sections from the uterus immediately above the cervix were taken to detect upward extension.

When vaginal cuff was present, it was trimmed circumferentially and embedded. Lymph nodes received as a part of sampling procedure for cancers, was bisected and embedded in toto.

The tissues were processed routinely to obtain 4-5 microns thick paraffin sections and stained with Haematoxylin and Eosin. Special stains like PAS and mucicarmine and immunohistochemical markers were employed wherever necessary.

Lesions of the cervix were classified into premalignant and malignant, which were further typed using the World Health Organisation histological classification for tumours of the uterine cervix [8].

The histopathologic features analysed were: Pattern of infiltration, nuclear pleomorphism, character of tumour stromal border or mode and stage of invasion, degree of stromal inflammatory cell infiltrate, presence or absence of lymphovascular invasion, mitotic index and degree of tumour differentiation [9,10].

Mode of invasion: It was defined as 'pushing' if orderly and well demarcated or 'spreading' if diffuse and infiltrating.

Lymphovascular invasion: It was said to be present if tumour cells were found in an endothelial lined space.

Mitotic index: Mitotic figures were counted in 10 High Power Field (HPF) under 400X magnification and mitotic index was calculated. Based on the number of mitosis/HPF malignant lesions were classified into tumours with few (0-1), moderate (2-4) and many (≥5) mitosis.

Stromal inflammatory cell infiltration: Lymphoplasmacytic stromal infiltration was classified as mild, moderate or marked according to the degree of the infiltration in majority of field of examination.

Histopathologic Malignancy Grading System (MGS): A useful diagnostic tool for predicting relapse in patients of cervical carcinoma was calculated based on grading of pattern, cell differentiation, nuclear pleomorphism and mitotic figures, while tumour host relationship included mode of invasion, stage of invasion, vascular invasion and degree of lymphoplasmacytic infiltration. These morphologic parameter permitted grading with 8 to 24 points. Index was divided into low (8 to 13), intermediate (14 to 16) and high grade (17 to 24) [10].

Degree of stromal eosinophilic leucocytic infiltrate in malignant tumours was graded as per criteria suggested by van Driel WJ et al., [11].

Mild: < 10 eosinophils in 3 HPF;

Moderate: 10-50 eosinophils/ HPF or series of hot spots between infiltrate;

Severe: >50 eosinophils/HPF.

Histologic grade: Squamous cell carcinomas were graded according to the modified Broder method [12]. Cervical adenocarcinomas were graded according to the degree of differentiation into poorly, moderate, and well differentiated tumours and according to nuclear atypia in nuclear Grade 1-3 [8,13].

SPSS version 19.0 was used for descriptive data analysis.

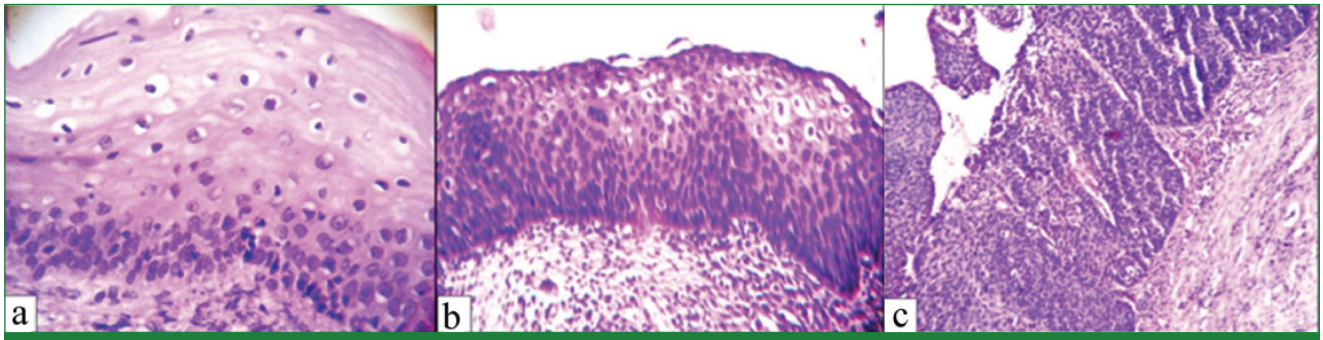
RESULTS

During this study period a total of 2656 cervical biopsies and hysterectomy specimens were received. Premalignant and malignant lesions were reported in 110 cases (4.1%).

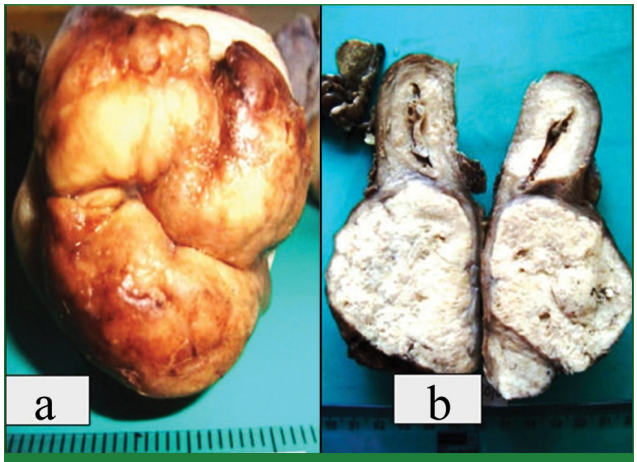
Of the total 110 cases, diagnosis of intraepithelial neoplasia was made in 36 cases (32.7%) and invasive carcinoma was found in 74 cases (67.3%). Fifty one were hysterectomy specimens including 25 wertheim's hysterectomy, 16 total abdominal hysterectomy and 10 vaginal hysterectomy. Fifty nine specimens were cervical biopsies.

Age of the patients ranged from 26 to 80 years. Majority of patients were in the age group of 31-40 years (34.5%). All patients were parous. In 70 cases (72.7%) parity was more than two and most common presentation was white discharge per vaginum followed by abnormal vaginal bleeding.

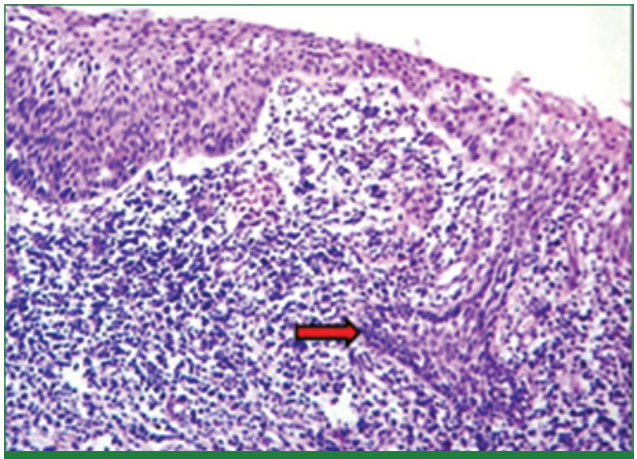
Total 36 cases of CIN were further graded into CIN 1 (13 cases; 36.1%), CIN 2 (12 cases; 33.3%), and CIN 3 (11cases; 30.6%) [Table/Fig-1a-c]. Mean age of patients with CIN 1 was 38.9 years, CIN 2 was 41.3 years and CIN 3 was 46.4 years. Of the 11 cases of CIN 3, intraglandular extension was seen in 5 cases (45.5%). One case showed extension of CIN 3 into the endometrium. Koilocytosis was seen in 8 cases (22.2%) of CIN which included 4 cases each of CIN 1 and CIN 2.



[Table/Fig-1]: Microscopic images showing CIN- a) Cervical intraepithelial neoplasia 1 (H&E, 40X); b). Cervical intraepithelial neoplasia 2 (H&E, 40X); c) Cervical intraepithelial neoplasia 3 (H&E, 40X).



[Table/Fig-2]: Gross morphology of specimens- a) Exophytic growth; b) Endophytic growth in SCC.



[Table/Fig-3]: Image showing microinvasive carcinoma (arrow) (H&E, 10X).

Invasive carcinoma was diagnosed in 74 cases (67.3%) with a mean age of 48.5 years. Cervical biopsy were obtained in 40 cases (54.1%) and hysterectomy specimens in 34 cases (45.9%). On gross examination ulceroproliferative (16 cases), ulceroinfiltrative (10 cases), and endophytic (7 cases) features were seen.

Squamous cell carcinoma was diagnosed in majority of cases [63 (85.1%)] [Table/Fig-2], including one microinvasive carcinoma [Table/Fig-3], followed by 6 cases (8.2%) of adenocarcinoma, 4 cases (5.4%) of neuroendocrine carcinoma and 1 case (1.3%) of adenosquamous carcinoma [Table/Fig-4].

Tumour Type	Number of Cases	Percentage (%)
Microinvasive SCC	01	1.35
LC NK SCC	32	43.25
Keratinizing SCC	28	37.85
Small Cell NK SCC	01	1.35
Papillary SCC	01	1.35
Endocervical Adenocarcinoma	04	5.40
Endometrioid Adenocarcinoma	01	1.35
Villoglandular Adenocarcinoma	01	1.35
Adenosquamous Carcinoma	01	1.35
Small Cell Neuroendocrine Carcinoma	02	2.70
Large Cell Neuroendocrine Carcinoma	01	1.35
Atypical Carcinoid Tumour	01	1.35
Total	74	100

[Table/Fig-4]: Histologic types.

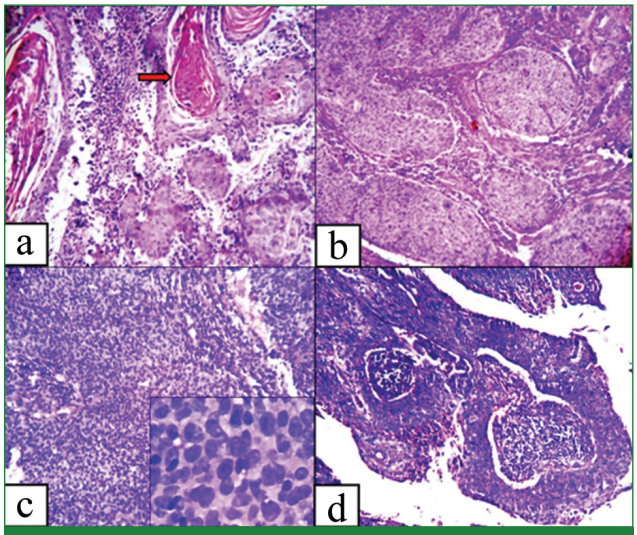
Morphological features of different variants of invasive squamous cell carcinoma were analysed [Table/Fig-5-7]. Malignancy grading was done based on these morphological features, mode and stage of invasion was observed in hysterectomy specimens while other parameters were graded in both biopsies and resected specimens. Majority of tumours were Grade 1 (50.9%), followed by Grade 2 (34.0%) and Grade 3 (15.1%).

Grading was also done based on differentiation. Predominantly, tumours were moderately differentiated in 30 cases (49.4%). 28 cases (45.1%) were well differentiated and 4 (6.5%) were poorly differentiated.

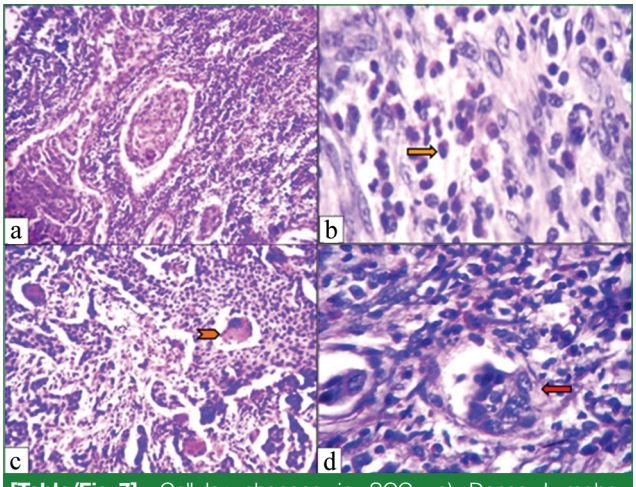
Radiation induced changes was seen in one case of NK SCC with an infiltrating tumour composed of large and bizarre tumour cells with vacuolated eosinophilic cytoplasm. Pleomorphic hyperchromatic nucleus, exhibiting karyorrhexis and vacoulations. Few multinucleated forms, atypical mitosis and apoptotic bodies were present.

Microscopic Feature (63 Cases)		LC NK SCC [H- 12 CB 21]	Keratinizing SCC [H 14 CB 14]	SC NK SCC [CB -1]	Papillary SCC [H-1]	Total [H27 CB 36]
Pattern (63)	Nests, Sheets	27	26	1	1	55
	Cords, Groups	4	2	-	-	6
	Dissociated	2	-	-	-	2
Nuclear Pleomorphism (63)	>75% mature nuclei	14	11	-	-	25
	25-75%	15	15	1	1	32
	<25%	4	2	-	-	6
Mode of Invasion (27)	Well defined border	2	2	-	1	5
	Less defined border	5	5	-	-	10
	Diffuse ill defined border	5	7	-	-	9
Stage of Invasion (27)	Microinvasive	1	-	-	-	1
	Nodular into connective tissue	7	11	-	1	16
	Infiltrative into muscle	6	4	-	-	10
Lympho Vascular Invasion (63)	Present	1	3	-	1	5
Mitosis/HPF (63)	0-1 (Few)	20	16	-	-	36
	2-4 (Moderate)	10	8	-	-	18
	≥5 (Many)	3	4	1	1	9
Lympho Plasmacytic Response (63)	Marked	6	5	-	-	11
	Moderate	19	17	-	1	37
	Mild	8	6	1	-	15
Eosinophilic Infiltrate (17)	Mild	5	5	1	-	11
	Moderate	4	1	-	-	5
	Marked	1	-	-	-	1
Giant Cells	Present	8	4	-	1	13
Associated CIN 3	Present	11	12	-	1	24

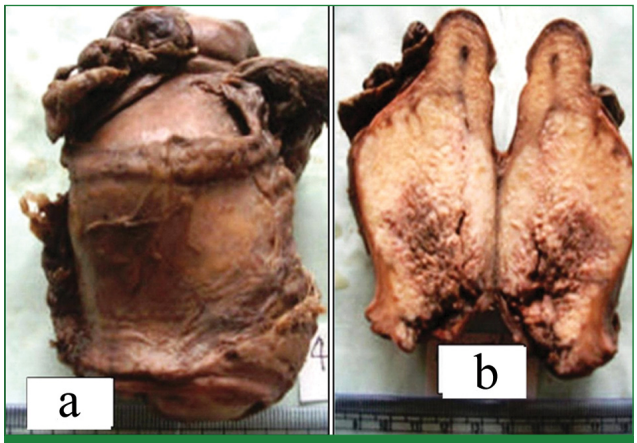
[Table/Fig-5]: Microscopic features of different subtypes of SCC.



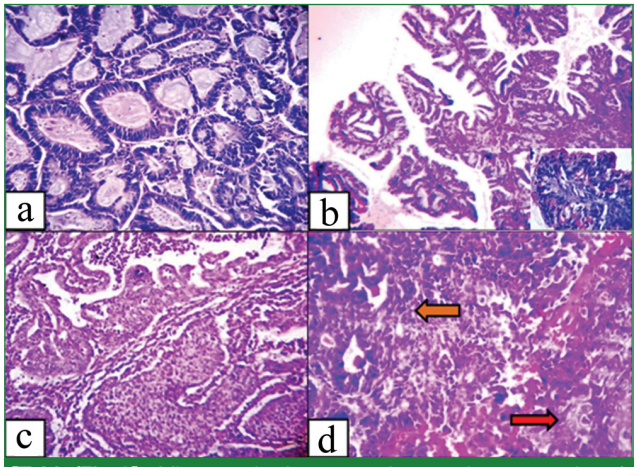
[Table/Fig-6]: Microscopy squamous cell carcinoma- a) Keratinizing SCC (arrow- keratin pearl) (H&E,10X); b) Non keratinizing SCC (H&E,10X); c) Small cell type SCC (H&E,10X Inset H&E,40X); d) Papillary SCC (H&E,10X).



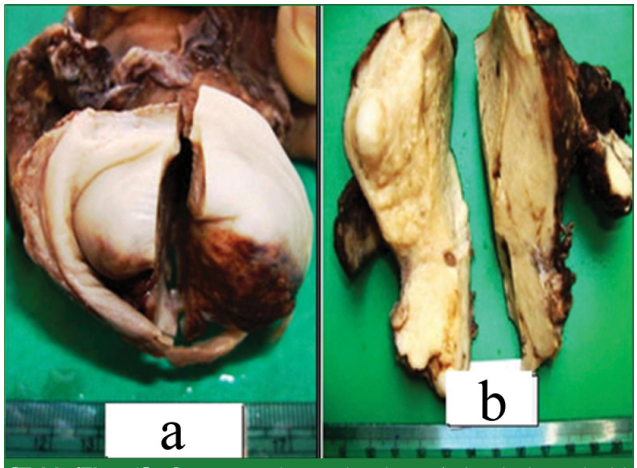
[Table/Fig-7]: Cellular changes in SCC- a) Dense Lympho-plasmacytic infiltrate around nests of tumour cells (H&E,10X); b) Moderate eosinophilic (arrow) infiltrate (H&E,40X); c) Giant cell reaction (arrowhead) (H&E,10X); d) Lympho-vascular invasion (arrow) (H&E,40X).



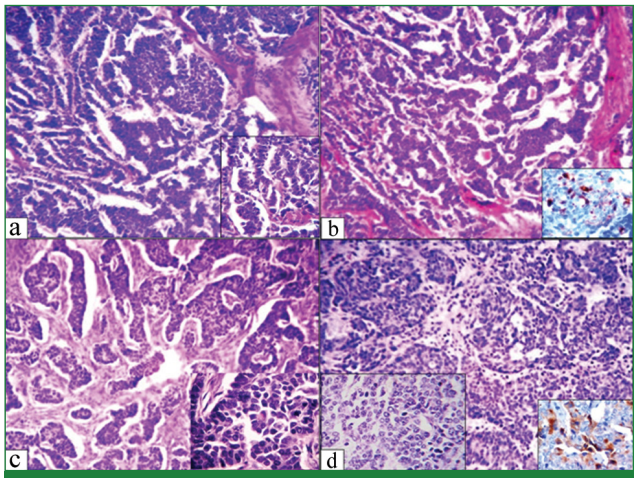
[Table/Fig-8]: Gross specimen showing- a) Barrel shaped cervix; b) Ulceroinfiltrative growth in adenocarcinoma cervix.



[Table/Fig-9]: Microscopic features adenocarcinoma cervix- a) Endocervical type (H&E 10X); b) Villoglandular type H&E 10X); Inset Mucicarcine stain positive in tumour cells X40; c) Endometrioid ;d) Adenosquamous carcinoma (Adenocarcinoma component yellow arrow; SCC component Red arrow) H&E 10X).



[Table/Fig-10]: Gross specimen showing- a) Atypical carcinoid - ulceroproliferative growth on both lips of cervix; b) Large cell neuroendocrine carcinoma- infiltrative yellow grey endophytic tumour infiltrating wall of endocervix with extension into uterus and ovaries.



[Table/Fig-11]: Microscopic features neuroendocrine carcinoma-a,b). Small cell carcinoma in nests, trabeculae and rosette-like structures. (H&E,10X). a) hyperchromatic moulded nuclei withfinely dispersed chromatin and scanty cytoplasm (H&E,40X); b) Chromogranin positive in tumour cells, 40X; c) Large cell neuroendocrine carcinoma (H&E,10X) (Inset-H&E,40X); d) Atypical carcinoid nests and trabacular pattern with few enclosing tubular structures (H&E,10X) Inset-Chromogranin positive in tumour cells, 40X.

Adenocarcinoma [Table/Fig-8,9] was diagnosed in six cases (8.1%). Two were cervical biopsies and four were on hysterectomy specimens. Most tumours were arranged in acinar, cribriform and solid pattern with one case exhibiting villoglandular arrangement. Four out of six cases were moderately differentiated. Adenosquamous carcinoma was diagnosed in one case.

Neuroendocrine carcinomas [Table/Fig-10,11] were seen in four cases of which three were diagnosed on hysterectomies. Small cell carcinoma was diagnosed in two cases, tumour cells were arranged in cords, trabeculae and sheets of small cells with inconspicuous cytoplasm and round to spindled shaped nuclei. Nuclear moulding and rosette like structures were seen. Foci of glandular differentiation and lymphovascular invasion were seen in one case. Immunohistochemistry with chromogranin was positive in the tumour cells. Large cell neuroendocrine carcinoma exhibiting tumour cells arranged in insular, trabecular pattern and in sheets with gland like lumen and peripheral palisading. More than 10 mitosis/HPF were present. Similar tumour deposits were seen in myometrium and bilateral ovaries. One case was of atypical carcinoid with cells arranged in nests, trabaculae and cords. Cells were of small to medium size having round nucleus and stippled chromatin. Numerous mitosis and lymphovascular invasion was seen. Chromogranin was positive in the tumour cells.

DISCUSSION

Cervical carcinoma is the most common cancer in Indian women. It is a leading cause of death in women worldwide and develops from cervical intraepithelial neoplasia [14].

Histopathology continues to determine treatment of cancer and precancer by classifying into a specific type depending

on the patterns of microscopic organisation of cells in tissue sections from biopsy or surgical specimens. Although, morphological concepts of cervical cancer and precancer evolution are exhibiting paradigm shift to viral and molecular knowledge, histopathology still remains important as the most widely used clinical end points by which the performance of new techniques for cervical cancer prevention, HPV vaccines and biomarkers are currently evaluated [15].

A preneoplastic cervical intraepithelial neoplasia can regress, persist or progress towards invasive carcinoma. Thus, the goal of cervical cancer prevention program is to detect and treat all committed cancer precursors before invasion develops [14,16].

Mean age of patient in present study of CIN 1 was 38.9 years, CIN 2 was 41.3 years, CIN 3 was 46.4 years and Invasive carcinoma was 48.5 years, correlating with the mean ages observed by Fadare O et al., [17]. These studies substantiate that the disease process starts approximately 10-12 years before the development of invasive carcinoma [18].

The frequency of different types of cervical malignancies in the present study is in accordance with other studies [18-21]. [Table/Fig-12]. Out of 62 invasive squamous cell carcinomas studied, large cell non keratinizing type was the commonest seen in 32 cases (50.8%) followed by keratinizing type seen in 28 cases (44.1%).

Small cell non keratinizing type and papillary SCC was in one case (1.5%) each. Our observation regarding the predominant cell type of squamous cell carcinoma correlates with the study by Lowe D et al., [19].

Histopathologic MGS of invasive squamous cell carcinoma assessed that mode of invasion in form of pushing with well defined borders (69.4%) was more compared to diffuse with ill defined borders (30.6%); majority of tumours showed few to moderate number of mitotic figures (85.5%), lymphovascular invasion was observed in five cases (8%) which is less compared to other studies. Lymphoplasmacytic stromal response was moderate to severe (75.8%). Similar findings were observed by Gauthier P et al., [9] and van Nagell JR et al., [22]. Eosinophilic infiltrate was observed in 17 cases and was mild in most of the cases (64.7%). Similar findings were observed by van Driel WJ et al., however, data concerning the prognostic value of a high proportion of eosinophil granulocytes in the inflammatory infiltrate are conflicting [11].

The objective of determining tumour grade (degree of differentiation) is to estimate biologic behaviour and aid in patient management [23]. In the present study majority of tumours were moderately differentiated (49.4%).

Associated CIN 3 was seen in 24 cases (38.7%) of a total of 62 invasive squamous cell carcinoma. Similar findings have been reported by Czernobilsky B et al., who in a study of 40 cases of invasive carcinoma observed that dysplasia was coexisting in 23 (57.5%) cases [24]. Squamous cell carcinoma of the cervix with higher uterine involvement has been considered to be an infrequent variation in anatomic involvement. The frequency of this type of cancer growth is reported to vary between 4% and 17%. In the present study, extension of squamous cell carcinoma into endometrium and/or myometrium was seen in 9 out of 25 cases (36%) of hysterectomy specimens. Wentz WB et al., reported uterine corpus involvement in 7 of a total 15 patients (46.7%). This observation focuses attention on the need for a more complete biopsy procedure and pretreatment workup prior to initiation of therapy [25].

Morphological changes after radiotherapy include both nuclear and cytoplasmic alteration and pronounced stromal changes. In one similar case diagnosed in present study features of partial pathological response were reported. Primary adenocarcinoma of the cervix is an unusual lesion. In recent years it has been suggested that there has been a relative and absolute increase in the incidence of adenocarcinoma of the uterine cervix as shown in studies of Chen J et al., which was done on a large population based database [21]. In the present study, adenocarinoma formed 8.1% of the total malignant tumours diagnosed in the uterine cervix.

Mean age of patients with adenocarcinoma of uterine cervix was 46.3 years. Few authors have reported that adenocarcinomas tend to occur in older population [26]. However, recent study by Alfsen GC et al., have noticed a shift towards younger age [13]. Out of six, four cases of adenocarcinoma for which hysterectomy specimens were received, two cases (50%) had endophytic growth. The significance of an endophytic or exophytic growth pattern has been debated. Most lesions of adenocarcinoma appearing as endophytic growth may be a manifestations of site of origin of adenocarcinoma within glandular epithelium of endocervix.

Whereas, appearance of an exophytic lesions is a result of extension from endocervical glands or its development in a congenital ectropion [26]. Endocervical carcinoma was the most common subtype (66.7%), followed by villoglandular and endometrioid type. This observation is similar to Hurt WG et al., [26].

Studies	Squamous Cell Carcinoma (%)	Adenocarcinoma (%)	Adeno Squamous Carcinoma (%)	Neuro-Endocrine Carcinoma (%)	Total Cases
Momtahen S et al., [18]	94.8%	5.2%	-	-	77
Lowe D et al., [19]	94.70%	5.30%	-	-	455
Brewer R et al., [20]	85.2%	13.6%	12.3%	-	81
Chen J et al., [21]	82.9%	16.2%	-	0.9%	33048
Present Study	85.1%	8%	1.3%	5.4%	74

[Table/Fig-12]: Comparative analysis of histological types of cervical carcinoma.

Adenosquamous carcinomas previously considered as a subtype of cervical adenocarcinomas is now considered a special and rare histological type accounting for 5-10% of cervical carcinoma and has a poor outcome [27]. In the present study one case with morphological features of adenosquamous carcinoma was reported.

In the present study, neuroendocrine tumours formed 5.4% of the total malignant lesions. Similar to the present study, Wang T et al., has reported 6% cases of large and small cell neuroendocrine tumours in his study of 250 malignant tumours [2]. However, no large series of neuroendocrine tumours of cervix has been reported to allow comparison of their behaviour.

Carcinoma cervix is more common in the low socioeconomic class, with lack of awareness of risk factors and presenting at an advanced stage. There is a need for national cervical screening and education programmes for women especially in rural areas. Studies show that histologic assessment is strongly associated with decreased risk of invasive carcinoma compared to repeated cytology in women with low grade squamous abnormalities [28].

LIMITATION

The limitation of present study was that the follow-up was not available in cases with malignancy as they were referred to higher centre for further management. Also, in cases diagnosed as intraepithelial neoplasia on cervical biopsy, we were not able to observe its progression or regression. Further follow-up studies and correlation with coexistence of HPV infection may help in management and prognostication of the disease.

CONCLUSION

Cervical cancer continues to be the most common cancer of females in developing countries. One of the most significant advances in the management of cervical neoplasms has been the realisation that cervical intraepithelial lesions behave as progressive stages of a biologic continuum towards the development of invasive cancer. Histopathological examination is considered gold standard for diagnosis of intraepithelial neoplasia and cervical carcinoma. Light microscopy is sufficient for the diagnosis of virtually all cases, with a need for histochemical stains and immunohistochemistry in only a few histologic types, particularly in poorly differentiated carcinoma and neuroendocrine tumours. Histologic evaluation of intraepithelial neoplasia and cervical carcinoma should be attempted at an early stage of disease to provide better prognosis, treatment and protection against invasive cervical carcinoma.

With recent advancements in molecular techniques more studies comparing different histological features and biomarkers need to be conducted to ensure development of targeted therapy and prevention of invasive carcinoma.

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AUTHOR(S):
1. Dr. Mamta Gupta
2. Dr. PK Basavaraj

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pathology, Subharti Medical College, Meerut, Uttar Pradesh, India.
2. Professor, Department of Pathology, Basaveshwara Medical College, Chitradurga, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mamta Gupta,
Associate Professor, Department of Pathology,
Subharti Medical College, NH-58,
Meerut-25005, Uttar Pradesh, India.
E-mail: drmamtagupta2016@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS:
None.
Date of Publishing: **Jan 01, 2018**