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**Original Research Article**

# Histological spectrum and diagnostic challenges in endometrial carcinoma of the uterus

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## ABSTRACT

**Background:** Endometrial carcinoma is the most common type of malignancy of the uterine corpus accounting for 95% of all primary malignancies. Epidemiological studies have proved the role of unopposed estrogen as an important factor in pathogenesis of endometrial carcinoma. Pathologists play an important role not only in the histological confirmation of the diagnosis, but in subtyping, grading and staging of the tumor. Current study is undertaken to study the histological spectrum in endometrial carcinomas.
**Methods:** Present study includes histologically confirmed cases of endometrial carcinoma of uterine corpus over a period of 24 months (July2020 to June 2022) in a tertiary health care center in central India. After gross examination, and standard sectioning, all these tumors were subtyped on histology and grading, staging was done as per WHO and FIGO recommendations. In cases with diagnostic dispute and overlapping features, IHC markers were applied.
**Results:** Amongst total 30 confirmed cases of endometrial carcinoma, endometrioid type was most common (25) followed by villoglandular and serous type of adenocarcinoma. Architectural and nuclear grading was done in all cases. Staging could be done in hysterectomy specimens only. Difficulties encountered while grading and staging are discussed.
**Conclusions:** Endometrial carcinoma was the most common type of malignancy. Other types were villoglandular and serous adenocarcinoma. Various additional histological features were also observed. Grade I tumors were commonly seen. Depth of myometrial invasion was measured in hysterectomy specimens. Various diagnostic challenges encountered are discussed.

**Keywords:** Endometrial carcinoma of uterus, Endometrioid adenocarcinoma, Villoglandular adenocarcinoma, Serous adenocarcinoma, Architectural and nuclear grading

## INTRODUCTION

In last few years there has been constant increase in the incidence of endometrial cancer in India, which may be attributed to the changing trends in the lifestyle and reproductive profile of women, especially in urban areas. Endometrial carcinoma is the most common type of malignancy of the uterine corpus accounting for 95 % of all primary malignancies.[1,2] Epidemiological studies have proved the role of unopposed estrogen as an important factor in pathogenesis of endometrial carcinoma. Other risk factors include genetic factors, pelvic radiation, obesity and tamoxifen therapy.[3] In order to explore new therapeutic regimens for endometrial carcinomas, histomorphological confirmation of the diagnosis in association with its clinical outcome is most important.[4] The pathologist might be involved in four phases of endometrial carcinoma management, including (1) detection of the tumour on Papanicolaou smear; (2) interpretation of a biopsy or curetting, which may be prompted by the cytology but much more frequently by abnormal bleeding; (3) intraoperative assessment of the

uterus to facilitate staging; and (4) postoperative evaluation of the hysterectomy specimen to determine the risk of recurrence and to guide therapy.[5] Present study highlights the importance of histomorphological features in typing, subtyping, grading and staging of endometrial carcinomas.

***Aims and objectives***

Present study is carried out with following aims and objectives;

To subtype endometrial carcinomas histologically along with grading and staging as per WHO classification.

To study the spectrum of histomorphological features in endometrial carcinomas of the uterine corpus.

## METHODS

Present study is a cross sectional observational study of two years duration (from July 2020 to June 2022) carried out in Pathology Department of government medical college and hospital Nagpur, which is a tertiary care hospital. The study is carried out after obtaining clearance and approval from the Institutional thesis and ethics committee.

Inclusion criteria: the study included histologically confirmed cases of endometrial carcinomas which were received as specimens from suspected uterine malignancy in patients attending gynae OPD or admitted in gynae wards who underwent either biopsy or hysterectomy as a diagnostic or therapeutic procedure.

Exclusion criteria: All other types of malignancies apart from endometrial carcinomas and other non-malignant lesions confirmed after histopathology in clinically suspected cases were excluded.

Detailed clinical history and general examination findings, radiological details and clinical details were noted in these patients in a proper predesigned proforma. The study included patients with endometrial carcinoma from July 2020 to June 2022. (2 years). The types of samples included were 1. Endometrial biopsy/ curettings and 2. Hysterectomy specimens (total or radical). In case of endometrial biopsy and curettings, whole tissue was embedded. In case of hysterectomy specimens, standard protocol of grossing was followed including weight, measurements, endometrial thickness, type of growth-exophytic or infiltrative. The serosal surface was marked by ink for taking sections for assessment of serosal involvement. The depth of invasion in myometrium, and the tumour free myometrial thickness in mm was measured as seen on gross for staging. Grossing of the specimen was done using standard protocol as mentioned in TATA Technical manual for grossing and with few guidelines from CAP protocols.[6,7]

Apart from the main tumour, any other lesion (e.g., polyp or blood clot) if present, was noted.

Any lesion/pathology in the cervix was noted and at least one section was taken from the, uninvolved endomyometrium.

Each ovary was examined and its dimensions and cut surface appearance was noted.

Both fallopian tubes were examined and their length for presence of any paratubal cysts were noted.

Both sided parametria were examined totally along with the tissue submitted separately.

Minimum Sections submitted, included: Four sections of the tumour (4)

One from adjacent endometrium (1)

Two sections from grossly unremarkable cervix (anterior and posterior lips) (2)

Right tube, ovary, parametrium (3)

Left tube, ovary, parametrium (3)

Bilateral pelvic nodes or sent as per the nodal stations.

Additional sections if required, depending on the lesion.

The hysterectomy report included patient's details, gross examination findings, type of specimen, description of gross findings and microscopic diagnosis including histologic type, subtype and grade of malignancy, depth of myometrial invasion, status of lympho-vascular invasion, extension into adjacent tissues and involvement of margins and lymph nodes in case of radical hysterectomy specimen. Staging and typing was done as per WHO classification 2014.8 In selected cases with overlapping features, a panel of IHC markers was applied for final diagnosis.

## RESULTS

Our study found total 30 cases of endometrial adenocarcinoma confirmed on histology.

**Table 1: Age wise distribution.**

| Age group | No of cases | Percentage of cases |
|---|---|---|
| **<30** | - | - |
| **31-40** | 04 | 13.3% |
| **41-50** | 08 | 26.6% |
| **51-60** | 13 | 43.3% |
| **61-70** | 03 | 10% |
| **71-80** | 02 | 6.6% |
| **Total cases** | 30 | 100% |

Maximum cases (13 out of 30 cases) of epithelial tumours belonged to age group of 51 to 60 age group in our study. Youngest patient was of age 32 years, that presented with primary infertility and eldest of age 77 years. Commonest presenting symptom was postmenopausal bleeding followed by abdominal pain and discomfort and one case presented with infertility. Amongst primary epithelial malignancies of uterine corpus, most common type of malignancy was endometrioid carcinoma. Other types of carcinomas were villoglandular type and serous type of endometrial carcinoma. (Table 2).

The sample types were hysterectomy 22/30 and endometrial biopsy/curettings 8/30.

**Table 2: Split up of endometrial carcinoma.**

| Histopathological diagnosis | No. of cases | Percentage (%) |
|---|---|---|
| **Endometroid** | 25 | 83.3% |
| **Villoglandular** | 03 | 10% |
| **Serous** | 02 | 6.66% |
| **Total** | **30** | **100%** |

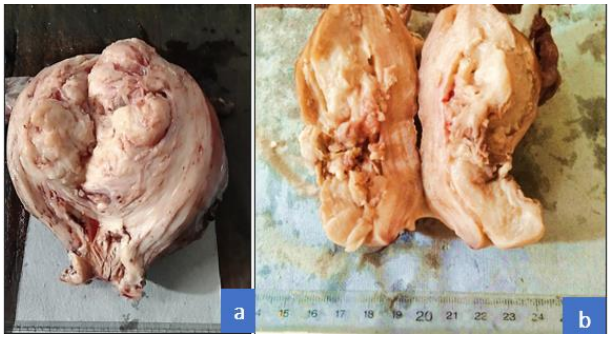


**Figure 1: a) Exophytic mass in endometrial carcinoma, b) Polypoidal mass filling endometrial cavity in hysterectomy specimen.**

**Table 3: Microscopic grade in endometrioid carcinomas.**

| Architectural grade No. of cases | Nuclear grade No. of cases | Tumor grade |
|---|---|---|
| **14** | 13 | 13 (52%) |
| **8** | 9 | 9 (36 %) |
| **3** | 3 | 3 (12 %) |
| **25** | 25 | 25 (100%) |

Microscopic findings in endometrioid carcinoma: Endometrioid carcinomas were graded by both architectural grading and nuclear grading as per WHO histopathological classification of uterine carcinoma recommendations and recent revision of FIGO staging system.[9]

Apart from architectural grading and nuclear grading, we observed various other microscopic findings in all cases of endometrioid carcinomas. These findings are tabulated in Table 5.

**Table 4: Depth of myometrial invasion in 22 cases of hysterectomy specimens of endometrial carcinoma.**

| Depth of myometrial invasion | No. of cases |
|---|---|
| **More than 50 percent** | 11 |
| **Less than 50 percent** | 11 |
| **Total** | 22 |

**Table 5: Microscopic features.**

| Microscopic features | No. of cases |
|---|---|
| **Involvement of lower uterine segment** | 14 |
| **Lympho-vascular space invasion** | 9 |
| **Squamous metaplasia** | 8 |
| **Necrosis** | 8 |
| **Stromal lymphocytic infiltration** | 4 |
| **Clusters of foamy histiocytes** | 2 |
| **Desmoplastic stroma** | 2 |
| **Mucinous areas** | 2 |
| **Foci of adenomyosis in surrounding endometrium** | 2 |
| **Cytoplasmic vacuolation or clear areas** | 2 |
| **Ciliated cell metaplasia** | 1 |
| **Papillary tufting** | 1 |
| **Foci of endometrial intraepithelial carcinoma** | 1 |
| **Keratin granulomas/ giant cell reaction** | 1 |
| **Eosinophilic metaplasia** | 1 |
| **Psammoma bodies** | 1 |
| **Any other findings: ovarian involvement** | 3 |

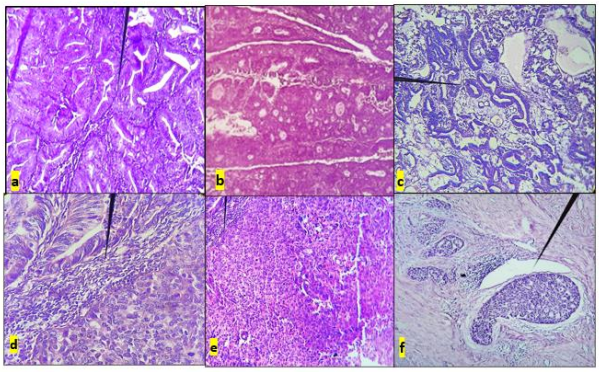


**Figure 2: Histological findings in endometrial carcinoma; a) Confluent glandular pattern, b) Cribriform pattern, c) Tubulo-cystic pattern, in endometrioid adenocarcinoma, d) Papillae and solid areas in grade II endometrial carcinoma, e) Solid area in grade III endometrial carcinoma, f) Sertoliform pattern in endometrial carcinoma.**

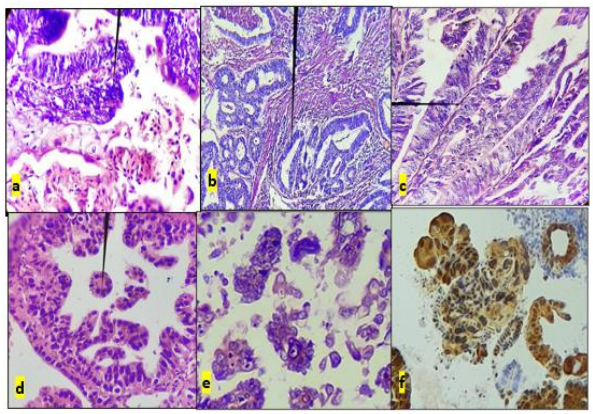


**Figure 3: Histological spectrum in endometrial carcinoma; a) Squamous metaplasia in endometrial carcinoma, b) Desmoplastic stroma in between glands, c) Papillae with fibrovascular core in villoglandular adenocarcinoma, d) Intraluminal papillary tufting in serous endometrial carcinoma, e) Psammoma body and macro-nucleoli in serous adenocarcinoma, f) p16 positivity in tumour cells in serous carcinoma.**

The microscopic grading in 22 cases of hysterectomies in endometrial carcinoma was: Grade I - 10 cases (45.45%), grade II - 09 cases (40.9%) and grade III - 03 cases (13.6%).

***IHC study in selected cases***

Following were the categories of tumours selected or IHC study along with their findings.

Grade III endometrial carcinoma versus serous carcinoma - markers applied were PR, p53 and p16. Grade III endometrial carcinoma (3 cases) showed diffuse PR positivity, weak p53 staining and patchy/focal p16 positivity; whereas in serous endometrial carcinoma (2 cases), PR staining was negative, p53 was strongly positive and p16 showed diffuse positivity.

Endometrioid adenocarcinoma versus endocervical adenocarcinoma- markers applied were ER, PR & p16. Endometrial adenocarcinomas (2cases) were strongly positive for ER and PR and negative for P16; whereas one cases of endocervical adenocarcinoma showed reverse pattern. i.e., negative staining for ER, PR and diffuse strong positivity for p16.

## DISCUSSION

In this descriptive cross-sectional study entitled "histological spectrum and diagnostic challenges in endometrial carcinoma of the uterus", we came across with total 30 cases of histologically proved endometrial carcinoma. 22 cases were hysterectomy specimens and 8 cases were endometrial biopsy/ curettings. In our study, maximum cases of endometrial carcinoma were seen between 51 to 60 years age group. A study by N'Dah KJ.et al mentioned that 80% of the endometrial carcinomas occur in post-menopausal women.[10] In our study, 21/30 (70%) cases were postmenopausal patients. Youngest patient with endometrial carcinoma was 32 years of age. Endometrial carcinomas below 40 years of age are usually seen in patients with polycystic ovary disease or with clinical features like irregular menses, infertility, obesity and hirsutism. In our study, this patient presented with infertility and irregular menses. USG pelvis findings were suggestive polycystic ovary disease and D& C specimen showed features of atypical endometrial hyperplasia versus well differentiated adenocarcinoma. Patients with polycystic ovary disease are known to present at younger age as they come for investigations for infertility.

Commonest presenting symptom in our study was postmenopausal bleeding. (67.4%) which is parallel with other studies. Other symptoms were abdominal pain, abdominal discomfort and infertility in two patients. Krissi et al in 1996 in their study found 69.9% cases with postmenopausal bleeding followed by irregular bleeding (21%), abdominal pain 3.9% and other symptoms (5.5%).[11]

**Table 6: Distribution of cases and their comparison with other studies.**

| Study | Endometrioid carcinoma | Serous carcinoma | Villoglandular carcinoma | Clear cell carcinoma | Squamous cell carcinoma |
|---|---|---|---|---|---|
| **Tanvir I et al[12] 2014** | 42/52 (80 %) | 6/52 (11%) | - | 3/52 (5%) | 2/52 (4%) |
| **Zahida OA et al 2020[1]** | 5/10 (50 %) + 1/10 (10 %) with squamous differentiation | 1/10 (10%) | 3/10 (30%) | | |
| **Present study 2023** | 25/30 (83.3 %) | 2/30 (6.66%) | 3/30 (10%) | - | - |

In our study, amongst total 30 cases of endometrial adenocarcinoma of uterine corpus, endometrioid type accounted for 25/20, (83.3%) cases. Remaining types were serous type (2 cases) and villoglandular type (3 cases) of endometrial adenocarcinoma. This distribution is similar to the study by Tanvir et al 2014.[12]

The frequency of endometrioid carcinoma in our study was similar to that of study Tanvir et al 2014.[12] Serous

carcinoma in their study was 11%, while in our study it was 6.66% only. The number of cases in our study were only 30 as compared to 55 cases in their study. The case number in the study by Zahida et al was very small, only.[10] They have included endometrial carcinoma with squamous differentiation as a separate variant, whereas in our study we have included it in total number of endometrioid carcinomas. As far as other variants are concerned, in few cases of endometrioid carcinoma we could get focal changes like clear cell change, mucinous areas and secretory change also. But the variant could not be diagnosed as the diagnostic criteria of 50% areas showing that changes were not fulfilled.

Most of the cases in our study showed exophytic and polypoidal growth in hysterectomy specimens. No gross appearance is related to any histological subtype of a tumour; however, in general, high-grade tumours show more areas of haemorrhage and necrosis giving a friable appearance on gross.[5]

***Histological spectrum in endometrial carcinomas***

In our study, histological spectrum of all cases of endometrial carcinoma was studied. Apart from histological diagnosis and subtyping, it included architectural and nuclear grading based on recommendations by WHO and FIGO classification system. Grade I architectural pattern was seen in 14/25 (56%) cases, 8 cases showed grade II features and 3 cases with more than 50% solid component and extensive necrosis were labelled as grade III. Various morphological patterns seen were papillary (commonest), glandular, tubulo-cystic and a rare feature of Sertoli-form areas. This later case was a diagnostic challenge, since it needs to be differentiated from sertoliform variant of ovarian endometrioid carcinoma. Final diagnosis was offered after IHC confirmation, in addition to the features such as simultaneous involvement of both tubes, ovaries and presence of tumor cell nodules on serosal aspect of uterus.[13,14]

***Nuclear grading***

Nuclear grading was based on nuclear size and shape variation, chromatin distribution and the size of nucleoli. Mildly enlarged oval nuclei with dispersed chromatin were graded as grade I nuclei whereas markedly enlarged pleomorphic nuclei with irregular coarse chromatin and prominent eosinophilic nucleoli were graded as Grade III nuclei. Nuclei showing features in between, these two grades, were graded as grade II nuclei.

In our study, 13 cases showed Grade I nuclei, 9 cases showed grade II nuclei and 3 cases had grade III nuclei. As per latest revisions of FIGO system and WHO classification, tumours with nuclear grade higher than architectural grade features should be graded as one higher grade. Although architectural and nuclear grades correlate in endometroid carcinoma, occasional cases may show discrepancy, especially those with areas of necrosis or degenerative changes. We found 14 cases with architectural grade I, of which 13 cases showed grade I nuclei. Nuclear features were of higher grade in 1 case, so the tumour was graded as grade II. Thus, grade II included total 9 cases, although architectural grade II pattern was seen, only in 8 cases. In 3 cases, architectural and nuclear grading correlated as grade III.[5,10]

Various patterns of myometrial invasion have been described, such as invasion along a broad front in pushing manner, diffuse infiltration in cell masses, cords or clusters or even individual glands.[15] In our study amongst total 30 cases, 22 were hysterectomy specimens in which we could look for different patterns of myometrial invasion. Various patterns observed in our study were diffuse infiltrative pattern which was most common, occasional cases showed single cell pattern resembling lympho-vascular invasion. In few cases MELF (microcystic, elongated and fragmented pattern) pattern could also be appreciated. Proper sectioning, staining and good quality slides are essential for observing the patterns of invasion. In most of the well differentiated or grade I endometrioid carcinomas, the pattern of invasion was like a pushing front. Some of these patterns cause difficulty in assessment of myometrial invasion like diffuse infiltration along broad front. A study by Mateva et al in 2021 mentioned different types of infiltration patterns and their correlation with clinical behaviour.[16] Diffuse pattern of infiltration is found to have clinically aggressive disease course. Other patterns described include microcystic glands with surrounding fibromyxoid stromal response popularly known as MELF pattern, the adenoma magnum like pattern (invasion of well differentiated neoplastic glands with minimal stromal reaction), adenomyosis like pattern, and phyllodes tumour like pattern showing nodular ascites like stroma with elongated slit like glands. In our study, areas of adenomyosis deep in the myometrium and irregular endo-myometrial interface were problem areas in assessment of depth of myometrial invasion. Extent of myometrial invasion in our study was 50% each (less than and more than 50 % of the thickness of myometrium.

***Stromal invasion in biopsy specimens***

Differential diagnosis between atypical endometrial hyperplasia and well differentiated adenocarcinoma is always challenging, especially in biopsy specimens. Specific morphological patterns of stromal and epithelial alterations have been accepted as diagnostic of endometrial carcinoma. Features used to demonstrate stromal invasion includes;

Desmoplastic stroma associated with irregular infiltration of neoplastic glands.

Confluent glandular pattern and cribriform pattern showing no intervening stroma.

Extensive papillary pattern.

Although papillary pattern is commonly seen in complex papillary hyperplasia, other features like low mitotic activity, absence of stratification and bland cytological features in complex hyperplasia help to differentiate between the two.[17]

***Features of stromal invasion***

The desmoplastic stroma shows densely arranged fibroblasts which appear more eosinophilic due to densely arranged collagen. This feature cannot be applied to the specimen containing bits of polyps and lower uterine segment in biopsies. Application of certain specific and objective criteria is recommended for diagnosis of stromal invasion. These quantitative criteria are 1. Extensive glandular proliferation which involves half or more of the low power field or a distance of 2 mm at least. If the evidence of stromal invasion is seen in the biopsy specimen, then the diagnosis of adenocarcinoma can be applied irrespective of the quantitative criteria of glandular proliferation. In our case the quantitative criteria were fulfilled, and also clinically and radiologically there was a strong suspicion of malignancy.

***Confluent gland pattern***

This implies to glandular proliferation without intervening stroma. Since it reflects invasion, it's identification is very important. Two common patterns seen in this are cribriform pattern and complex labyrinth pattern. In cribriform pattern, the lumen is subdivided into smaller glandular spaces by trabeculae of cells without supporting stroma. Complex papillary structures showing branching fibrous processes containing fibrovascular core lined by epithelium and villoglandular pattern. In our study, this pattern was helpful in differentiating atypical endometrial hyperplasia from well differentiated endometrial adenocarcinoma.

***Desmoplastic/ altered stroma***

In this feature, the cells surrounding these proliferating glands are reactive fibroblastic rather than endometrial stromal cells. These cells are more spindle with elongated nuclei. It appears eosinophilic due to the presence of collagen in between these cells. Glands appear distorted due to stromal fibrosis.

Extensive papillary pattern: This pattern shows delicate, elongated, complex branching papillary fronds having thin fibrous cores. Such type of papillae is not seen in focal alterations or hyperplastic papillary proliferations. The papillary tufts seen in serous carcinomas are devoid of fibrovascular core.

In our study, out of 7 cases of epithelial tumours diagnosed on curettings, 4 were endometrioid adenocarcinoma, of which one patient was a young lady. Patient with clinically diagnosed PCOD who came or infertility and curettings showed features of adenocarcinoma. This case was a diagnostic challenge. In this case, confluent glandular pattern specially, cribriform pattern was very prominent. foci resembling villoglandular structures with long, slender papillae showing thin delicate fibrovascular core were also seen. Diagnosis of well differentiated adenocarcinoma was given in view of USG findings, clinical features and diagnostic histologic features in biopsy specimen.18 Immunohistochemistry does not play important role in the differential diagnosis of these two lesions as similar molecular alterations are seen in both.[19-21] Three more patients were diagnosed as endometrial adenocarcinoma on curettings, they were clinically suspected of endometrial carcinoma and had abnormal or postmenopausal bleeding and increased endometrial thickness on pelvic ultrasonography. Of them, one patient had poorly differentiated endometrial carcinoma (grade III).

***Villoglandular carcinoma***

Two patients were diagnosed as villoglandular type of adenocarcinoma in view of predominantly papillary architecture with delicate fibrovascular core lined by columnar cells with bland nuclear features. Nuclei are oval and stratification is common. Since they have good prognosis, their identification is very essential. In view of prominent papillary structures, serous carcinoma comes in the differential diagnosis of villoglandular carcinoma. Villoglandular carcinoma has very good prognosis as compared to serous carcinoma hence diagnosis is essential.[22]

***Serous carcinoma***

In our study, both the cases of serous carcinoma were diagnosed on curettings only. One of these two cases was a known treated case of carcinoma breast on tamoxifen therapy. The papillae in serous carcinomas were shorter, thick and showed fibrotic frond as compared to that in villoglandular carcinoma. Detached cell clusters in serous carcinoma form small round papillary structures known as papillary tufts giving a scalloped appearance to the luminal border, in contrast to the smooth luminal border of villoglandular carcinoma is a very helpful diagnostic feature.[23] The nuclei in serous carcinoma showed high grade features with marked pleomorphism. Occasional focus also showed eosinophilic macro-nucleoli.

Our study emphasizes the role of gross examination, sectioning and histological examination for proper diagnostic assessment and staging of the tumours of body of uterus.

***Limitations***

More number of cases need to be studied to comment on association between various morphological patterns including pattern of invasion and prognosis. In endometrial biopsy and curretings specimens, architectural grading and myometrial invasion cannot be commented

upon. Molecular and genetic studies could not be done in above cases.

## CONCLUSION

This cross-sectional observational study entitled "Histological Spectrum and Diagnostic Challenges in Endometrial Carcinoma of the Uterus" of two years duration at a tertiary health care centre included 30 histologically confirmed cases of endometrial carcinoma. Histological Subtyping, grading and staging of these tumours was done to find the diagnostic challenges and histological spectrum. Endometrioid type of endometrial adenocarcinoma was most common type of tumour followed by villoglandular and serous type of endometrial adenocarcinoma. Our study emphasizes the role of gross examination, sectioning and histological examination for proper diagnostic assessment and staging of the tumours of body of uterus. Proper selection of the panel of IHC markers is essential in cases of differential diagnosis.

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