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Histomorphological Pattern Analysis of Endometrial Carcinomas in a Tertiary Care Hospital

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ABSTRACT

Background: Endometrial carcinoma which has various histological types is the commonest invasive cancer of female genital tract. Two general groups of endometrial cancer include Type 1 and Type 2. Type 1 tumors are related to prolonged estrogenic stimulation and include endometrioid type and type 2 includes serous carcinoma, clear cell carcinoma and carcinosarcoma.

Materials and methods: The present study is a retrospective study conducted in the department of pathology at BGS GIMS from January 2018- January 2021. All the endometrial carcinoma specimens obtained from D&C and hysterectomy specimens were assessed on paraffin embedded sections stained with H&E stain and immunohistochemical study was done wherever required.

Results : In the present study 33 cases of endometrial carcinoma cases were analyzed. Majority of them were >60years (36.5%) and most were post-menopausal females .Most common clinical presentation was abnormal uterine / post-menopausal bleeding seen in 100% of cases . The most common histological type observed was endometrioid type (81.8%)of endometrial carcinoma followed by serous carcinoma(6.4%)and carcinosarcoma(6.4%). One case of endometrioid carcinoma with secretory differentiation was reported. Most of endoemetrioid carcinomas belonged to FIGO histological grade 1(71.4%) and the most common TNM stage was Stage 1A (60%) with majority of them showing less than half of myometrial invasion(60%). Importance of IHC in differentiating variants of endometrial carcinoma found to be very significant.

Conclusion: Endoemetrioid type of endometrial carcinoma was the most common histological type seen and generally present in early stage and carry good prognosis when compared to other variants like serous carcinoma, adenosarcoma which present in late stages and carry bad prognosis. Detailed study of histological appearance of endometrial carcinoma provides insight into prognosis and plays a role in determining therapy.

KEYWORDS: Endometrioid carcinoma, carcinoscarcoma. Myometrial invasion, prognosis Serous carcinoma , secretory carcinoma.

CITATION OF THE ARTICLE

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I. INTRODUCTION

Endometrial carcinoma is the commonest invasive neoplasm of the female genital system and is the fourth most common frequently diagnosed cancer in united states among women and 5th most common cancer in females worldwide.[1] Based on clinicopathologic and molecular genetic features endometrial carcinomas are broadly classified as Type I and type II. Type I is related to prolonged estrogenic stimulation and includes endometrioid type. Type II comprises special variants like clear cell carcinoma, serous carcinoma and carcinosarcoma.[2]

The histological variant and the grade of endometrial carcinoma are the important features which influence the likelihood of disease spread and recurrence along with factors like myometrial invasion, cervical stromal involvement and lymphovascular invasion.[3]

The most common type of endometrial carcinoma is endometrioid type. Histopathologicaly endometrioid adenocarcinomas exhibit a continual spectrum of appearances and this continuum is bracketed at one end by proliferations difficult to distinguish from atypical endometrial hyperplasia and at the other end by sheet like proliferation of malignant cells which is difficult to distinguish from uterine sarcoma.[4]

Many clinicopathological studies of endometrioid adenocarcinoma have shown that increasing loss of glandular and villo-glandular architecture positively correlates with higher stages and diminished survival rate. Likewise , some types of special variants of endometrial carcinomas are associated with high grade clinical behavior.

Thus the histological appearance of endometrial carcinoma provides important insight into prognosis and plays a role in determining therapy.

The present study was carried out to provide insight of morphological patterns of endometrial carcinoma and their incidence and prognosis.

II. METERIALS AND METHODS

Study design: Descriptive and retrospective study

Study period: The present study was conducted from January 2018- January 2021

Study settings: The present study was conducted in department of pathology at BGS GIMS. All the endometrial carcinoma specimens obtained from D&C and hysterectomy specimens were assessed with immunohistochemical study done wherever required.

Histopathological and Immunohistochemical study of specimens:

All the D&C and hysterectomy cases were received in 10% formalin and were processed using conventional method of paraffin embedding and sections were stained using hematoxylin and eosin . Immunohistochemical study was done for further evaluation of ER, PR, p53 and CD10 in required cases. Cases with nuclear marker demonstrating in at least 5% of epithelial cells were considered positive.

Statistical analysis :

The data collected were entered in excel sheets and then transferred to EPi-Info software for analysis according to aims and objectives. The descriptive results were shown in the forms of frequency and means.

Ethical clearance :

Ethical clearance was taken from institutional ethics committee

III. RESULTS

Maximum number of endometrial carcinomas observed in the present study were 33 over a period of 3 years of which 8 were reported on endometrial curetting's and 25 cases on endometrial curetting's followed by hysterectomy specimens.

Table 1: Age distribution of all the cases

Age	Number	Percentage (%)
0-10	0	0
11-20	0	0
21-30	0	0
31-40	3	9
41-50	8	24.2
51-60	10	30.3
61-70	7	21.2
71-80	4	12.1
81-90	1	3.2
91-100	0	0
Total	**33**	**100**

The most common age group affected by endometrial carcinomas in the present study was more than 60 years (36.5%) followed by 51-60 (30.3%) and most of them belonged to post-menopausal age group.

Table 2: Clinical presentation of all the cases

Symptom	Number
Post-menopausal bleeding	23
Abnormal uterine bleeding	10
Pain abdomen with bleeding	15

In our study most of the patients presented with either post-menopausal bleeding/abnormal uterine followed by pain abdomen.

Table 3: Histological types of endometrial carcinoma

Histological type	Number	Percentage (%)
Endometrioid carcinoma	27	81.8
Endometrioid carcinoma with secretory differentiation	01	3
Serous carcinoma	2	6.1
Carcino sarcoma	2	6.1
Metastasis	1	3
Total	**33**	**100%**

In the present study endometrioid type of endometrial carcinoma was the predominant histological type accounting for 80% followed by serous carcinoma and carcinosarcoma accounting for 6.4% each. One case each of endometrioid carcinoma with secretory differentiation and metastatic carcinoma was reported in our study.

Table 4: FIGO Histological grade

Histological grade	Number	Percentage
Grade 1	20	71.4
Grade 2	6	21.5
Grade 3	2	07.1
Total	**28**	**100%**

FIGO histological grading is applied only for endoemetrioid type of endometrial carcinomas and this is based on the percent of solid, non glandular and non squamous growth. Tumors showing < 5% , 6-50% and > 50% of solid, non glandular and non squamous growth are graded as 1, 2 and 3 respectively.

Most of the endometrioid tumors are grade 1-low grade(71.4%) , 6 cases(21.5%) were moderately differentiated and only 2(7.1%) cases showed grade 3 features.

Table 5: Depth of myometrial invasion

Depth of myometrial invasion	Number	Percentage(%)
Less than half of myometrium	15	60
More than half of myometrium	5	20
No invasion	5	20
Total	**25**	**100**

In our study myometrial invasion was assessed on 25 hysterectomy endometrial carcinoma specimens of which 20 cases (60%) showed less than half of myometrial invasion and the remaining 20% showed more than half of myometrial invasion. Myometrial invasion was absent in 20% of cases and were called endometrial intraepithelial neoplasia.

Table 6: UICC TNM staging for hysterectomy specimens

TNM(Stage)	Number	Percentage (%)
Stage 0 (Tis N0 M0)	5	20
StageIA (T1a N0 M0)	15	60
Stage Ib (T1b N0 M0)	4	16
Stage II (T2 N0 M0)	0	0
Stage IIIA(T3aN0 M0)	0	0
Stage IIIB(T3bN0 M0)	1	4
Stage IV (T4 any N M0/M1)	0	0
Total	**25**	**100**

All cases of endometrial carcinomas were staged according to Union For International Cancer Control (UICC) TNM Classification[5] Majority of the cases in present study belonged to stage 1A (60%) involving < 50% of the myometrium followed by stage 1b (16%)involving > 50% of the myometrium. We observed that only in case parametrium was involved and thus staged as Stage 3B.

IV. DISCUSSION

Endometrial cancer is the most commonest malignancy of female genital tract affecting predominantly post- menopausal females. Several risk factors have been described in the literature involved in the development of endometrial cancer and these include obesity, hyperinsulinemia, metabolic syndrome, oral contraceptive pills, smoking, alcohol and nulliparity.

According to Bokhman proposal endometrial carcinomas are divided into type 1 and type 2 based on clinic-pathologic and molecular genetic features.

According to WHO[5] the endometrial carcinomas are classified as endometrioid type and its subtypes includes variant with squamous differentiation, villo-glandular variant, secretory variant and ciliated variant. Other types are Mucinous adenocarcinoma, serous, clear cell, mixed cell, SCC, TCC, small cell and undifferentiated carcinoma.

AGE

The most common age group affected by endometrial carcinomas in the present study was more than 60 years(36.5%) followed by 51-60 (30.3%) and most of them belonged to post -menopausal age group.

Similar findings were observed by Jezan et al[3] and Sood Alshahrani[6]. Mitul modi et al[7] observed the most common age group between 41-60years.

CLINICAL FEATURES

In our study most of the patients presented with either post- menopausal bleeding/abnormal uterine bleeding (100%) followed by associated pain abdomen (45%). Mitul modi et al[7] observed the most clinical presentation was abdominal pain and pervaginal bleeding in 100% cases.

HISTOLOGICAL TYPE

The most common histological type of endometrial carcinoma observed in the present was endometrioid type (80%) followed by serous carcinoma and carcinosarcoma accounting for 6% each. Similar predominance of endometrioid carcinoma were observed by Deodhar et al[8](82.5%) and Saeed Jezan et al[3] (50.9%.)

Endometrioid carcinoma typically displayed glandular or villoglandular pattern lined by stratified columnar epithelium with crowded complex branching architecture and share common apical border. Nuclei showed mild to moderate atypia except in poorly differentiated carcinomas.

In the present study one case of endometrial carcinoma with secretory differentiation was observed in a post-menopausal female . Histological features observed were secretory endometrial glands with compact back to back arrangement and lined by columnar cells having stratified nuclei showing mild to moderate atypia with supra-nuclear and sub nuclear vacuolations.

Serous carcinomas displayed complex papillary architecture and solid pattern. Papillae varied from short, branching, and hyalinised to long thin and delicate lined by epithelial cells with large atypical nuclei, prominent nucleoli and scant cytoplasm and lack common apical border. High mitotic rate was observed.

2 cases of carcinosarcoma tumor was reported in the present study. Histology of these showed admixture of carcinoma with high grade features and mesenchyme with high grade nonspecific sarcoma features.

One case of secondary tumor of the endometrium was reported in the present study. This was 55 year old female patient of carcinoma cervix with extension to endometrium.

HISTOLOGICAL GRADE

In our study of 28 cases of endometrioid carcinoma majority belonged to grade 1- well differentiated , (71.4%) followed by grade 2-moderatly differentiated (21.5%). Mitul modi et al also observed well differentiated endometrial carcinomas as the most common grade (41%), followed by moderately differentiated (27%).

However Deodhar et al[8] observed Grade 2-moderately differentiated carcinoma as the most common grade (42%) followed by Grade 3 – poorly differentiated (35 %).

Grade 1 carcinomas are associated with good prognosis while grade 2 and grade 3 tumors behave aggressively and carry poor prognosis.

Depth of myometrial invasion

Depth of myometrial invasion was measured from the endomyometrial junction to the deepest point of myometrial invasion using soft ware PROGRESS CAPTURE PRO-2.10.0.1-JENOPTIC OPTICAL SYSYTEM GmbH and was expressed in mm.

In our study myometrial invasion was assessed on 25 hysterectomy endometrial carcinoma specimens of which 20 cases (80%) showed less than half of myometrial invasion and the remaining 20% showed more than half of myometrial invasion. Deodhar et al [8]also observed most cases of endometrial carcinomas showed less than half of myometrial invasion (50%). Mirela – Marinela et al[9] observed more than half of myometrial invasion in most cases(72%)

We also observed that the cases with > half of the myometrial invasion were seen in grade2 and grade 3 tumor and there was significant association between tumor grade and depth of myometrial invasion. This is consistent with the study published by Mirela – Marinela [9] in 2016.

Stage of endometrial carcinomas(UICC TNM staging for hysterectomy specimens)

All cases of endometrial carcinomas were staged according to Union For International Cancer Control (UICC) TNM Classification. Majority of the cases in present study belonged to stage 1A (60%) involving < 50% of the myometrium followed by stage 1b (16%) involving > 50% of the myometrium. We observed that only in case parametrium was involved and thus staged as Grade 3B. Jezan et al[3], Muhammad[10] and Lee[11] in their study noted that majority of the cases belonged to Stage 1 similar to our findings.

Lymphovascular invasion

Lymphovascular invasion was reported in 2 cases and were seen in cases of carcinosarcoma.

Diagnostic difficulties in categorization of endometrial tumors and the approach applied to arrive at proper diagnosis

1. ***Well differentiated endometrioid carcinoma versus endometrioid intraepithelial neoplasia***

Well differentiated endoemtrioid carcinoma was differentiated from endoemetrioid intraepithelial neoplasia based on the presence of stromal invasion alone. According to WHO stromal invasion is defined as loss of intervening stroma , an altered endometrial stroma with desmoplastic reaction or a complex architecture. [5]

2. ***High Grade Endometrioid Type of Endometrial Carcinoma Versus Serous Endometrial Carcinomas***

Differentiating high grade endoemtrioid carcinoma from serous carcinoma often poses diagnostic challenge. Serous carcinomas are aggressive in nature when compared to endoemtrioid carcinomas. Histologically serous carcinomass have complex papillary architecture and are lined by large atypical cells with prominent nucleoli while high grade endoemetrioid carcinomas often have solid sheets of tumor cells having atypical nuclei. However immunohistochemical marker helps in diagnosis. Serous carcinoma are negative or weak ER,PR positive and diffuse p53 positivity while endoemtrioid acrcinomas are ER, PR positive and p53 neagtive.

3. ***High Grade Endometrioid Type of Endometrial Carcinoma Versus clear cell Endometrial Carcinomas***

Differentiating serous carcinoma from clear cell carcinoma alos poses diagnostic challenge. Both and clear cells carcinomas are aggressive in nature when compared to endoemtrioid carcinomas. Histologically these tumors have complex papillary architecture and are lined by large atypical cells with prominent nucleoli while clear cell carcinomas often have tubule cystic pattern and polygonal tumor cells with clear cytoplasm having atypical nuclei and variably sized nucleoli. Serous carcinoma show negative or weak ER,PR positivity and diffuse p53 positivity while clear cell cacrcinomas are ER, PR negative and p53 negative.

4. ***Endometrioid carcinoma with secretory differentiation versus secretory phase and secretory hypertrophy***

Normal secretory phase endometrium is distinguished by absence of crowded glands, nuclear atypia, nuclear stratification and myometrial invasion.

5. ***Endometrioid carcinoma with secretory differentiation versus atypical secretory huperlasia***

Atypical secretory hyperplasia closely mimics secretory carcinoma histologically but careful evaluation for myometrial invasion seen in secretory carcinoma helps in differentiating it from atypical secretory hyperplasia

6. ***Endometrioid carcinoma with secretory differentiation versus clear cell carcinoma***

The key differentiating features of clear cell carcinoma are a papillary and tubulo-cystic architecture with round to polygonal tumor cells showing severe nuclear atypia. Immunohistochemistry can be used as an adjuvant test in differentiating secretory carcinomas from clear cell carcinomas. Secretory carcinomas are positive for ER, PR and p53 while clear cell carcinomas are negative. Our serous carcinoma case expressed ER, PR, p53 positivity along with a high proliferative index (ki67). High proliferative index indicates bad prognosis.

LEGENDS FOR IMAGES

Fig 1 - H&E, 10X; Well differentiated endometrioid carcininoma showing less than 1/2 of myometrial invasion

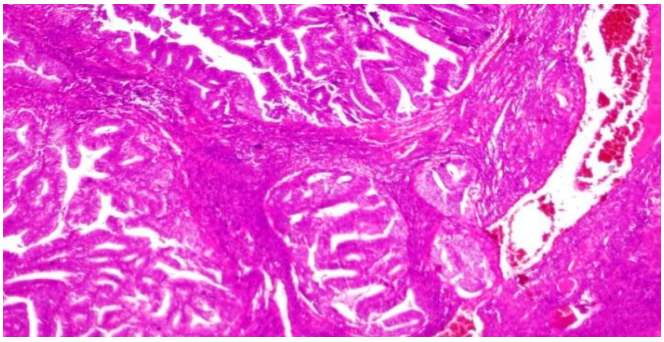


Fig 2a - H&E, 10X; Secretory endometrial carcininoma showing secretory atypical glands.

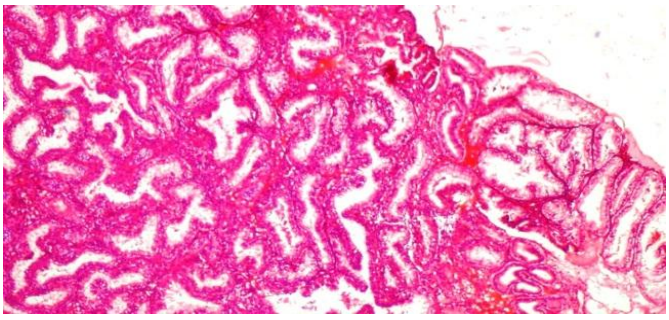


Fig 2b - H&E, 10X; Secretory endometrial carcininoma showing secretory atypical glands showing less than ½ of myometrial invasion

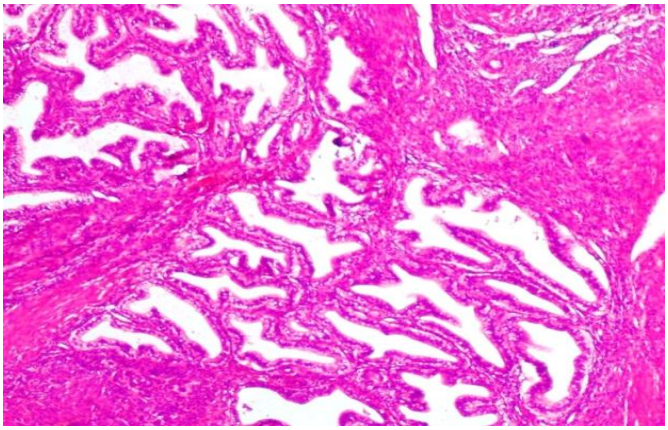


Fig 3a and 3b - H&E, 10X; Serous endometrial carcinoma showing papillary and glandular spaces lined by highly pleomorphic cells with hyperchromatic nucleoli and frequent mitosis

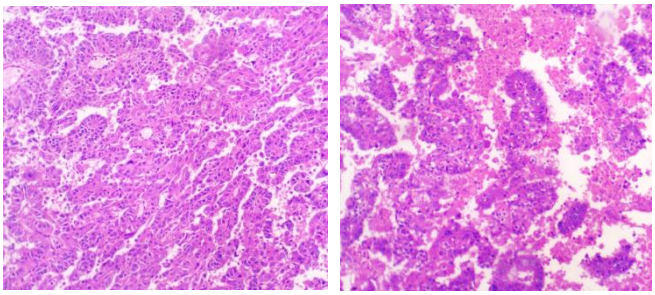


Fig 4a and 4b - H&E, 10X; Carcinosarcoma endometrium showing biphasic tumor with both carcinomatous(high grade serous type) and sarcomatous (chondroid type) elements.

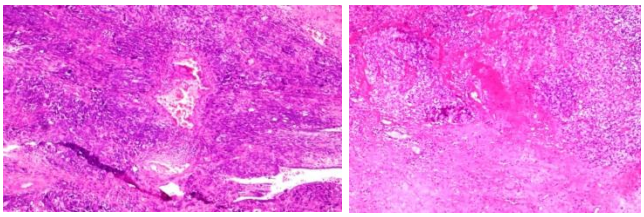


Fig 5a and 5b - H&E, 10X;endometrial carcininoma with mucinous differentiation showing glandular spaces lined by mucin secreting columnar cells

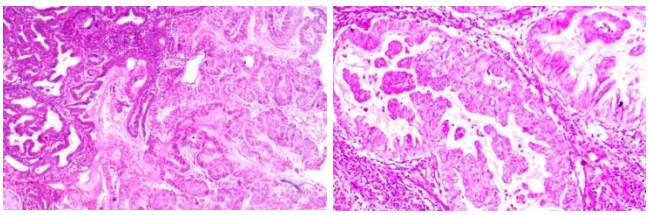
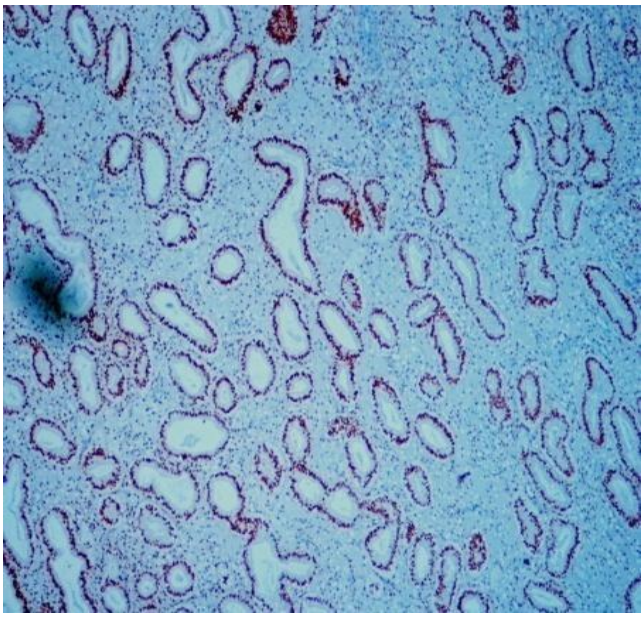
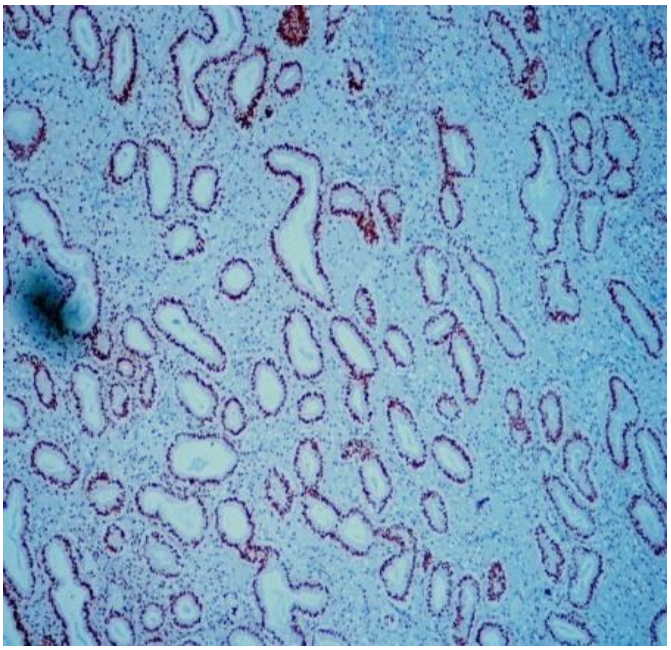
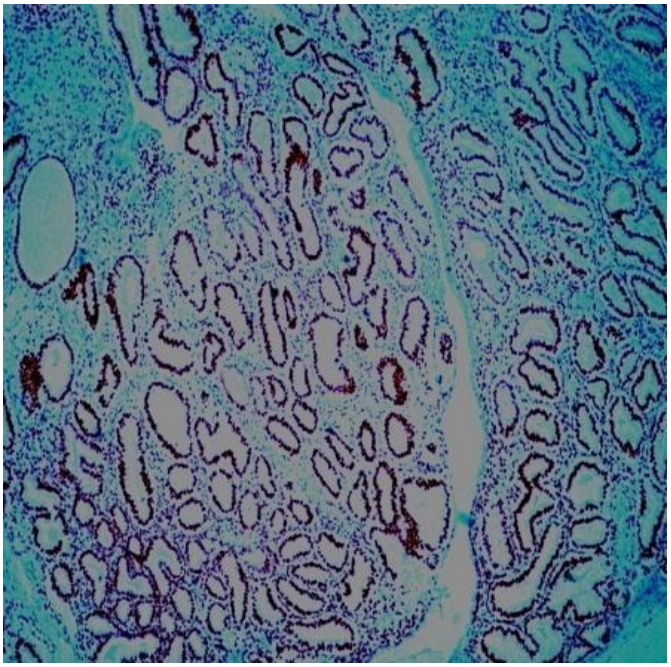


Fig 6a, 6b, 6c- 10X; Immunohistochemistttry ER, PR AND P53 – tumor cells are ER,PR, AND p53 postive.







V. CONCLUSION

Endometrioid endometrial carcinomas are the most common histological type of endometrial carcinomas and generally they carry good prognosis when diagnosed early. Serous and carcinosarcomas generally carry bad prognosis irrespective of the stage unlike endometrioid carcinomas. Endometrioid carcinoma with secretory differentiation has very good prognosis and need to be differentiated from other histological mimickers. Immunohistochemical markers when used appropriately helps in arriving at proper diagnosis. Differentiating various histological patterns of endometrial carcinomas becomes important because of variable prognosis of each type. Thus histological appearance of endometrial carcinoma provides important insight into prognosis and plays a role in determining therapy.

VI. ACKNOWLEDGEMENT

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