ORIGINAL ARTICLE DOI: https://doi.org/10.52206/jsmc.2024.14.4.940 OPEN ACCESS

Expression of Estrogen Receptor, Progesterone Receptor, and Human Epidermal Receptor 2 in Endometrial Carcinoma

Shamsul Hadi,[1] Rabia Mukhtar,[2] Nasim Aslam Ghumman,[3] Aisha Jamil,[1] Maria Tasneem Khattak,[1] Latifullah Khattak,[4] Iqbal Muhammad[1]

1. Rehman Medical Institute, Peshawar, KP Pakistan.
2. Shaikh Zayed Hospital, Lahore, Pakistan.
3. Rashid Latif Medical College, Lahore, Pakistan.
4. Allama Iqbal Open University, Islamabad, Pakistan.

ABSTRACT

Background: Endometrial cancer EC is the most common gynecologic malignancy diagnosed globally as well as in South Asia, with most cases diagnosed as low-grade, early-stage disease. Although most patients get cured with current treatment strategies, a subset of patients develop recurrent disease. Detailed and extensive studies performed by researcher in the past. Briefly an EC is one of the common cancers of the uterus. It arises from continuous endometrial proliferation due to estrogen stimulation; mainly in postmenopausal life.

Objective: To evaluate the expression of ER, PR and HER2 in Endometrial Carcinoma

Materials and Methods: This was a prospective, observational study conducted at the Histopathology department, RMI the largest public sector tertiary care hospital in Peshawar, from 20th May 2023 to 20th march 2024. A non-probability purposive sampling technique was used to include 32 cases of EC. The specimens were tested for ER, PR and HER-2 expression using immunohistochemical analysis. Data was analyzed in SPSS and the significance of association of expression of the receptors with histological types, grades and stages of the tumor was assessed.

Results: Significant association of Her-2 overexpression with histological types and grades of EC was seen, whereas the association of ER and PR expression with histological types, grades and stage of EC was statistically insignificant.

Conclusion: This study investigated the status of ER, PR, and HER-2 in Endometrial Cancer at RMI KPK. The results showed that ER and PR positivity was consistently high in Type-I EC, consistent with literature. HER-2 positivity was associated with more aggressive features.

Keywords: Endometrial Carcinoma, ER, PR, HER-2

This article may be cited as: Hadi S, Mukhtar R, Ghumman NA, Jamil A, Khattak MT, Khattak L, et al. Expression of Estrogen Receptor, Progesterone Receptor, and Human Epidermal Receptor 2 in Endometrial Carcinoma. J Saidu Med Coll Swat. 2024;14(4):296-301. DOI: https://doi.org/10.52206/jsmc.2024.14.4.940

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy diagnosed globally as well as in South Asia, with most cases diagnosed as low-grade, early-stage disease.[1] Although most patients get cured with current treatment strategies, a subset of patients develop recurrent disease.[2] Detailed and extensive studies performed by researcher in the past.[3] Briefly an EC is one of the common cancers of the uterus[4]. It arises from continuous endometrial proliferation due to estrogen stimulation; mainly in postmenopausal life.[4] EC is the most common malignancy worldwide and almost 417,000 new cases were registered in 2020 that was the top 10 cancers among the women.[5] Over 60,000 new cases diagnosed yearly in the USA of uterine malignancy.[6] The most i.e. forth common cancer out of these are EC 83% and the most lethal of them Papillary serous carcinoma and clear cell carcinoma 4-6% and 1-2% respectively.[3-4] Bokhman JV et al. 1983 describes their types, etiology, clinical signs and symptoms and treatment approach[7]. EC up to 3% malignancies in women in Pakistan.[8]

Correspondence: Dr. Maria Tasneem Khattak
Associate Professor,
Rehman Medical Institute, Peshawar, KP Pakistan.
Email: accesstomaria@yahoo.com

Received: March 27th, 2024 - 1st Revision: May 21st 2024
2nd Revision: June 12th 2024 - 3rd Revision: June 23rd 2024
Accepted: July 19th, 2024

Immunohistochemistry used widely in the diagnosis and management of these malignancies. Currently, prediction tools rely on clinical, pathologic, and molecular characteristics and their performance is far from ideal. Therefore, new prognostic biomarkers are needed to improve patient risk classification. Immunohistochemistry his a wide role in the diagnosis, prognosis and treatment of multiple oncogenic malignancies.[9]

Molecular classification of endometrioid endometrial carcinoma EEC[10,11]

- Four molecular groups include POLE-ultra-mutated, MMR-deficient, P-53 mutant and NSMP no specific molecular profile endometrioid carcinomas.
- Molecular classification correlates with clinical outcomes and prognosis. P53-mutant poor prognosis, MMR-deficient intermediate, NSMP intermediate to excellent and POLE ultra-mutated excellent prognosis.
- Polymerase ε POLE ultra-mutated groups have a better prognosis despite showing high grade morphology.
- Around 1/3rd cases of NSMP display CTNNB1 mutation usually associated with nuclear expression of β-catenin.

ER/PR and HER-2 are widely used as a supportive marker for the prognosis management of luminal breast cancer.[13] ER/PR as a theranostic marker of lymph node metastasis in endometrioid carcinoma.[14] Interpretation of ER/PR outlined by ASCO / CAP recommendation on estrogen and progesterone receptor testing in breast cancer.[15] The hormone receptors most frequently expressed in mammary carcinoma are for sex steroid hormones which are involved in breast cancer behavior and management.[16] An elderly patients its appearance in ER +ve breast cancers.[17] PR expression is associated with improved clinical consequences, self-determining from ER[18] ER positivity indicates a better prognosis and a higher likelihood of the cancer being estrogen-dependent. ER-positive tumors tend to be less aggressive and more responsive to hormone therapy.[18-19] Similar to ER, PR positivity is associated with a better prognosis and a higher likelihood of the cancer being hormone-sensitive. PR-positive tumors may benefit from hormone therapy.[19]

HER-2 is the human epidermal growth factor receptor 2, also called ERBB2 HER-2 gene Cytoplasmic tyrosine kinase is constitutively active when overexpressed due to homo heterodimerization.[19]

The benefits of positivity including, improved treatment outcomes: ER and PR positivity may enhance the effectiveness of hormone therapy, while HER2 positivity can benefit from targeted therapies.[17-19] Moreover better prognosis: ER and PR positivity are generally associated with less aggressive disease and improved survival rates. Personalized treatment: Determining the status of these biomarkers helps guide personalized treatment strategies, leading to more effective management and improved patient outcomes.[15-20]

By investigating the expression of these biomarkers, the study aims to contribute to a better understanding of the molecular mechanisms underlying endometrial carcinoma, which can ultimately lead to improved diagnosis, treatment, and patient outcomes.

MATERIALS AND METHODS

It is a prospective, observational study carried out at the Histopathology department, RMI, a tertiary care hospital in Peshawar. All patients' samples receiving at the Department of Pathology, RMI Peshawar, from 20th May 2023 to 20th March 2024. Tissue samples were stored at Histo-lab and analyzed according to standard protocols, including formalin-fixed paraffin-embedded (FFPE) processing, sectioning, and immunohistochemical (IHC) staining, with appropriate quality control measures in place. EC cases were collected from surgical specimens obtained from Departments of Obstetrics and Gynecology at RMI and nearby hospitals. Clinical data collected include age, presenting symptoms, comorbidities diabetes, hypertension, etc., seizures, and other relevant details. The ethical approval for this study granted by the Research Ethics Committee of Rehman Medical Institute RMI/Article/Histo-150 April 2022.

A total of 32 samples were collected using a cross-sectional study design. The sample size was calculated using the formula: n = Z^2 * p * (1-p) / E^2, where n is the sample size, Z is the Z-score corresponding to the desired level of confidence, p is the expected proportion of the population with the characteristic of interest, and E is the desired level of precision. CL 1.96 95% confidence level, p = 0.05, Sample size was calculated as, n = 1.96^2 * 0.05 * 1-0.05 / 0.05^2 ~ 32

The inclusion criteria was, total Abdominal Hysterectomy with Bilateral Salphingo-Oophorectomy TAH-BSO and Veginal hysterectomy, histologically confirmed endometrial carcinoma and availability of tissue blocks and relevant clinical data

The following was the exclusion criteria, autolyzed specimens and endometrial biopsy specimens were excluded, insufficient tissue material and incomplete clinical data.

The SPSS-22 was used for analyzing data. The chi-square test was performed to observe statistical significance among variables.

IHC analysis was performed to determine the expression of HER-2, ER, and PR in the tissue samples. HER-2 status was categorized into three groups based on the intensity of membrane staining: Negative (0-1+): No or weak staining in <10% of tumor cells, Borderline or Equivocal (2+): Weak to moderate staining in =10% of tumor cells, and Positive (3+): Strong staining in =10% of tumor cells. Hormone receptor status was grouped into two main categories: ER and PR Positive: Tumors with positive staining (=1% nuclear staining) for both ER and PR, and ER and PR Negative: Tumors with negative staining (<1% nuclear staining) for both ER and PR. The expression levels of these biomarkers were then correlated with clinic-pathological parameters, including tumor grade, stage, and patient survival rates, to investigate their potential prognostic value in endometrial carcinoma. The P value of = 0.05 was considered as significant. The data were showed in tables and graphical illustration.

RESULTS

Thirty two women were diagnosed with EC from 20th May 2023 to 20th March 2024. The mean age of patients was 55.5 ± 16.5 years. Six (19%) women were below 50 years old while, the majority of them i.e., 26 81% of the patients were above 50 years old at the time of presentation Figure 1. Hypertension was the most common co-morbidity, affecting 21.5% of the patients in the study. A majority of patients 58.5% reported no known comorbidities.

Females with a positive family history of endometrial carcinoma accounted for 34.6% of the study population. Patients with a family history of endometrial cancer have a relative risk of 1.82 95% confidence interval CI, 1.65-1.98 compared to patients without a family history of endometrial cancer. A family history of colon cancer also increases the risk of endometrial cancer, but a family history of breast cancer, ovarian cancer or cervical cancer does not increase the risk.

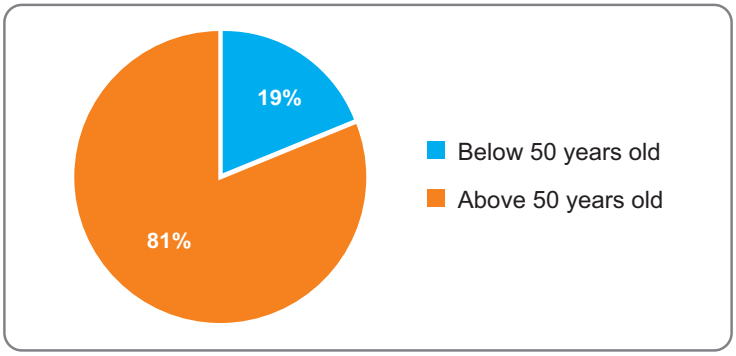


Figure 01. Age Category

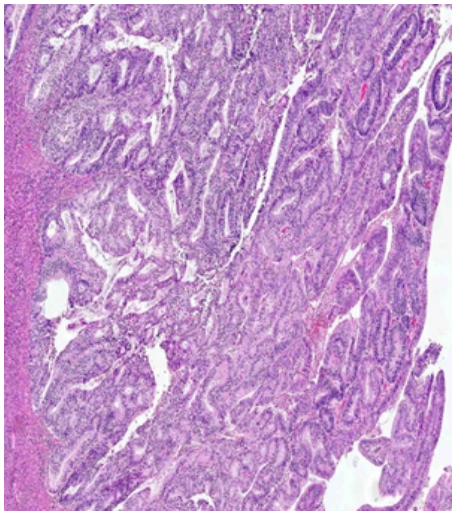


Figure 02. Confluent glands with papillary growth H&E x10

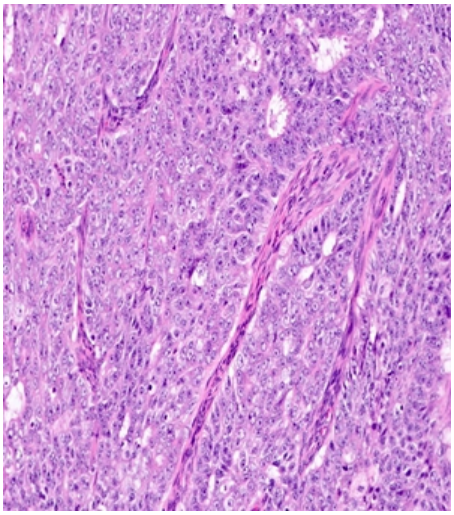


Figure 03. Solid growth with foci of confluent and tight microacinar structures. H&E x10

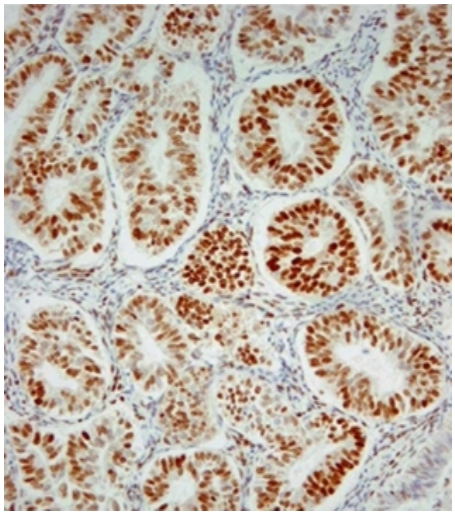


Figure 04. Diffuse ER expression in EC-1 IHC x40 (Nuclear staining)

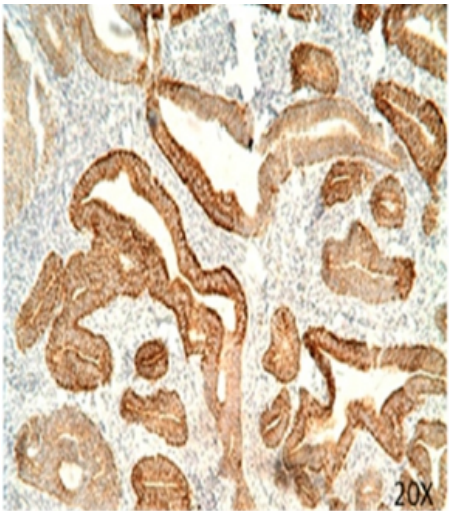


Figure 05. HER-2 Expression IHC x40 (membrane staining)

Table 01. ER, PR and HER-2 Expression

	%	Estrogen receptor			Progesterone receptor			HER-2		
		Positive %	Negative %		Positive %	Negative %		Positive %	Negative %	
EC	75.4	42.85	44.6	0.351	58.9	28.6	0.604	92.9	7.1	0.002
SC	10.8	0	5.4		3.6	1.8		3.6	1.8	
CCC	6.2	0	1.8		0	1.8		0	1.8	
MC	6.2	0	1.8		0	0		0	1.8	
Carcinosarcoma	6.2	0	1.8		1.8	1.8		0	3.6	
EC Endometrial carcinoma, SC Serous carcinoma, CCC clear cell carcinoma and MC mucinous carcinoma.										
Grading										
I	19.6	30.4	0.222	30.4	19.4	0.538	0	50	0.000	
II	12.5	19		19	5.4		0	28.6		
III	8.9	12.5		12.5	8.9		7.1	14.3		
Total				31	31		31			
Staging										
I	33.9	37.5	0.519	48.2	23.2	0.668	5.4	66.1	0.774	
II	5.4	8.9		7.1	7.1		0	14.3		
III	3.6	8.9		8.9	3.6		1.8	10.7		
IV	1.8	0		1.8	0		0	1.8		

P =0.05 considered significant.

In the Tab 01, shows endometrioid adenocarcinoma 75.4% is the commonest histopathological variant of EC, followed by Serous 10.8%, and clear cell 6.2%. Moreover 50% of the specimens are positive for both ER and PR, while 41.5% negative. Only, 4.6% patients were positive for ER only while 3.1% patients were positive for PR only. Her-2 was positive in 7.1% and negative in 92.9%. Both ER and PR positive were 48.21%. CCC is negative for all markers. PR positive cases were 30.4% in grade I, 19.6% 30.4% in grade II and 12.5% in grade III. There was no HER-2 neu positive case in grade I and II. III. Very significant association was seen between grades of EC and Her-2 positive receptors with p value of 0.000., whereas the p-values of ER and PR were not significant. Table 01

DISCUSION

Endometrial cancer is a disease that affects postmenopausal women, with an incidence of 2.4% and mortality of 1.7% of all newly diagnosed malignancies. It is the most common gynecological cancer in the United States, with an estimated 70,000 new cases diagnosed annually. In the present study the majority fig 01 81% of patients were above 50 year old i.e. post-menopausal.[1214] These result also confirmed by various previous studies. However it can occur in any age group even during pregnancy. As our study shows that type-1 i.e. well differentiated most commonly occur in 40 year old and early age women, contrariwise type-2 mostly occur in elderly women.[14]

The endometrium is exquisitely sensitive to steroid hormones, and hormonal changes have a profound impact on the growth and development of endometrial tissue. Receptor status is anticipated to be a key factor in the classification, treatment, and prognosis of endometrial cancer, guiding clinical decisions and patient outcomes. The expression of ER and PR have been reflected to be associated with favorable prognosis in the majority of type-1 EC.[12,13] Although, the prognostic effect of ER and PR is still unclear. In our study both ER and PR protein were expressed fig 03 and fig 04 in the cell nucleus. The positive expression ER and PR were 43 and 59 percent tab 01 respectively. These results are similar as in previous studies.[13,15,16]

Studies on the molecular heterogeneity of breast cancer have shed light on the complex biology of the disease, driving progress and paving the way for targeted therapies that improve patient outcomes. "Endometrial cancer molecular subtypes exhibit distinct differences in prognosis, clinical characteristics, histopathology, and molecular behavior. Notably, the subtypes defined by ER, PR, and HER-2 status show significant variation, with the HER-2 subtype displaying particularly aggressive features.[17]

The above study was conducted at RMI KPK showing status of ER, PR and Her-2/ neu in EC. In literature, ER and PR positivity is consistently seen in Type-I EC.[24] It was found that 44.6% cases were positive for *ER,*

66.1% cases for PR and 7.1% were HER-2/neu positive. Similar results have been seen in other studies[18.] According to Sirijaipracharoen et al., included 108 patients, ER, PR and HER-2 expression in 59.3%, 65.7% and 2.8% respectively[1] In this study results showing that, in low grade tumors grade I and II, total ER positive cases were 35.7%, PR positive cases were 53.6% and HER-2/neu were nil 0.0%. In grade III tumors, ER positive cases were only 8.9%, PR positive were 7 12.5% and HER-2 cases were 7.1%. These results are in concordance with previous studies.[1,18-19] According to it, ER positive cases in Grade I and II were 36.2%, PR positive cases were 21.44% and HER-2 positive cases were 4.3%.[19]

HER-2 positive results have previously been observed in high-grade malignant tumors and serous carcinomas.[20] This study shows that 18% of serous carcinomas have increased HER-2 expression. In this study, none of the three serous carcinomas were positive for HER-2 66.6%. This percentage is much higher than the study mentioned above. This may be due to the small sample size. Other studies have also shown high levels of HER-2 overexpression in high-grade EC. Santin et al.[21] Approximately 80% of SCs were found to express HER-2[21-23] Purtle et al., Barchak et al.[22] Khalifa et al. and Coronado et al found HER-2/neu expression in 40%, 25%, and 18%, respectively.[23]

CONCLUSION

This study investigated the status of Estrogen Receptor ER, Progesterone Receptor PR, and Human Epidermal Growth Factor Receptor 2 HER2 in Endometrial Cancer EC at RMI KPK. The results showed that ER and PR positivity was consistently high in Type-I EC, consistent with literature Oncotarget, 2017.

HER2/neu positivity was associated with more aggressive features. These findings highlight the importance of hormone receptor and HER2 status in EC classification, prognosis, and treatment strategies.

Further research is needed to explore targeted therapies and improve patient outcomes.

Abbreviation

EC Endometrial Carcinoma
EEC Endometrioid Endometrial Carcinoma
ER Estrogen Receptor
PR Progesterone Receptor
HER-2 Human Epidermal Growth Factor receptor 2
RMI Rehman Medical Institute
KPK Khyber Pakhunkhwa

Ethical Consideration

This study was approved by the ethical board of Rehman Medical Institute, Peshawar, Pakistan.

Funding

There is no role of any funding agency in this study.

Conflict of Interest

Authors declared no conflict of interest

REFERENCES

1. 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;111:215-20. PMID: 20593959
2. Przewoźny S, Rogaliński J, de Mezer M, Markowska A, Markowska J, Żurawski J. Estrogen Receptor ER and Progesterone Receptor PgR Expression in Endometrial CancerAn Immunohistochemical Assessment. Diagnostics. 2024;143:322. DOI: https://doi.org/10.3390/diagnostics14030322
3. Cagnacci A, Londero AP. Hormone therapy in endometrial cancer survivors: time for a change. Gynecol Endocrinol. 2022;3810:7956. DOI: https://doi.org/10.1080/09513590.2022.2128105
4. Wang C, Tran DA, Fu MZ, Chen W, Fu SW, Li X. Estrogen receptor, progesterone receptor, and HER2 receptor markers in endometrial cancer. J Cancer. 2020;117:1693. DOI: https://doi.org/10.7150/jca.41943
5. Cagnacci A, Londero AP. Hormone therapy in endometrial cancer survivors: time for a change. Gynecol Endocrinol. 2022;3810:7956. DOI: https://doi.org/10.1080/09513590.2022.2128105
6. Mahdy H, Casey MJ, Crotzer D. Endometrial Cancer. In: StatPearls. StatPearls Publishing; 2021.
7. Recent Multiomics Approaches in Endometrial Cancer. Int J Mol Sci. 2022;233:123-7. DOI: https://doi.org/10.3390/ijms23031237
8. Waqar S, Khan SA, Sarfraz T, Waqar S. Expression of Estrogen Receptors ER, Progesterone Receptors PR and HER-2/neu receptors in Endometrial Carcinoma and their associations with histological types, grades and stages of the tumor. Pak J Med Sci. 2018;342:266. DOI: https://doi.org/10.12669/pjms.342.13637
9. Kong W, Tu Y, Jiang P, Huang Y, Zhang J, Jiang S, et al. Development and Validation of a Nomogram Involving Immunohistochemical Markers for Prediction of Recurrence in Early Low-Risk Endometrial Cancer. Int J Biol Markers. 2022;374:395-403. DOI: https://doi.org/10.1177/03936155221132292
10. Modi RD. The cancer genome atlas-TCGA molecular classification: A changing paradigm in the management of endometrial cancers. Current Medicine Research and Practice. 2023;132:69-73. DOI: https://doi.org/10.4103/cmrp.cmrp_125_22
11. Britton H, Huang L, Lum A, Leung S, Shum K, Kale M, et al. Molecular classification defines outcomes and opportunities in young women with endometrial carcinoma. Gynecol Oncol. 2019;1533:487-95. DOI: https://doi.org/10.1016/j.ygyno.2019.03.098

12. Tong N, Kumar A, Gelowitz G, Tinker A, Holloway C, Ko J. Impact of the adjuvant management and risk factors on survival in FIGO stage 3 endometrial cancer patients. Frontiers in Oncology. 2023;13:1035511. DOI: https://doi.org/10.3389/fonc.2023.1035511
13. Khan S, Varricchio A, Ricciardelli C, Yool AJ. Invasiveness of endometrial cancer cell lines is potentiated by estradiol and blocked by a traditional medicine Guizhi Fuling at clinically relevant doses. Frontiers in Oncology. 2023;12:1015708. DOI: https://doi.org/10.3389/fonc.2022.1015708
14. Wang C, Tran DA, Fu MZ, Chen W, Fu SW, Li X. Estrogen receptor, progesterone receptor, and HER2 receptor markers in endometrial cancer. Journal of Cancer. 2020;117:1693. DOI: https://doi.org/10.7150/jca.41943
15. Tomica D, Ramić S, Danolić D, Šušnjar L, Perić-Balja M, Puljiz M. Impact of oestrogen and progesterone receptor expression in the cancer cells and myometrium on survival of patients with endometrial cancer. J Obstet Gynaecol. 2018;381:96-102. DOI: https://doi.org/10.1080/01443615.2017.1328591
16. Gupta PK, Singh S, Gupta R, Lal P, Rastogi N. A Fifteen Years Audit of Endometrial Cancer Referred for Adjuvant Treatment to a Tertiary Care Hospital in Northern India. Journal of Clinical & Diagnostic Research. 2023;177. DOI: https://doi.org/10.7860/JCDR/2023/63369.18095
17. Lapinska-Szumczyk S, Supernat A, Majewska H, Gulczynski J, Luczak A, Biernat W, et al. HER2-Positive Endometrial Cancer Subtype Carries Poor Prognosis. Clin Transl Sci. 2014;76:482-8. DOI: https://doi.org/10.1111/cts.12207
18. Triarico S, Capozza MA, Mastrangelo S, Attinà G, Maurizi P, Ruggiero A. Gynecological cancer among adolescents and young adults AYA. Annals of translational medicine. 2020;86. DOI: https://doi.org/10.21037/atm.2020.02.41
19. 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;111:215-20. PMID: 20593959
20. Slomovitz BM, Broaddus RR, Burke TW, Sneige N, Soliman PT, Wu W, et al. Her-2/neu overexpression and amplification in uterine papillary serous carcinoma. J Clin Oncol. 2004;2215:312632. DOI: https://doi.org/10.1200/JCO.2004.11.154
21. Santin AD, Bellone S, Gokden M, Palmieri M, Dunn D, Agha J, et al. Overexpression of HER-2/neu in uterine serous papillary cancer. Clin Cancer Res. 2002;85:12719. PMID: 12006548
22. Yadav G, Roque DM, Bellone S, Manavella DD, Hartwich TM, Zipponi M, et al. Synergistic activity of neratinib in combination with olaparib in uterine serous carcinoma overexpressing HER2/neu. Gynecologic Oncology. 202;1662:351-7. DOI: https://doi.org/10.1016/j.ygyno.2022.05.021
23. Díaz-Montes TP, Ji H, Sehdev AES, Zahurak ML, Kurman RJ, Armstrong DK, et al. Clinical significance of Her-2/neu overexpression in uterine serous carcinoma. Gynecol Oncol. 2006;1001:139-44. DOI: https://doi.org/10.1016/j.ygyno.2005.08.017
24. Shen F, Gao Y, Ding J, Chen Q. Is the positivity of estrogen receptor or progesterone receptor different between type 1 and type 2 endometrial cancer? Oncotarget. 2017;81:506-511. DOI: https://doi.org/10.18632/oncotarget.13471. PMID: 27888807; PMCID: PMC5352172.

DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

AUTHORS' CONTRIBUTION

The following authors fullfill authorship criteria as per ICMJE guidelines;

Hadi S, Mukhtar R:	Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Ghumman NA, Jamil A:	Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Khattak MT, Khattak L:	Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Muhammad I:	Analysis and interpretation of data, critical revision,final approval, agreed to be accountable for all the work.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License, which permits unrestricted use, distribution & reproduction in any medium provided that original work is cited properly.