e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(5); 1116-1123

Original Research Article

Evaluation of ER, PR, P53 and HER2 Neu Biomarkers in Endometrial Cancers

Arasi Rajesh[1], Dina Mary M[2], Maheswari S[3]

[1]Professor and Head, Department of Pathology, Government Thoothukudi Medical College, Thoothukudi
[2]Associate Professor, Department of Pathology, Government Tirunelveli Medical College, Tirunelveli
[3]Associate Professor, Department of Pathology, Government Thoothukudi Medical College, Thoothukudi

Received: 25-02-2024 / Revised: 23-03-2024 / Accepted: 26-04-2024
Corresponding Author: Dr. Maheswari S
Conflict of interest: Nil

Abstract:

Introduction: Endometrial cancer (EC) is the most common gynecological malignancy. Factors reported to be predictive of response to endocrine therapy include low grade, endometrioid histology, and positive estrogen receptor (ER)/progesterone receptor (PR) status. The prognostic value of ER/PR is well established, with higher levels of ER and PR expression associated with longer overall Survival, longer cancer-specific survival, and longer Progression Free Survival.

Methods: In our study, a panel of immunohistochemical markers ER, PR, Her-2, and p53 were done in 50 cases of endometrial carcinoma and their relationships with the histopathological and prognostic parameters were analysed.

Results: in our study ER, PR expression was noted commonly in Grade I, Grade II endometrioid carcinoma whereas Type II endometrial carcinoma was negative for these markers. p53 mutation and Her2 neu overexpression was found commonly in Type II endometrial carcinoma.

Conclusion: The absence of hormone receptors, Her2 Neu overexpression, p53 mutation indicates aggressive tumor and poor prognosis.

Keywords: endometrial carcinoma, ER, PR, HER2 NEU, P53.

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries [1] like USA. In India, it ranks third after Carcinoma cervix and Carcinoma ovary. [2] The burden of endometrial cancer is increasing worldwide and hence there is increased need to investigate its causes to improve prevention and for early diagnosis and treatment. The escalation in the number of women entering menopause in addition to risk factors, such as obesity and diabetes, may explain a fraction of the increased incidence of endometrial cancer 3. The median age at diagnosis is 61 years with approximately 85% of the cases being diagnosed after 50 years of age. Consequently, this is generally a disease of postmenopausal women Most cases are diagnosed in early stages owing to the clinical symptoms of postmenopausal bleeding and abnormal discharge. [3]

Endometrial carcinomas are divided into two broad histologic types. Type 1 includes Endometrioid and mucinous carcinoma accounting for about 80% of the cases wherein there is unopposed estrogen stimulation and is associated with precursor lesions such as Atypical Endometrial Hyperplasia (AEH)/Endometrial Intraepithelial Neoplasia (EIN). Type I tumor presents with low tumour grade and show distinct genetic abnormalities such as PTEN, PAX2and k-ras mutation. Type 2 includes Serous Carcinoma, Clear Cell Carcinoma, undifferentiated carcinoma and carcinosarcoma accounting for about 10% of the cases, less associated with estrogen stimulation, presenting with higher tumour grade and stage. Serous Carcinoma exhibit early TP53 mutations and serous intraepithelial carcinoma is proposed as its preinvasive precursor [4]

The Undifferentiated Endometrioid Carcinoma (UEC) is a solid-pattern tumor without specific morphologic evidence of epithelial differentiation. It has an aggressive growth pattern and tends to be diagnosed at an advanced International Federation of Gynecology and Obstetrics (FIGO) stage and is resistant to conventional chemotherapy. Dedifferentiated Endometrioid Carcinoma (DEC) is characterized by the coexistence of low-grade EC and UEC. DEC has not been widely recognized due to its solid part usually being misdiagnosed as a

grade 3 EC, but has a worse outcome than grade 3 EC. In a recent population-based study using the National Cancer Database of the United States (2004–2013), 1.1% of all ECs met the criteria of UEC, which may reflect an underdiagnosed in earlier years [5]. Loss of PAX 8, E-cadherin ER and PR, focal expression of cytokeratin, and EMA can support a diagnosis of undifferentiated/ dedifferentiated carcinoma over Grade 3 or Grade 2 endometrial carcinoma. [6] The dedifferentiated rhabdoid variant is characterised by the presence of an undifferentiated component which shows rhabdoid cells embedded in myxoid stroma. This variant is often misdiagnosed as a Mixed Mullerian tumour (MMMT).

UEC harbors specific genetic features different from endometrioid carcinoma. Generally, endometrioid carcinoma is a hormone-dependent tumor that expresses hormone receptors that may respond to hormone therapy. Unfortunately, UEC seldom has detectable hormone receptors and its tumorigenesis pathway has distinct features, such as microsatellite instability (MSI-H)/mismatch repair (MMR) protein and the genomic inactivation of core components of the SWI/SNF chromatin-remodeling complex [5].

In the regular progression of the menstrual cycle, the lining of the uterus is subject to pair of steroid hormones, estrogen and progesterone, that each exerts an opposing effect on the endometrial glandular epithelium. In particular, estrogen has a mitogenic effect that drives the proliferation of the endometrial epithelium via Estrogen Receptor (ER). Left unopposed, estrogen can lead to the rapid onset of endometrial hyperplasia and consequently, the development of Endometrial Carcinoma. Progesterone, however, acts as an antagonist to estrogen by down regulating ER expression, inhibiting active cell division, and promoting cell differentiation through Progesterone Receptor (PR).

As the endometrium expresses both ER and PR, the lining of the uterus is highly sensitive to hormone activity. Therefore, any shift to the endocrine balance in favor of high estrogen level will ultimately stimulate oncogenesis. Such overexposure to estrogen arises in the majority of type I tumors. This is high risk factor among women undergoing estrogen-only hormonal therapy, using tamoxifen as adjunct therapy for breast cancer and in obese women as adipose tissue releases estrone, which is converted into estradiol in the uterus.

HER2, a well characterized oncogene in the pathogenesis of breast cancer, has also been implicated as a potential biomarker for type II endometrial tumors. Overexpression of HER2 results in sustained cell proliferation via constitutive activation of the kinase domain in a ligand-independent manner. HER2 expression is mostly associated with a poor prognosis in type II lesions. Recent studies suggest HER2 overexpression is also found in advanced and recurrent type I endometrioid Carcinomas. Hormone receptor status may therefore be a valuable prognostic marker for EC development and progression. [7] The tumor suppressor gene p53 is activated in response to various stress signals in the cell and it acts on several pathways leading to inhibition of growth, cell cycle arrest and apoptosis. In type II endometrial cancers, the most common mutation identified have been in p53 with mutations Iin over 90% of serous carcinomas compared with only 20% of type I cancers. [3] Some studies suggest that loss-of-function mutations in p53 may be an early event in serous carcinogenesis since it is found in approximately 75% of precursor lesions. In addition to the association with type II histology, p53 mutations are also associated with poor clinical outcome3.In a multivariate analysis adjusting for histology grade, FIGO stage and lymph nodes metastasis, there was an 11-fold increased risk of death in patients with p53 mutations compared to those without.[3]

Factors reported to be predictive of response to endocrine therapy include low grade, endometrioid histology, and positive estrogen receptor (ER)/progesterone receptor (PR) status [8] The prognostic value of ER/PR is well established, with higher levels of ER and PR expression associated with longer overall Survival, longer cancer-specific survival, and longer Progression Free Survival.

In our study, a panel of immunohistochemical markers ER, PR, Her-2, and p53 were done in 50 cases of endometrial carcinoma and their relationships with the histopathological and prognostic parameters were analysed

Aim of the study:

1. To evaluate the expression of ER, PR, Her2neu, p53 in endometrial adenocarcinomas.
2. To analyse ER, PR, Her-2neu & P53 expression with histological Type and grade.

Materials and Methods

The study includes analysis of 50 cases of endometrial carcinoma received in the Department of Pathology, Government Tirunelveli Medical College, Tirunelveli from 2018- 2020. This study included 50 histopathologically confirmed cases of endometrial carcinoma diagnosed from endometrial biopsy or hysterectomy specimens. The biopsy tissue and hysterectomy specimens were fixed in 10% formalin solution. Sections were stained with routine Haematoxylin and Eosin (H and E) and were examined under the microscope For IHC,

sections of 4 microns thickness were cut, immunohistochemical staining for ER, PR, HER-2/neu and p53 was performed. Her2 score was assessed using guidelines by the American Society of Clinical Oncology and the College of American Pathologists. Scoring of HER2/neu was done as follows: Score 0: no immunostaining/membrane staining in less than 10% of neoplastic cells; Score 1+: weak staining in more than 10% of neoplastic cells in only portions of the membrane; Score 2+: weak/ moderate circumferential membranous staining in >10% of tumor cells; Score 3+: strong complete membranous staining in more than 10% of tumor cells. Meanwhile, scores equal to 2+ and 3+ were considered as HER2/neu positive. HER2 expression was scored on epithelial component in carcinosarcoma case.

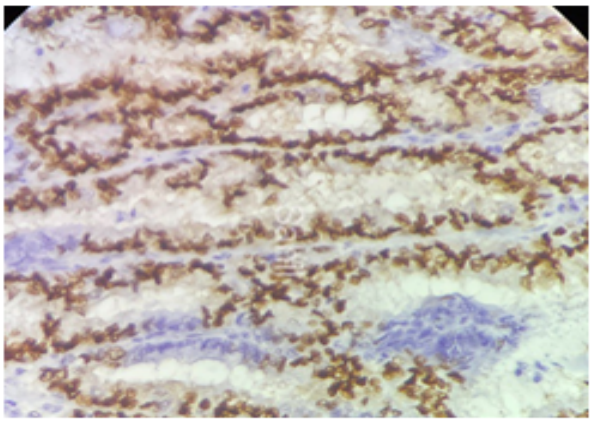

Figure 1: Photomicrograph showing ER expression (40X)

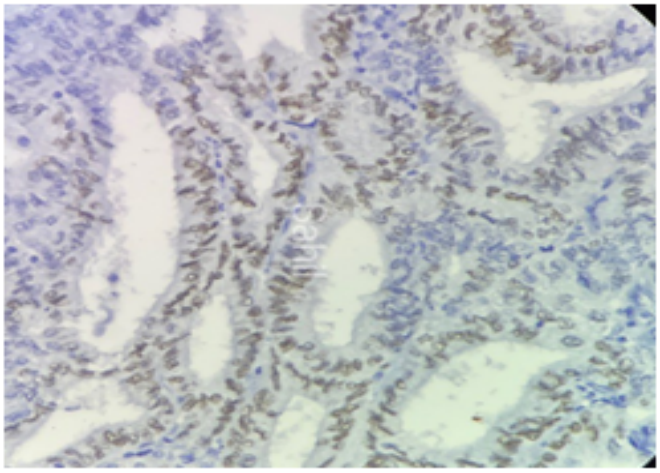

Figure 2: Photomicrograph showing PR expression (40X)

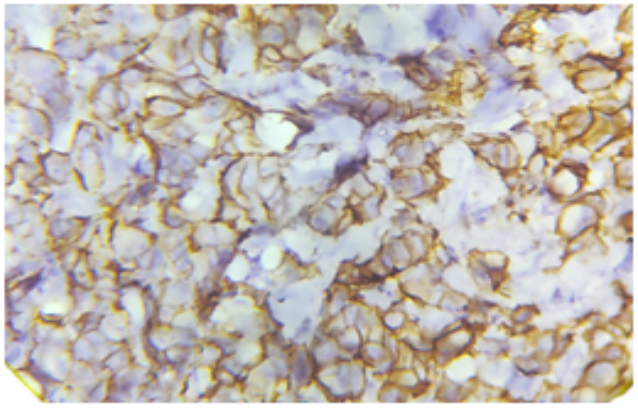

Figure 3: Photomicrograph showing Her2 overexpression (40 X)

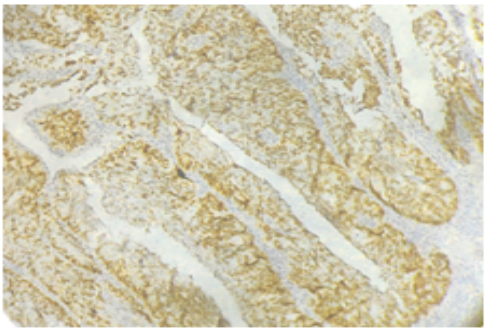

Figure 4: Photomicrograph showing mutant p53 (40 X)

Results: Total of 50 cases were included in our study, of which majority of cases (38%) were in the age group of 51-60 years followed by 61-70 years (28%). Only one patient was diagnosed before 40 years. Mean age at diagnosis is 56.5 years.

Table 1: Age Distributions of Patients

Age in years	No of patients	Percentage
<40	1	2%
40-50	12	24%
51-60	19	38%
61-70	14	28%
>70	4	8%
Total	50	100%

Among 50 cases studied 42 cases (84%) were endometrioid carcinoma, of which 21 cases were grade I, 18 cases were grade II, 3 cases were grade III. The other 16 % included 8 cases of serous carcinoma, 2 cases of clear cell carcinoma, 1 case of carcinosarcoma and 2 cases of dedifferentiated carcinoma.

Table 2: Histological Type and Grade

Tumor Type	No of cases	Percentage
Endometrioid carcinoma grade I	21	42%
Endometrioid carcinoma grade II	18	36%
Endometrioid carcinoma grade III	3	6%
Serous carcinoma	3	6%
Clear cell carcinoma	2	4%
Carcinosarcoma	1	2%
Dedifferentiated carcinoma	2	4%
Total	50	100%

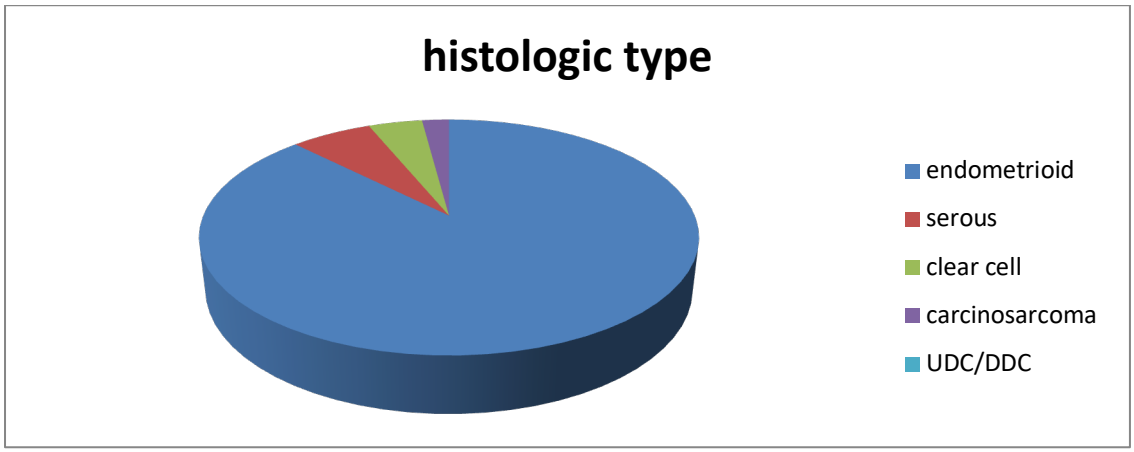

Figure 5:

86% of grade I endometrioid carcinoma, 89% of grade II endometrioid carcinoma and 33% of garde III endometrioid carcinoma showed positivity for ER. All cases of non endometrioid cancers were ER negative.

Table 3: ER Expression in Tumors

Tumor	ER Positive	ER Negative	Total
Endometrioid carcinoma grade I	18(86%)	3(14%)	21(100%)
Endometrioid carcinoma grade II	16(89%)	2(11%)	18(100%)
Endometrioid carcinoma grade III	1(33%)	2(67%)	3(100%)
Serous carcinoma	0	3(100%)	3(100%)
Clear cell carcinoma	0	2(100%)	2(100%)
carcinosarcoma	0	1(100%)	1(100%)
Undifferentiated/ dedifferentiated carcinoma	0	2(100%)	2(100%)
Total	35(70 %)	15(30%)	50(100%)

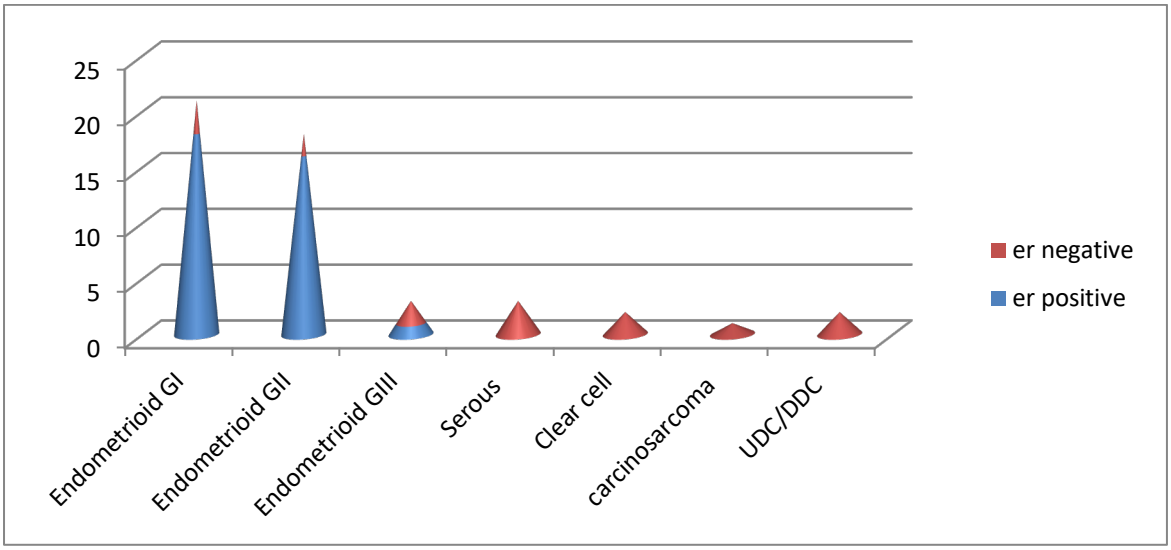

Figure 6:

76% cases of grade I Endometrioid carcinoma, 83% of grade II Endometrioid carcinoma were PR positive. All cases of grade III Endometrioidcarcinoma, serous carcinoma, clear cell carcinoma. Carcinosarcoma, dedifferentiated carcinoma was negative for PR.

Table 4: PR Expression in Tumors

Tumor	PR Positive	PR Negative	Total
Endometrioid carcinoma grade I	16(76%)	5(24%)	21(100%)
Endometrioid carcinoma grade II	15(83%)	3(17%)	18(100%)
Endometrioid carcinoma grade III	0	3(100%)	3(100%)
Serous carcinoma	0	3(100%)	3(100%)
Clear cell carcinoma	0	2(100%)	2(100%)
carcinosarcoma	0	1(100%)	1(100%)
Undifferentiated/ dedifferentiated carcinoma	0	2(100%)	2(100%)
Total	31(62%)	19(38%)	50(100%)

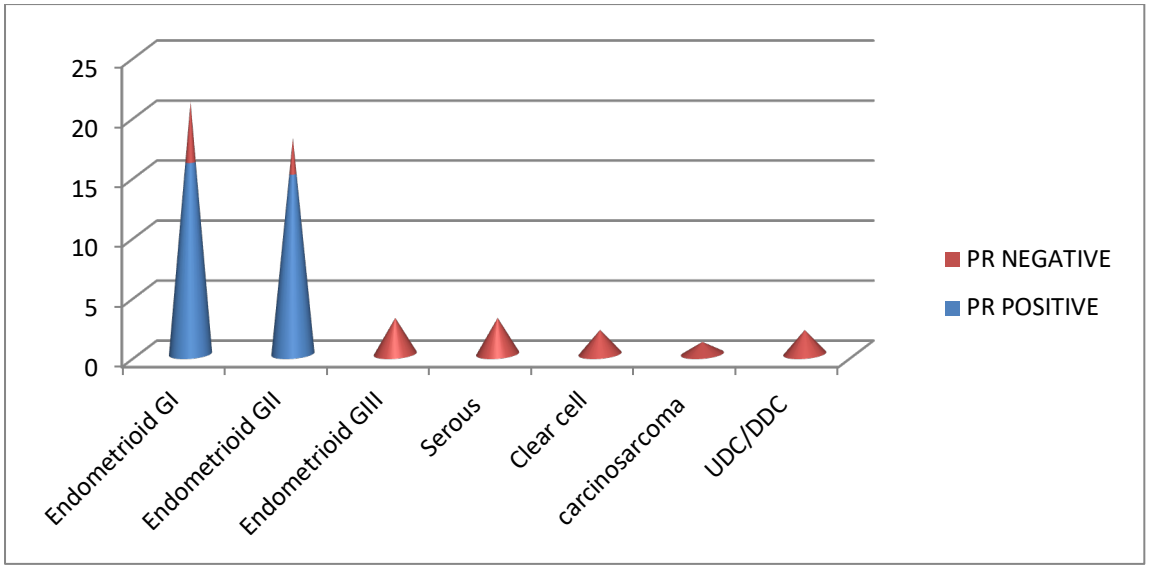

Figure 7:

In contrast to ER and PR HER2Neu overexpression was commonly found in serous carcinoma (100%), clear cell carcinoma (50%) and carcinosarcoma (100%). Among endometrioid carcinomas grade III tumors show over expression in 67% cases, grade II tumors show over expression in 11% cases and grade I tumors show over expression in 5% cases.

Table 5: Her 2 over Expression In Tumors

Tumor	Her2 (2+&3+)	Her2 Negative (0 &1+)	Total
Endometrioid carcinoma grade I	1(5%)	20(95 %)	21(100%)
Endometrioid carcinoma grade II	2(11%)	16(89%)	18(100%)
Endometrioid carcinoma grade III	2(67%)	1(33%)	3(100%)
Serous carcinoma	3(100%)	0	3(100%)
Clear cell carcinoma	1(50%)	1(50%)	2(100%)
carcinosarcoma	1(100%)	0	1(100%)
Dedifferentiated carcinoma	0	2(100%)	2(100%)
Total	10(20%)	40(80%)	50(100%)

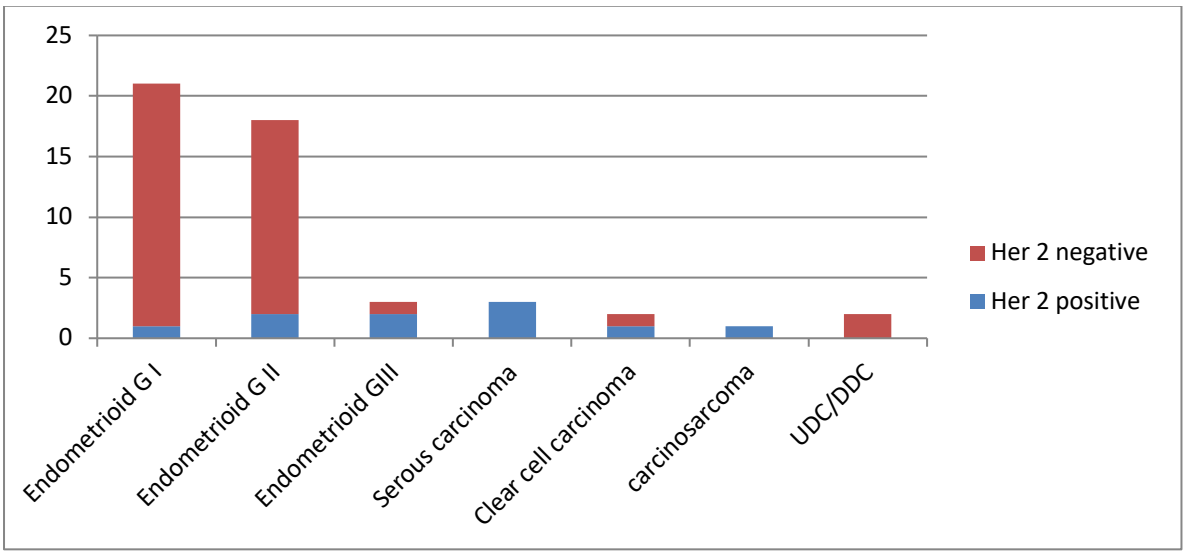

Figure 8:

All cases of serous carcinoma, clear cell carcinoma, carcinosarcoma showed mutant p 53 expression, whereas all cases of undifferentiated carcinoma, grade I and II endometrioid carcinoma showed wild type P53. 33% of grade III endometrioid carcinoma showed mutant P 53 and 67% showed wild type P 53.

Table 6: P53 Expression in Tumors

Tumor	P53 mutant	P53wild type	Total
Endometrioid carcinoma grade I	0	21(100%)	21(100%)
Endometrioid carcinoma grade II	0	18(100%)	18(100%)
Endometrioid carcinoma grade III	1(33%)	2(67%)	3(100%)
Serous carcinoma	3(100%)	0	3(100%)
Clear cell carcinoma	2(100%)	0	2(100%)
carcinosarcoma	1(100%)	0	1(100%)
Undifferentiated/ dedifferentiated carcinoma	0	2(100%)	2(100%)
Total	7(14%)	43(86%)	50(100%)

Discussion

We have included 50 cases of endometrial carcinomas in our study with mean age of 56.5 years. Highest incidence of endometrial carcinoma was found in 51 - 60 years in our study. This correlated with studies by Bhawani Shekar et al [2] who reported a mean age of 58.4 years and Afaf.T.Elnashar et al [9] whose study showed mean age of 59.4 years. AMANY SALAMA et al [10] reported a mean age of 59.8 years, Nayar Musfera Abdul Masjeed et al [4] reported mean age of 58.14 years, Samina Wagar et al [11] reported mean age of 58.3 years which also correlated with our study.

In our study 84% of cases were endometrioid carcinoma and 16% were non endometrioidcarcinoma. Our results were compared with other studies.

Table 7:

Study	Endometrioid Carcinoma	Nonendometrioid
Bhawani Shekar et al [2]	66.67%	33.33%
Afaf.T.Elnashar et al [9]	74%	26%
Jasmine Kaur et al [12]	84%	16%
Sunamchoksrijaipracharoen et al [13]	86.1%	13.9%
Our Study	84%	16%

In our study all cases of nonendometrioid carcinoma, were negative for ER, whereas 86% of grade I Endometrioid carcinoma, 89% of grade II Endometrioid carcinoma and 33% of grade III Endometrioid carcinoma were positive for ER. Similarly PR also showed negativity in all non endometrioid carcinoma and also in grade III endometrioid carcinoma. 76% of grade I and 83% of grade II showed positivity for PR. Overall 70% cases were positive for ER and 62% cases were positive for PR. Our study was comparable with Caifeng Wang Davis A. Tranz et al [7] whose study showed ER positivity in 59.8% of cases and PR positivity in 75% of cases. Jasmine Kaur et al [12] showed ER positivity in 64% of cases and PR positivity in 60% of cases; Nayar Musfera Abdul Masjeed et al [4] reported ER positivity in 60.7% of cases and PR positivity in 64.28% of cases.

They also reported all cases of grade III endometrioid carcinoma and all non endometrioid carcinoma were ER, PR negative. Also most ER, PR expression was seen in Grade II endometrioid carcinoma, which was true in our study too. Samina Waqar et al [11] noted PR positivity in 66.1% of cases which correlated with our study, but ER positivity was seen in 55% of cases which was little low compared to our study. Her2Neu overexpression was noted in 100% of cases of Serous carcinoma, Carcinosarcoma and 50% cases of Clear Cell Carcinoma. Among Endometrioid carcinoma grade III showed 67% cases with overexpression. This is comparable with Bhawani Shekar et al [2] whose study also revealed non endometrioid carcinoma was more common with Her 2 Neuoverexpression. Similarly Samina Waqar et al [11] noted Her2 Neu overexpression in grade III endometrioid carcinoma and Serous carcinoma with no cases of Grade I, Grade II tumor showing overexpression.

In our study all cases of serous carcinoma, clear cell carcinoma, carcinosarcoma and 33% of grade III endometrioid carcinoma showed muthant p53. Our results were comparable with RAVI M SWAMI et al [14] who also showed 100% p53 positivity in grade III endometrioid and serous carcinoma.

Conclusion

ER,PR expression decreased with increase in grade, Her-2neu and P53 expression were present in higher grade tumour. ER, PR, Her-2Neu & P53 status if included in pathology reports, will improve the understanding of behaviour of tumors and aid in management of patients. (The absence of hormone receptors, Her2 Neu overexpression, and p53 mutation indicates aggressive tumor and poor prognosis).

References

1. Guan J, Xie L, Luo X, Yang B, Zhang H, Zhu Q, Chen X. The prognostic significance of estrogen and progesterone receptors in grade I and II endometrioid endometrial adenocarcinoma: hormone receptors in risk stratification. J GynecolOncol. 2019 Jan; 30(1):e13.
2. Shekhar B, Kumar S, Mathur S, Singhal S, Meena J, Sharma DN, Singh N. Evaluation of prevalence and prognostic significance of human epidermal growth factor receptor 2/neuexpression in carcinoma endometrium. International Journal of Molecular and Immuno Oncology. 2020 Jan 21; 5(1):8-13.
3. Binder PS, Mutch DG. Update on Prognostic Markers for Endometrial Cancer. Women's Health. 2014; 10(3):277-288.
4. 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.
5. Tung HJ, Wu RC, Lin CY, Lai CH. Rare Subtype of Endometrial Cancer: Undifferentiated/Dedifferentiated Endometrial Carcinoma, from Genetic Aspects to Clinical Practice. Int J Mol Sci. 2022 Mar 30; 23(7):3794.
6. Giordano G, Ferioli E, Guareschi D, Tafuni A. Dedifferentiated Endometrial Carcinoma: A Rare Aggressive Neoplasm-Clinical, Morphological and Immunohistochemical Features. Cancers. 2023 Oct 26; 15(21):5155.
7. 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;11(7):1693.
8. MacKay HJ, Freixinos VR, Fleming GF. Therapeutic Targets and Opportunities in Endometrial Cancer: Update on Endocrine Therapy and Nonimmunotherapy Targeted Options. Am Soc Clin OncolEduc Book. 2020 Mar;40:1-11.
9. Noha Ed. Hassab Elnaby, M.D. Atem, Mohamed N. Salem, M.D. Aaam. Her-2 Neu Expression in Endometrial Carcinoma. The Medical Journal of Cairo University. 2018; 860:69-6.
10. Salama A, Arafa M, ElZahaf E, Shebl AM, Awad AAE, Ashamallah SA, Hemida R, Gamal A, Foda AA, Zalata K, Abdel-Hady EM. Potential Role for a Panel of Immunohistochemical Markers in the Management of Endometrial Carcinoma. J PatholTransl Med. 2019 May; 53(3):164-172.
11. 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 Mar-Apr; 34(2):266-271.
12. Jasmeen Kaur, Anil Suri, Manjit Kaur. A Clinicopathological Study: Expression of ER, PR and HER/2neu in Endometrial Carcinoma. Obstetrics and Gynecology Research.2022; 5: 41-53.
13. Srijaipracharoen S, Tangjitgamol S, Tanvanich S, Manusirivithaya S, Khunnarong J, Thavaramara T, Leelahakorn S, Pataradool K. Expression of ER, PR, and Her-2/neu in endometrial cancer: a clinicopathological study. Asian Pac J Cancer Prev. 2010; 11(1):215-20.
14. Swami R M, Lakhe R, Doshi P, Karandikar M N, Nimbargi R, Immunohistochemical study of ER, PR, p53 and Ki67 expression in patients with endometrial adenocarcinoma and atypical endometrial hyperplasia. IP Arch CytolHistopathol Res 2020; 5(4):274-279.