DOI: 10.7860/JCDR/2026/78519.23176

Original Article

Pathology Section

HER2/neu Expression in Endometrial Carcinoma: A Cross-sectional Study on Immunohistochemical Positivity and Tumour Grade

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ABSTRACT

Introduction: Endometrial carcinoma is the most common invasive cancer of the female genital tract. Serous carcinoma of endometrium is highly aggressive and has a predilection for deep myometrial and lymphovascular invasion, peritoneal and distant metastatic spread. HER2/neu is an important prognostic protein in high-grade and higher-stage endometrial serous carcinomas

Aim: To study the expression of HER2/neu in relation to tumour grade in endometrial carcinoma.

Materials and Methods: The present cross-sectional study was conducted in the Department of Pathology, Government medical college, Thrissur, Kerala, India, over a period of 18 months from 1st January 2018 to 30th June 2019. A total of 63 cases of both hysterectomy specimens and endometrial biopsies whose histopathologic diagnosis was endometrial adenocarcinoma were included. Four micrometer thick sections were obtained for Haematoxylin and Eosin (H&E) and immunohistochemical staining with rabbit monoclonal HER2 antibody following antigen retrieval was done. H&E staining was done to assess the tumour grade. HER2/neu staining was evaluated using regular light microscope at the magnification of 40x. The Immunohistochemistry (IHC) score was determined by evaluating subcellular localisation, circumferential versus incomplete staining, intensity and the percentage of cells positive. Intensity of HER2 expression was graded according to the 2014 American Society of Clinical Oncology/College of American Pathologist (ASCO/CAP) guidelines for HER2 reporting. Data thus obtained was analysed using software Statistical Package for Social Sciences (SPSS) version 20.0. The statistical test used is the Fisher's-exact test and p-value<0.05 was considered statistically significant.

Results: Most of the patients were in the age group of 51-60 years (23 out of 63 patients, 36.50%). Among the 63 patients seven were nulliparous and 56 were post menopausal women. Most of the patients presented with complaints of post menopausal bleeding which was noted in 85.71% of patients (54 out of 63). More than half of myometrial invasion was noted in 33 cases of hysterectomy specimens. HER2 positivity (score 2 and score 3) was observed in 7 (11.11%) cases. None of the grade 1 endometrial carcinoma showed HER2 positivity. Grade 2 endometrial carcinoma showed HER2 positivity in 1 (6.67%) case. Grade 3 tumours showed HER2 positivity in 6 (28.57%) cases. Compared to grade 1 and grade 2 endometrial carcinoma, grade 3 endometrial carcinoma showed increased HER2 expresssion. A statisticaly significant association between HER2 expression and tumour grade was obtained (p-value=0.004).

Conclusion: As tumour grade in endometrial adenocarcinoma increases expression of HER2/neu also increases. A statistically significant association between HER2 expression and tumour grade was obtained (p-value=0.004). The study suggests that endometrial carcinoma shows HER2/neu expression in significant proportion of cases and its expression is more in high-grade endometrial carcinoma. Patients with HER2/neu positive endometrial carcinoma may benefit from adjuvant HER2/neu targeted therapies like trastuzumab. Further clinical studies are necessary to establish the prognostic and therapeutic significance of HER2/neu in endometrial adenocarcinoma.

Keywords: Adenocarcinoma, Distant metastasis, Female genital tract, Serous carcinoma

INTRODUCTION

Endometrial carcinoma is the most common invasive cancer of the female genital tract. It accounts for 7% of all malignancies occurring in women [1]. Histologic types of endometrial carcinoma are grouped into two different types. Type I endometrioid accounts for 80% of all tumours and shows low grade endometrial morphology and have a favourable clinical outcome. Type I tumours are often preceded by endometrial hyperplasia and generally express oestrogen and progesterone receptors. Patients with type I tumours are generally younger (premenopausal or perimenopausal), present at an early stage. Type II endometrial cancer which is less common (20% of cases) are characterised by high histologic grade and serous or clear cell morphology [2]. Uterine serous carcinoma is highly aggressive and has a predilection for deep myometrial and lymphovascular invasion, peritoneal and distant metastatic spread. There are high chances of recurrence even in the presence of minimal uterine disease. This aggressive clinical course associated with uterine serous carcinomas necessitates the need for improved therapeutic strategies. HER2/neu (ERbB2) is a member of human epidermal growth factor receptor family of transmembrane tyrosine kinase. Ligand binding results in dimerisation of receptors which leads to phosphorylation of intracellular domains, which subsequently activate various pathways involved in proliferation, survival, migration and differentiation [3]. HER2/neu overexpression results in ligand independent dimer formation and constitutive activation of kinase domain leading to increased cell proliferation. HER2/neu amplification and overexpression is seen associated with advanced stage, decreased differentiation, aggressive cell types, increased depth of myometrial invasion and poor prognosis in endometrial adenocarcinomas. The pathogenic role and prognostic significance of HER2/neu in endometrial carcinomas, especially

in serous carcinomas (high-grade), has recently become the focus of several studies, providing the scientific basis for targeted immunotherapy against these highly aggressive tumours.

This study tries to evaluate the expression of HER2/neu in endometrial carcinoma by immunohistochemistry.

Study objectives:

- To study the expression of HER2/neu in relation to tumour grade in endometrial carcinoma using immunohistochemistry;
- To analyse the association between HER2/neu expression and the histological grade of endometrial carcinoma;
- To determine if higher tumour grades, particularly grade 3 are associated with increased HER2/ neu expression;
- To provide data that may support the potential use of HER2/ neu targeted therapies in patients with HER2/neu positive endometrial carcinoma, while acknowledging the need for further clinical studies.

MATERIALS AND METHODS

The present cross-sectional study was done in Department of Pathology, Government Medical College, Thrissur, Kerala, India. The duration of study was 18 months from 1st January 2018 to 30th June 2019. The study commenced after taking approval from Institutional Ethics Committee (IEC NO-B6-8772/2016 MCTCR).

Inclusion and Exclusion criteria: The study included cases of endometrial carcinoma whose endometrial biopsies/hystercectomy specimens received in the Histopathology Lab for a period of 18 months. A total of 63 cases were included in the study. Biopsies received after chemotherapy or radiotherapy were excluded from the study.

Study Procedure

Four micrometer thick sections were obtained from formalin-fixed paraffin-embedded tissue. H&E staining was done to assess the tumour grade. Antigen retrieval was performed by pressure cooking and stained with HER2/neu immunohistochemical marker. For detection of HER2/neu antigen rabbit monoclonal antibody of clone EP1045Y was used. A known HER2/neu positive case with grade 3 expression was taken as control. HER2/neu staining was evaluated using regular light microscope at the magnification of 40x. The IHC score was determined by evaluating subcellular localisation (membranous, circumfrential versus incomplete staining, intensity and the percentage of cells positive. Intensity of HER2 expression was graded according to the 2014 American Society of Clinical Oncology/College of American Pathologist (ASCO/CAP) guidelines for HER2 reporting [4] which was commonly employed during the study period [Table/Fig-1].

Intensity of HER2/neu expression	Characteristic features
0	No staining is observed or shows membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of tumour cells
1+	Membrane staining that is incomplete and is faint/barely perceptible and within >10% of tumour cells.
2+	Circumferential staining that is incomplete and/or weak/moderate within >10% of tumour cells OR Complete intense circumferential membrane staining within ≤10% of tumour cells
3+	Complete intense circumferential membrane staining within >10% of tumour cells.

[Table/Fig-1]: ASCO/CAP guidelines for HER2 reporting.

STATISTICAL ANALYSIS

Data thus obtained was entered in Microsoft office excel sheet 2016. This was then analysed using software SPSS version 20.0. The statistical test used is the Fisher's exact test. The p-value <0.05 was considered statistically significant.

RESULTS

The age of the patients ranged from 41-80 years. The maximum number of patients was in the age group of 51-60 years which were 23 in number (36.50%) The mean age was 59 years [Table/Fig-2].

Age group (years)	Frequency	Percentage
41-50	9	14.28%
51-60	23	36.50%
61-70	22	34.92%
71-80	9	14.28%

[Table/Fig-2]: Age distribution.

Majority presented with bleeding per vaginum, 54 cases (85.71%), followed by abdominal pain four cases (6.35%), abdominal mass three cases (4.76%) and discharge per vaginum two cases (3.17%). A total of 52 cases were hysterectomy specimens (82.54%) and 11 cases were endometrial biopsies (17.46%).

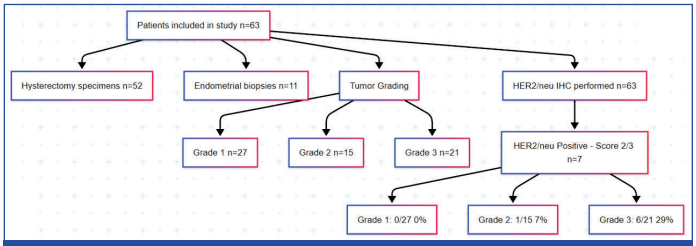
A total of 27 cases were Grade 1 (42.86%), 15 cases (23.81%) were Grade 2, 21 cases were Grade 3 (33.33 %). Majority of cases had a HER2 score of 0 (55 cases, 87.30%). Out of 27 grade 1 tumours, all cases showed HER2 staining intensity score 0 [Table/Fig-3]. One case had a score of 1, two cases had a score of 2, five cases had a score of 3. Out of 63 cases seven cases were positive (score 2 and 3) for HER2/neu expression [Table/Fig-4]. Flow chart depicting the distribution of patients included in the study by specimen type, tumour grading, and HER2/neu IHC results is shown in [Table/Fig-5].

Grade of tumour	Frequency	Percentage
Grade 1	27	42.85%
Grade 2	15	23.80%
Grade 3	21	33.33%

[Table/Fig-3]: Grade of Tumour.

HER2 intensity score	Frequency	Percentage
Score 0	55	87.30%
Score 1	1	1.58%
Score 2	2	3.17%
Score 3	5	7.93%

[Table/Fig-4]: Distribution of intensity of HER2 staining.

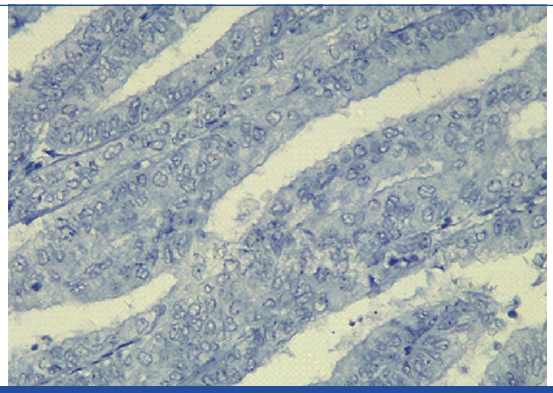


[Table/Fig-5]: Flow chart depicting the distribution of patients included in the study by specimen type, tumour grading, and HER2/neu Immunohistochemistry (IHC) results.

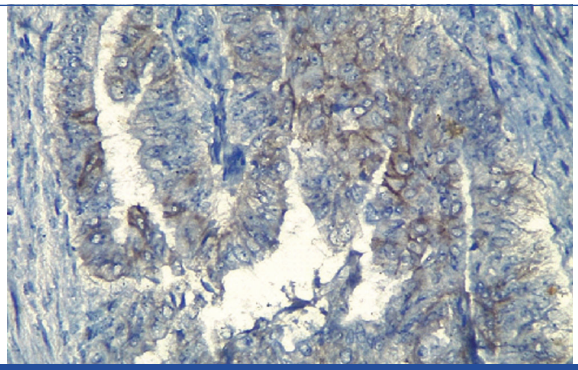
All 27 cases of grade 1 endometrial carcinomas were negative (score 0) for HER2 expression. Out of 15 grade 2 endometrial adenocarcinomas, 13 cases showed score 0, one case showed score 1, one case showed score 2. Out of 15 cases of grade 2 tumours, one case showed HER2 positivity (score 2). None of Grade 1 endometrial adenocarcinomas, 6.67% of Grade 2 endometrial adenocarcinomas and 28.57% of Grade 3 endometrial adenocarcinomas showed positive HER2 expression [Table/Fig-6-10]. Statistically significant association was found between HER2/neu expression and tumour grading (p-value 0.004 which is less than 0.05).

HER2 score	Grade 1 tumour	Grade 2 tumour	Grade 3 tumour
0	27	13	15
1	0	1	0
2	0	1	1
3	0	0	5
Total	27	15	21

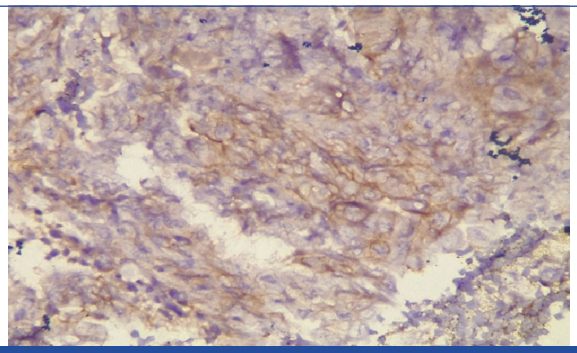
[Table/Fig-6]: Distribution of tumour grading according to Her2 score.



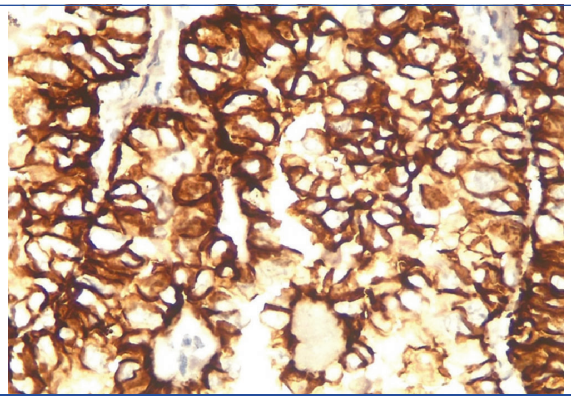
[Table/Fig-7]: HER2 score 0 - No staining.
IHC stain -HER2/neu antigen rabbit monoclonal antibody of clone EP1045Y magnification is 40X



[Table/Fig-8]: HER2 score 1 - Incomplete barely perceptible membrane staining in >10% of tumour cells (IHC stain, 40X).



[Table/Fig-9]: HER2 score 2-Incomplete moderate staining in >10% of tumour cells (IHC stain, 40X).



[Table/Fig-10]: HER2 score 3 - Complete circumferential staining in >10% of tumour cells (IHC stain, 40X).

DISCUSSION

Uterine carcinoma is one among the few carcinomas in women with increasing incidence and mortality. The age standardised incidence rate of endometrial adenocarcinoma in India is 2.1/100,000 women [5]. Most of them have a favourable histologic subtype and good prognosis. But around 20% of women have high-grade endometrial carcinoma and thus poor outcome. Histopathologic grading of endometrioid carcinomas into FIGO grade 1, 2 and 3 is done by assessing the percentage of solid areas. Grade 1 with 5% or less than 5% of solid growth, grade 2 with 6% to 50% of solid growth and grade 3 with more than 50% of solid growth. Numerous genomic alterations are explained leading to the development of high-grade endometrial carcinomas. One among them is HER2/neu. Among the 27 grade 1 endometrial carcinoma all cases showed score 0 HER2 staining.

All 27 grade 1 endometrial adenocarcinomas in this study were negative for HER2 staining. Among the 15 grade 2 tumours, 13 cases showed a score of 0, one case showed a score of 1, and one case showed a score of 2 for HER2 staining. Thus, only one grade 2 tumour was considered positive for HER2 expression. In the group of 21 grade 3 tumours, 15 cases had a score of 0, one case had a score of 2, and five cases had a score of 3. Therefore, six grade 3 tumours were positive for HER2 expression. Overall, these results demonstrate a statistically significant association between higher tumour grade and increased HER2/neu expression in endometrial adenocarcinoma (p-value=0.004).

The authors observed that HER2 expression is more in high-grade endometrial carcinomas (grade 3) than in grade 2 and grade 1 tumours. The findings of this present study are similar to the studies conducted by Rolitsky CD et al., Wilczyński M et al., Morrison C et al., [6-8]. Their studies also got a direct correlation between tumour grade and HER2 expression in endometrial carcinoma. Morrison C et al., studied the expression of HER2/neu in 483 patients of endometrial cancer and found highest rate of HER2/neu expression in serous carcinoma (43%) while grade 3, grade 2 and grade 1 showed 31%, 7% and 3%, respectively [8]. In uterine serous carcinoma, the reported rates of HER2/neu expression ranges between 14% to 80% and HER2 amplification by FISH ranging from 21 to 47% [9]. The highest frequency (80%) of HER2/neu expression has been reported by Santin AD et al., in which eight out of 10 serous carcinoma showed overexpression (score 2+ and 3+) by immunohistochemistry [10]. However, the overall lower frequency of HER2/neu positivity in the present study population compared to western cohorts may reflect population specific genetic or environmental factors, differences in case selection, sample size variations and selection bias in immunohistochemical protocols (antibody clones, scoring systems, tissue fixation) and application of more stringent scoring criteria involving FISH/ISH.

HER2/neu amplification/overexpression has been associated with aggressive disease and poor prognosis in endometrial carcinoma, especially in serous and high-grade subtypes. Numerous studies have supported that HER2 is a promising target for the treatment of high-grade endometrial carcinomas which are not curable with surgery or radiation. Early phase II trials investigating anti-HER2 therapy, such as trastuzumab, in recurrent endometrial carcinoma reported limited clinical benefit. A notable phase II trial by Fleming GF et al., (2010) is most prominent among them in evaluating trastuzumab monotherapy in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu [11]. In this study no objective responses were observed, and the median progression-free survival was only 1.8 months, indicating minimal efficacy of trastuzumab as a single agent in this setting [11].

However, more recent studies have demonstrated improved outcomes with HER2-targeted therapies in select populations. The most prominent is the randomised phase II trial by Fader AN et al., (2018), which assessed the addition of trastuzumab to standard

chemotherapy (carboplatin and paclitaxel) in patients with advanced or recurrent uterine serous carcinoma with HER2/neu overexpression [12]. In this trial, the combination arm showed a significant improvement in median progression-free survival (12.6 months vs. 8.0 months for chemotherapy alone) and a trend toward improved overall survival, particularly in the recurrent disease subgroup. Fader AN et al., demonstrated that the addition of trastuzumab to carboplatin and paclitaxel chemotherapy significantly improved progression-free survival in patients with advanced or recurrent serous endometrial carcinoma overexpressing HER2/neu [12].

The initial studies found limited anti-tumour activity, with most patients not achieving objective responses or meaningful progression-free survival. One proposed reason for this limited efficacy is the presence of the p95HER2 variant in endometrial carcinomas, which lacks the trastuzumab binding site and may confer resistance to therapy. Growdon WB et al., demonstrated that HER2 over-expressing high-grade endometrial cancer expresses high levels of p95HER2 variant [13]. In their comparative study, high-grade endometrial carcinomas exhibited significantly higher levels of p95HER2 than breast carcinomas. This variant lacks the Extracellular Domain (ECD) required for trastuzumab binding but retains the active kinase domain, allowing continued oncogenic signaling However, combining trastuzumab with lapatinib, a small-molecule inhibitor targeting the intracellular tyrosine kinase domains of HER2 and EGFR produced synergistic antitumour activity in HER2-overexpressing models, suggesting that dual targeting of both the intracellular and ECDs of HER2 may help overcome resistance. In-vitro and in-vivo studies have consistently demonstrated that trastuzumab (an antibody targeting the ECD of HER2) and lapatinib interact synergistically to inhibit the growth of HER2-amplified tumour cells. Growdon WB et al., showed that while HER2-amplified endometrial cancer xenografts were resistant to trastuzumab monotherapy, the combination of trastuzumab and lapatinib resulted in a significant reduction in tumour growth compared to either agent alone [13]. Importantly, lapatinib retains activity in trastuzumab-resistant models, including those with PTEN loss or expression of truncated HER2 forms such as p95HER2.

Although HER2-targeted therapies (such as trastuzumab) have shown promise in certain high-grade endometrial carcinomas, especially serous subtypes, clinical trials have produced mixed results, and resistance mechanisms (like p95HER2 expression) complicate treatment. Thus, larger, multicenter, prospective clinical trials are needed to validate HER2 as a reliable prognostic marker, develop predictive biomarkers to determine which patients will benefit most from HER2-targeted therapies, as well as to optimise treatment protocols, and improve outcomes for this subset of patients.

Limitation(s)

Sample size was only 63 affecting the generalisibilty of the findings. Small biopsies were also included in the study in which grading of the tumour may not be always accurate. The study used immunohistochemistry for HER2/neu assessment, but did not include confirmatory testing (e.g., FISH), which is standard in updated ASCO/CAP guidelines. Due to logistic and financial reasons In situ hybridisation were not done for equivocal cases. The single centre design is also a limitation. Further multicentre studies with larger cohorts and comprehensive clinical data are warranted to validate these findings.

CONCLUSION(S)

The study showed that HER2/neu expression demonstrated a clear correlation with tumour aggressiveness, showing absent positivity in the lowest-grade tumours and progressively increasing expression in higher-grade malignancies. A statistically significant association emerged between elevated HER2 levels and advanced tumour grades, reinforcing its potential utility as a prognostic indicator for disease severity. The findings underscore the importance of standardised testing criteria and population-specific considerations when evaluating HER2 status in clinical practice.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 19, 2025
- Manual Googling: Jul 08, 2025
- iThenticate Software: Jul 11, 2025 (13%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 18, 2025**
Date of Peer Review: **May 06, 2025**
Date of Acceptance: **Jul 15, 2025**
Date of Publishing: **May 01, 2026**