International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Immunohistochemical Study of Estrogen and Progesterone Receptor Expression in Endometrial Carcinoma

Dr. Ankita Srivastava[1], Dr.Manju Singh Sirohi[2], Dr. Aviral Srivaastava[3], Prof. (Brig.) Nikhilesh Kumar[4]

[1]Associate Professor, Dept. of Pathology, TS Misra Medical College & Hospital, Lucknow.
[2,3]Post Graduate Junior Resident, Dept. of Pathology, TS Misra Medical College & Hospital, Lucknow.
[4]Prof. & Head, Dept. of Pathology, TS Misra Medical College & Hospital, Lucknow.

ABSTRACT

BACKGROUND: Endometrial cancer is the fourth most common cancer affecting the women both from the point of view of incidence as well as mortality. ER/PR positivity helps to determine the need for hormonal treatment for endometrial cancer.

METERIAL AND METHOD: It is a reterospective study on 22 histopathologically proven cases of endometrial carcinoma between the age group 30 to 80 yr from1 Jan 2021 to 30 June 2022. Those cases with inadequate sample or with history of pregnancy were excluded from study.ER and PR expression was seen with Immunohistochemistry kit protocol.

RESULTS: Mean age of patients was57.77 yrs.Endometrial carcinoma is more common in postmenopausal females.Bleeding per vaginum is the chief complaint.Most of the cases were well differentiated and of low grade.ERexpression is positive in (15/17 88.2%)of cases of low grade /well differentiated , (4/4,100%)in moderately differentiated and not seen in high grade/ poorly differentiated endometrial carcinoma .PR expressionseen in low grade/well differentiated is (14/17,82.4%) , in moderately differentiated is(4/4,100%) and in high grade /poorly differentiated is (1/1, 100%)and not seen in high grade or poorly differentiated endometrial carcinoma.As the tumor invadesdeep in the myometrium ER and PR expression decreases.

CONCLUSION: ER and PRare important prognostic biomarkers to predict response to anti hormonal therapy.

KEYWORDS: Est*rogen receptor, Progesterone receptor.

INTRODUCTION

Endometrial cancer is the fourth most common cancer affecting the women both from the point of view of incidence as well as mortality.During the year 2020, a total of 417,367 new cases of endometrial cancer were diagnosed throughout the world and it resulted in 97,370 deaths during that period(1). Its incidence is higher in economically advanced developed countries and the prognosis is generally not good(2).

The progression of endometrial hyperplasia to cytological atypia and finally into endometrial carcinoma is marked by a multitude of clinical, pathological and physiological changes. A number of biomarkers *viz.,*

"P53, KRAS, PTEN, EGFR, FGFR, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), *etc.*" have been shown to have a role in this progression. The role of hormone receptors in this direction is one of the most widely studied phenomenon as they tend to govern various physiological functions during this progression. Epithelial proliferation is marked by binding of estrogen to its receptors,however progesterone is responsible for inhibition of growth and differentiation of cells. It may be noted that ovulating women producing progesterone are protected against endometrial cancer. In contrast, irregularly in hormone receptor functions can end up in various malignant conditions[3].

Dependency of endometrial carcinoma on hormonal receptors has also helped to differentiate it into two types, *viz.*, estrogen-dependent (type 1) and estrogen independent (type 2) respectively[4]. Of the two, type-1 endometrial cancer is known to be resulted by excessive production of estrogen. This generally occurs just near the time of menopause, especially in women receiving estrogen supplementation without the balancing supplementation of progesterone resulting in a disturbed estrogen-progesterone ratio and subsequently in endometrial cancer[5]. On the other hand, type-2 endometrial cancer is independent of estrogen levels and generally occurs in post-menopausal women in older ages[6].

Evaluation of estrogen and progesterone receptors plays an important role in prognosis of endometrial cancer. They are helpful in determining the survival length and function[7,8]. ER/PR positivity helps to determine the need for hormonal treatment for endometrial cancer[9]. Study of ER/PR in pre-cancerous and cancerous conditions also helps to study the tumour biological behaviour which determines the subsequent pathways for appropriate treatment strategy formulation[10].

METERIALS AND METHOD

The study was conducted at T S Misra Hospital,Lucknow in collaboration with the King George's medical University,Lucknowfrom 1 stJan 2021 to 30 June 2022 (Total duration 1.5 yrs).The study was conducted on 22histopathologically proven cases of endometrial carcinoma in the age group(30 to 80 yrs).Those cases of endometrial carcinoma with inadequate sample or with history of pregnancy was excluded from study.Informed consent was taken from the patients included in study.All the demographic details,clinical profile,medical,surgical, obstetric,family and personal history was taken from the clinical records and detailsof investigations and treatment availed was noted.Immunohistochemistry for ER and PR status was done using IHCprotocol.ER and PR staining reactions was evaluated as brown nuclear staining in the glandular epithelium and stroma of all cases as a positive reactions.Staining was scored taking consideration of both intensity as well as percentage of cells stained in glands and stroma.

RESULTS

Most patients were in the age group 50 to 60 years. Youngest patient was 28years old.No patient was found between 30 to 40 years.The oldest age was 78 .Mean age was 57.77 yrs.

Per vaginum bleeding is the most common complaint (21/22). Only one patient did not give history of per vaginum bleeding followedbypain abdomen (7/22).

Except for two (9.09 %) women, all the other women were married.

There were 3 (13.6%) nulliparous, 4 (18.18%) primiparous, 4 (18.18%) para 2, 5 (22.72%) para 3 and 6 (27.2%) para 4 and above women.

Majority of women (n=18; 81.81%) were in their post-menopausal state whereas 4 (18.18%) women were in postmenopausal state.

Among 22 malignant cases, maximum (n=19/22; 86.4%) were endometrial adenocarcinoma. There was 1/22 (4.5%) case each diagnosed as endometrial carcinoma villoglandular type, serous endometrial carcinoma and endometrioid endometrial carcinoma NOS respectively

Out of 22 malignant cases, more than three-fourth (77.3%) were low grade/well differentiated, 4 (18.2%) were moderate grade/moderately differentiated and only 1 (4.5%) was high grade/poorly differentiated carcinoma (Table 5).

15/17(88.23%) well differentiated cases showed estrogen receptor positivityand 14/17(82.3%)cases showed progesterone receptor positivity.4/4(100%)of moderately differentiated endometrial carcinoma showed estrogen and progesterone receptor positivity. 1/1(100%) of poorly differentiated endometrial carcinoma were estrogen receptor negative(0%) but progesterone receptor positive. No significant association of PR expression status with grade of endometrial carcinoma was observed (p=0.600). However, as compared to high grades, ER expression in moderate and low grades was significantly higher (p=0.030) (Table 6).

With no invasion of myometrium ER and PR expression is 100% positive (8/8),ER and PR positivity decreases with the increasing depth of myometrium (Table 7).

DISCUSSION

Endometrial carcinoma not only is amongst the most common cancers in women but also carries high mortality rate. In the past few decades, there has been a high increase in the incidence of endometrial cancer, particularly in developing world, as a result of increasing life-expectancy and changing lifestyle contributing to an increase in obesity which is a recognized risk factor for endometrial cancer[1,11,1]. In the present study most of the cases were in the age group 51to 60 yrs. In one such study, Goswami*et al.*[12] carried out their study in 34 diagnosed cases of endometrial carcinoma. Consecutively, the average age of patients in their study was also higher (60.36 years). Some other studies conducted in an exclusive population of endometrial carcinoma cases have also reported the mean age of patients to be ten or more years higher as compared to that in the present study[13,14,15].

Vaginal bleeding is the most common symptom in endometrial carcinoma which is due to postmenopausal bleeding in majority of cases. In present study majority of cases were endometroid endometrial Carcinoma (19/22).However villoglandular (1/22), serous (1/22), NOS (1/22) are also present in minority. In the present study 17/22 (77.3%) cases being low grade (well differentiated) and only 1 (4.5%) case being high grade (poorly differentiated) carcinoma. Similar to the present study, RamanaKumari*et al.*[16] also reported a dominance of low grade (66%) but had moderate grade as the least common one (12%). However, in the study by Zidan*et al.*[17], all the cases were endometrioid carcinoma but representation of all the three grades was much homogenous with grade 1, 2 and 3 being represented by 38.9%, 27.8% and 33.3% cases respectively. In the study by Socolov*et al.*[18] too though there was a dominance of endometrial adenocarcinoma of endometrioid type and they also did not have any cases in higher grade (23 WD, 22 MD). Moreover, in their study there were adequate number of non-endometrioid adenocarcinoma (9 clear cell and 10 serous type). Similar to the present study, Masjeed*et al.*[19] too found endometrioid type to be most dominant type (78.6%) and also found low grade (50%) to be most common and high grade (9.1%) being least common.

Ramana kumara et al.[16] in their study the expression rate for ER and PR was 58% and 76% respectively in malignant cases Though, in the present study, the expression rate, in malignant cases, it was much higher than that in their study. The reason for this could be the fact that in the present study, we assessed

expression of ER and PR in both stroma as well as epithelium and we considered any specimen to be positive even if it was positive in either of these two. Moreover, in the present study, we considered even the low intensity (score 1) as positive.

In the present study we see that with no invasionof myometrium ER and PR expression is 100% positive and as the tumour invades deeply in the myometrium ER and PR positivity decreases where as in Mangal S et al.[20] study PR positivity reduced as the depth of invasion increased from 100% (no invasion) to 66% (2/3rd invasion), but it was not so with ER.However this was in agreement with study done by Mahdi et al.[21].In Kamal et al study there is positive correlation of decrease PR positivity and increase in ER positivity with myometrial invasion.

CONCLUSION

PR expression is associated with longer disease free survival as apposed to ER whose higher levels are associated with shorter disease free survival.ER and PR are the important prognostic biomarkers to predict response to the anti hormonal therapy.

ACKNOWLEDGEMENT

I would to like to acknowledge my Prents and family , teachers ,seniors and juniors, Department of Pathology T S Misra Medical College And Hospital and King George's Medical University. UP, Lucknow for their continuous support guidance, cooperation, motivation which helped me in completing my work.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
2. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428.
3. Moore RL, Dai Y, Faller DV. Sirtuin 1 (SIRT1) and steroid hormone receptor activity in cancer. J Endocrinol. 2012;213(1):37–48.
4. Bokhman JV. Two pathogenetic types of endometrial carcinoma. GynecolOncol. 1983;15:10–7.
5. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol. 1995;85:304–13.
6. McMeekin DS. Corpus: Epithelial Tumors, in Principles and Practice of Gynecologic Oncology Vol. 5. Lippincott Williams & Wilkins; Baltimore: 2009. Crossref#12
7. Srijaipracharoen S, Tangjitgamol S, Tanvanich S, Manusirivithaya S, Khunnarong J, Thavaramara T, *et al*. Expression of ER, PR, and Her-2/neu in endometrial cancer: a clinicopathological study. Asian Pac J Cancer Prev. 2010;11:215–20.
8. Kobel M, Atenafu EG, Rambau PF, Ferguson SE, Nelson GS, Ho TC, *et al*. Progesterone receptor expression is associated with longer overall survival within high-grade histotypes of endometrial carcinoma: A Canadian high risk endometrial cancer consortium (CHREC) study. GynecolOncol. 2016;141:559–63.
9. Smith J, Jhingran A. Comprehensive Gynecology. In: Lentz GL, Gershenson DM, R A, Katz VL, editors. Principles of Radiation Therapy and Chemotherapy in Gynecologic Cancer. 6. Mosby; 2013. Crossref#15

10. Masjeed NMA, Khandeparkar SGS, Joshi AR, Kulkarni MM, Pandya N. Immunohistochemical Study of ER, PR, Ki67 and p53 in Endometrial Hyperplasias and Endometrial Carcinomas. J ClinDiagn Res. 2017 Aug;11(8):EC31-EC34.
11. Silverberg SG. Problems in the differential diagnosis of endometrial hyperplasia and carcinoma. Mod Pathol. 2000 Mar;13(3):309-27.
12. Goswami S, Sen A, Biswas M. Association of thehormonal receptor status of endometrial carcinomas with the markersoftumor aggression: A comparison with similar studies in developednations. Med J DY Patil Univ2017;10:334-8.
13. El Sabaa EM, Talaat IM. ER and PR Expression in Endometrial Carcinoma in DiabeticVersusNon Diabetic Patients. Egyptian J. Pathol. 2017; 37(1): 1-7.
14. Salama A, Arafa M, ElZahaf E, Shebl AM, Awad AAE, Ashamallah SA, *et al*. Potential Role for a Panel of Immunohistochemical Markers in the Management of Endometrial Carcinoma. J PatholTransl Med. 2019 May;53(3):164-172.
15. Odetola SS, Ajani MA, Iyapo O, Salami AA, Okolo CA. Hormonal receptor expression in endometrial carcinoma: A retrospective immunohistochemical study in a Nigerian tertiary hospital. J West AfrColl Surg2020;10:1-4.
16. RamanaKumari P, Renuka IV, Apuroopa M, Chaganti PD. A study of expression of estrogen and progesterone receptor, in atrophic, hyperplastic and malignant endometrial lesions, with emphasis on relationship with prognostic parameters.Int J Res Med Sci 2015;3:3318-25.
17. Zidan AA, Hassan AA, Seadah SS, Ibrahim EH, Attiah SM. Selected immunohistochemical prognostic factors in endometrial hyperplasia versus carcinoma. Journal of American Science. 2015;11(4):14–22.
18. Socolov D, Socolov R, Lupascu IA, Rugina V, Gabia O, Garauleanu DM, Carauleanu A. Immunohistochemistry in Endometrial Hyperplasia and Endometrial Adenocarcinoma. Rev Med ChirSoc Med Nat Iasi. 2016 Apr-Jun;120(2):355-62.
19. Wan J, Gao Y, Zeng K, Yin Y, Zhao M, Wei J, Chen Q. The levels of the sex hormones are not different between type 1 and type 2 endometrial cancer. Sci Rep 2016; 6: 39744.
20. Mangal S, Sharma M, Manjari M, Mannan R, TandonS : Expression Of Androgen Receptor, Estrogen Receptor And Progesterone Receptor In Endometrial Carcinoma (Immunohistochemical Study) Anmals of Pathology and Laboratory Medicine, 2020; 7(5): A248-A252.
21. Mahdi Z,AbdulfatahE,PerdeshiV,HassanO,ShultzD,MorrisR,etal.The impact ofAndrogen receptor expression on endometrial carcinoma.Recurrance and survival.Int J GynecolPathol 2017 sep;36(5);405-11

Table 1:Distribution of number of Cases according to age (n=22)

Age group	No of cases	Percentage
<30	1	4.54%
31—40	0	0%
41—50	3	13.63%
51—60	10	45.45%
61—70	5	22.8%
>70	3	13.63%

Table2:Distribution of number of Cases according to Chief Complaints (n=22)

Chief complaints	No of cases
Bleeding per veginum	**21**
Pain abdomen/dysmenorrhea	**07**
menorrhagia	**04**
Postmenopausal bleed	**17**
Discharge per vagina	**02**

Table 3: Marital, Obstetric and Menstrual Status

SN	Status	No. of women	Percentage
1.	Marital Status		
	Married	20	90.90%
	Unmarried	2	9.09%
2.	Parity		
	P0	3	13.6%
	P1	4	18.18%
	P2	4	18.18%
	P3	5	22.72%
	P4 and above	6	27.27%
3.	Menstrual status		
	Premenopausal	04	18.18%
	Postmenopausal	18	81.81%

Table 4: Distribution of cases according to histopathological diagnosis

Malignant	N=22	percentage
Endometrial adenocarcinoma	19	86.4%
Endometrial carcinoma villoglandular	1	4.5%
Serous endometrial carcinoma	1	4.5%
Endometroid endometrial carcinoma NOS	1	4.5%

Table 5: Distribution of Cases according to Grade of Malignancy (n=22)

SN	History	No. of women	Percentage
1.	Low grade/WD(well differentiated)	17	77.3
2.	Moderate grade/MD(moderately differentiated)	4	18.2
3.	High grade/PD(Poorly differentiated)	1	4.5

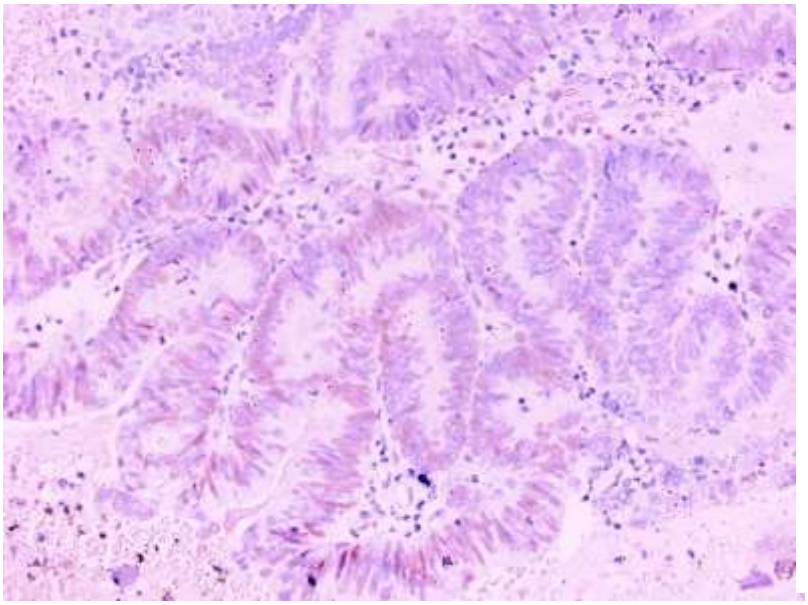
Table 6: Comparison of ER/PR Status among different grades of Malignancy

SN	Receptor	Grade	Positive		Negative		Statistical significance	
			No.	%	No.	%	χ^2	'p'
1.	ER	Low/WD	15	88.2	2	11.8	7.015	0.030
		Moderate	4	100	0	0		

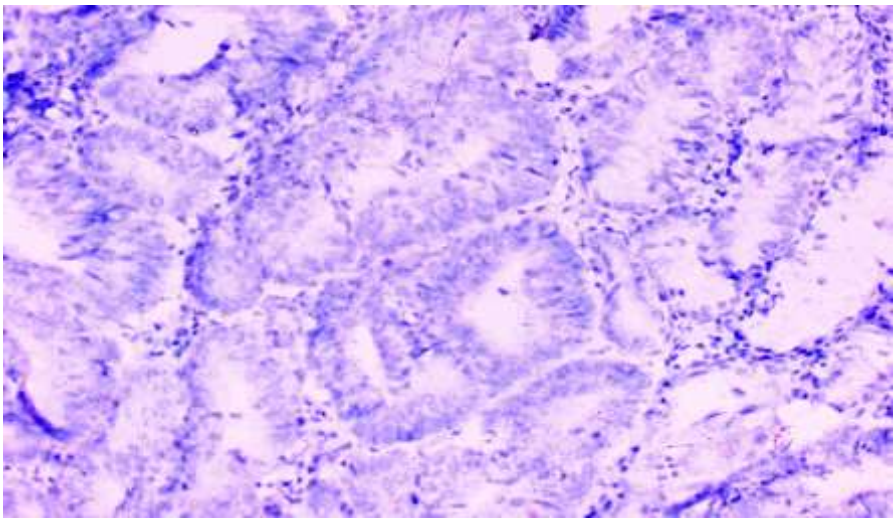
		High/PD	0	0	1	100		
2.	PR	Low/WD	14	82.4	3	17.6		
		Moderate	4	100	0	0	1.022	0.600
		High/PD	1	100	0	0		

TABLE 7: ER and PR expression with myometrial invasion

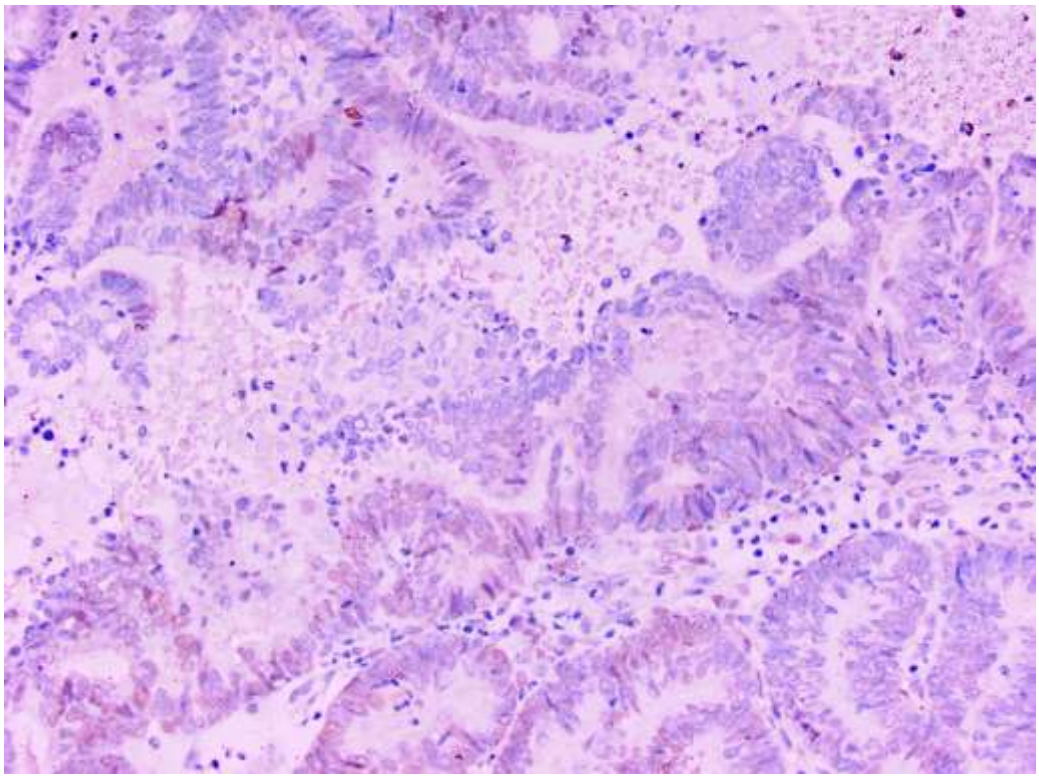
MYOMETRIAL INVASION	NO OF CASES	ER	PR
One third (33%)	**12**	**10(83.3%)**	**10(83.3)**
Half (50%)	**2**	**1 (50%)**	**1 (50)**
No invasion	**8**	**8(100)**	**8(100%)**



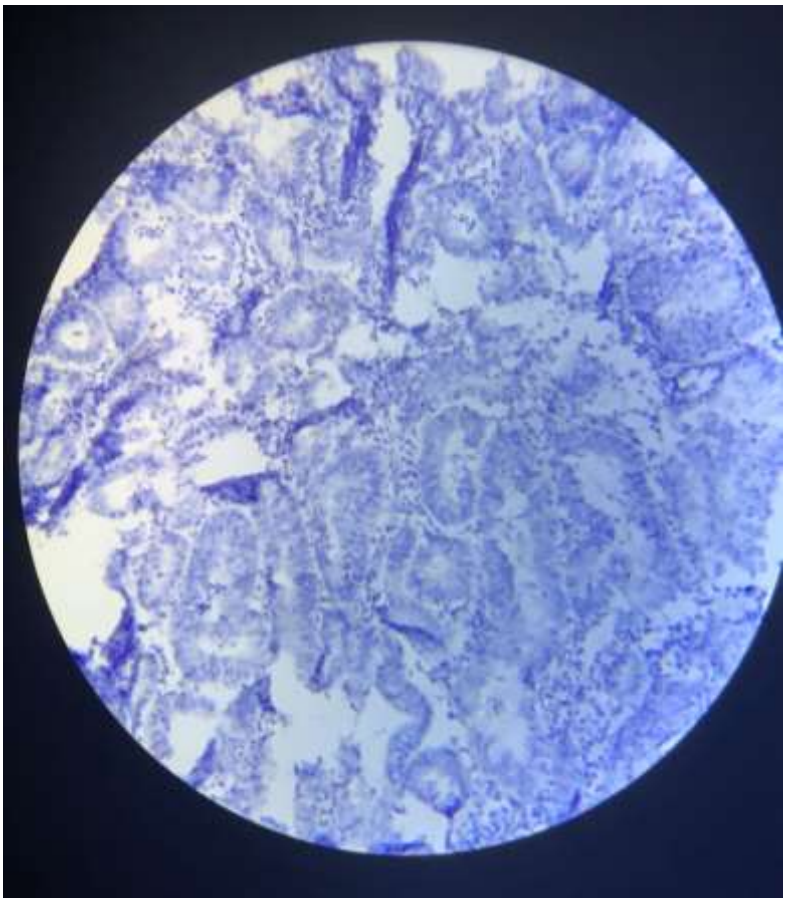
ENDOMETRIAL CA (ENDOMETROID VARIANT) PR 10 X FAINT POSITIVITY PR



ENDOMETROID ENDOMETRIAL CA ER 20 X



ENDOMETRIAL CA VILLOGLANDULAR ER 20 X



SEROUS ENDOMETRIAL CA 10X NEGATIVE ER AND PR