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Her-2neu Expression in Endometrial Carcinoma Patients- A Preliminary Study from Western India

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ABSTRACT

Background: Her-2neu is a gene from the epidermal growth factor receptor family. It regulates cell growth. HER-2neu overexpression or amplification is more common in type 2 endometrial cancer than in type 1. Overexpression of HerR-2neu has been associated with poor prognosis. This study aimed to evaluate Her-2neu expression in endometrial carcinoma patients.

Method: 50 endometrial carcinoma patients were enrolled in this study. Her-2neu expression was studied using the immunohistochemistry method on formalin-fixed paraffin-embedded tissue and correlated with clinical and pathological parameters as well as disease status.

Result: Her-2neu positivity was observed in 10% (5/50) of the cases. Her-2neu expression was more frequent in postmenopausal women (10%). Her-2neu expression was more common in patients with lymphovascular invasion (18%) and lymph node positivity (20%). A higher frequency of Her-2neu expression was observed in tumors of the following types: ER-negative (22%), p53 mutant (17%), WT1-positive (25%), and Vimentin-positive (12%). To disease-free survival, Her-2neu-positive tumors had a higher rate of relapse.

Conclusion: In the present study, higher expression of Her-2neu was observed in patients with lymphovascular invasion, lymph node positivity, ER-negative tumors, p53-mutant tumors, WT1-positive tumors, and those with reduced disease-free survival (DFS). These findings suggest that Her-2neu is associated with disease spread, aggressiveness, proliferation in a hormone-independent manner, its role in the EMT (Epithelial-Mesenchymal Transition) process, and negative prognostic implications.

Keywords: Endometrial Carcinoma; Her-2neu; Immunohistochemistry

INTRODUCTION:

Approximately 90% of endometrial cancers are sporadic, and 10% are hereditary. Bokhman generally classified endometrial cancer into two main groups based on clinical and pathological features: Type I (Estrogen-Dependent) endometrioid endometrial carcinomas (EECs) and Type II non-endometrioid endometrial carcinomas (NEECs). The Cancer Genome Atlas (TCGA) identified four genetic types of endometrial cancer: DNA polymerase ε (POLE, ultramutated), microsatellite instability (MSI, hypermutated), copy number low, and copy number high [1]. Type I tumors are typically low grade with a favorable prognosis, having a 5-year overall survival rate of 86%, whereas Type II tumors are associated with a poorer prognosis, with a 5-year overall survival (OS) rate of 59% [2].

Recent interest has grown in targeting the tyrosine kinase receptor Her-2neu, encoded by the erb-b2 receptor tyrosine kinase 2 (ERBB2) oncogene, as a therapeutic target for high-grade endometrial carcinomas (ECs) [3].

Her-2neu (ErbB2) is a member of the human epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinases, including EGFR (HER1, ErbB1), Her-2neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [4]. Her-2neu overexpression is used to predict both disease-free survival and overall survival in patients with different cancers, including breast, ovarian, and salivary gland cancers [5].

A randomized phase II study comparing carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in advanced and recurrent HER-2neu-overexpressing endometrial serous carcinomas showed improved progression-free and overall survival benefits compared to patients treated with chemotherapy alone, with the greatest benefit observed in those with stage III/IV disease [6].

Materials and methods:

Study Design and Patient Selection

This retrospective study included 50 patients diagnosed and treated with endometrial carcinoma at The Gujarat Cancer and Research Institute (GCRI) between 2021 and 2023. Relevant clinical details such as age, menopausal status, tumor grade, histopathological subtype, and treatment history were obtained from the institutional medical records. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrieved from the Histopathology Department of GCRI for immunohistochemical (IHC) analysis. The study was approved by the Institutional Scientific Review Board and Ethics Committee.

Clinical and Pathological Data

Demographic and clinical data showed that 52% (26/50) of patients were of ≤ 58 years of age, whereas 48% (24/50) of patients were of >58 years of age, and 96% (48/50) of patients were postmenopausal.

About pathological characteristics, 79% (34/43) of patients had T1 tumor size, 7% (3/43) of patients had T2 tumor size, and 14% (6/43) of patients had T3 tumor size. About histological subtype, the majority of patients had Endometroid Adenocarcinoma, 62% (31/50), 28% (14/50) patients had Serous Carcinoma, 6% (3/50) patients had Clear cell carcinoma, and 4% (2/50) patients had Mixed Endometrial Carcinoma. Tumor grade was available in 32 patients; 6% (2/32) of patients had grade 1 tumors, 22% (7/32) of patients had grade 2 tumors, 72% (23/32) of patients had grade 3 tumors. Regarding Myometrial Invasion (MI), 48% (21/44) of patients had ≤50% MI, and 52% (23/44) of patients had >50% MI. Lymphovascular Invasion (LVI) was present in 54% (20/37) of patients, and 46% (17/37) of patients had no LVI. Lymph node status was available in 40 patients; 25% (10/40) of patients had lymph node-positive and 75% (30/75) patients had lymph node-negative. Out of 50 patients, 26% (13/50) developed metastasis. Regarding Treatment modalities, 5 patients underwent surgery only;17 patients had surgery with chemotherapy (CT) and brachytherapy; 4 patients had surgery with radiotherapy (RT) and brachytherapy; 15 patients had surgery with CT, RT, and brachytherapy; and 7 patients were treated with CT, RT, or brachytherapy alone. Disease status during follow-up was assessed via clinical and radiological examination.

Immunohistochemistry (IHC) Protocol

IHC staining was performed using the Ventana Benchmark ULTRA autoimmunostainer. Sections (3–4 μm thick) were cut from FFPE blocks and taken on APES-coated slides. The slides were incubated overnight at 60°C. On the following day, deparaffinization and antigen retrieval were carried out using EZ Prep and Cell Conditioning Solution (CC1), respectively.

Primary antibody for Her-2-neu (ready-to-use) was applied and incubated for 32 minutes. Detection was achieved using the UltraView DAB Detection Kit, which includes HRP-conjugated secondary antibodies

and chromogen reagents. Haematoxylin and bluing reagent were used for counterstaining. Slides were dehydrated and mounted with DPX.

Scoring System

Her-2-neu expression was scored according to ASCO/CAP guidelines. Cases showing no staining or ≤10% of tumor cells with faint/incomplete membranous staining were scored as 0 or +1 and considered negative. Cases with >10% tumor cells showing weak to moderate or strong complete membranous staining were scored as +2 or +3 and considered positive.

Statistical Analysis

Statistical analysis was performed using SPSS version 20. Descriptive statistics were used to calculate mean, standard error, and median. Pearson's Chi-square test and Pearson's correlation coefficient were used for assessing relationships between variables. Where applicable, likelihood ratio statistics were used for small sample sizes. Kaplan–Meier survival analysis and the Log-rank test were employed to determine the prognostic significance of disease-free survival (DFS). A p-value ≤0.05 was considered statistically significant.

RESULTS:

Her-2neu Expression

Membranous expression of Her-2neu was also observed. Of 50 patients, 42 (84%) showed a score 0, 3 (6%) showed a score of +1, a +2 score was seen in 2 (4%), and a +3 score in 3 (6%) of the patients. Scores 0 & +1 were clubbed as negative, and scores +2 & +3 were clubbed as positive. So, Her-2neu expression was found in 10% (5/50) cases and while 90% (45/50) cases were negative for Her-2neu expression. (Figure 1, 2)

Correlation with clinical and pathological parameters

In the present study, Her-2neu expression was correlated with various clinical and pathological parameters. Similar Her-2neu expression was observed in patients aged ≤58 years (11%) and in patients aged >58 years (8%). With menopausal status, none of the premenopausal patients expressed Her-2neu, and all the patients expressing Her-2neu were postmenopausal, which was noted in 10% (5/48) of the patients.In relation to tumor size, Her-2neu expression was absent in T2 and T3 tumors and 12% (4/34) of T1 tumors expressed Her-2neu. In relation to histological subtypes, Her-2neu expression was absent in patients having mixed endometrial carcinoma. While in other histological subtypes, Her-2neu expression was seen in 33% (1/3) of clear cell carcinoma, 14% (2/14) of serous carcinoma and 6% (2/31) of endometrial adenocarcinoma. In relation to histological grade, higher Her-2neu expression was found in grade III (13%) tumors as compare to grade II (0%) tumors. Grade I tumors patients show 50% (1/2) Her-2neu expression, however there were only 2 patients of grade I tumors. In relation to myometrial invasion (MI), Her-2neu expression was observed in 14% (3/21) of cases with <50% myometrial invasion, while only 4% (1/23) of cases with >50% myometrial invasion showed Her-2neu expression. In relation to lymphovascular invasion (LVI), Her-2neu expression was higher in patients with LVI 18% (3/17) compared to those without LVI 5% (1/20). In relation to lymph node

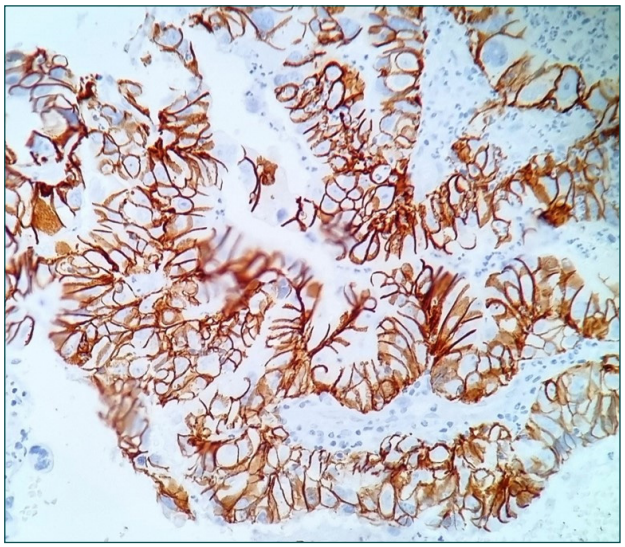

Figure 1: Positive staining of Her-2neu in EC patients

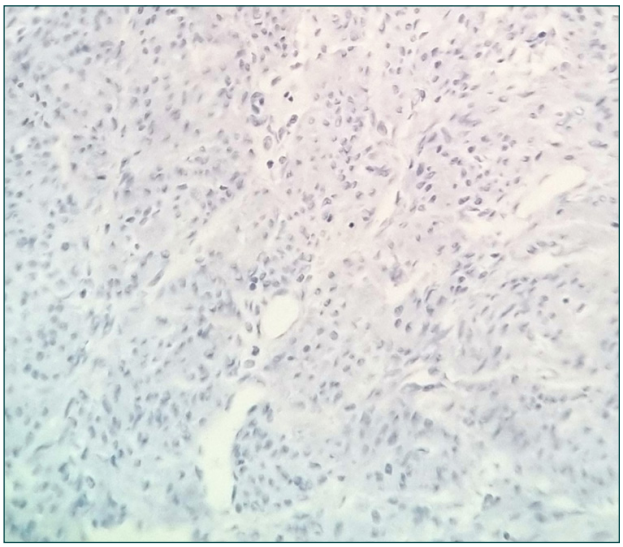

Figure 2: Negative staining of Her-2neu in EC patients

status, Her-2neu expression was higher in patients with lymph node positivity 20% (2/8) as compared to patients with lymph node negativity 7% (2/28). (Table 1)

Table 1. Correlation of Her-2neu Expression with clinical and pathological parameters

Parameter		Her-2neu				
	No. of Patients (% of the parameters available)	**Negative (%)**	**Positive (%)**	**χ2**	**r**	**p**
Age	**50 (100%)**	**45 (90%)**	**5 (10%)**			
≤58	26 (52%)	23 (89%)	3 (11%)	0.142	-0.053	5.39
>58	24 (48%)	22 (92%)	2 (8%)			
Menopausal status	**50 (100%)**	**45 (90%)**	**5 (10%)**			
Premenopausal	02 (04%)	2 (100%)	0 (0%)	0.231	0.068	0.808
Postmenopausal	48 (96%)	43 (90%)	5 (10%)			
Tumor size	**43 (100%)**	**45 (90%)**	**5 (10%)**			
T1	34 (79%)	30 (88%)	4 (12%)	1.167	-0.157	0.558
T2	3 (7%)	3 (100%)	0 (0%)			
T3	6 (14%)	6 (100%)	0 (0%)			
Histological type	**50 (100%)**	**45 (90%)**	**5 (10%)**			
Endometroid adenocarcinoma	31 (62%)	29 (94%)	2 (6%)	2.756	0.120	0.431
Serous carcinoma	14 (28%)	12 (86%)	2 (14%)			
Clear cell carcinoma	3 (6%)	2 (67%)	1 (33%)			
Mixed endometrial carcinoma	2 (4%)	2 (100%)	0 (0%)			
Histological grade	**32 (100%)**	**45 (90%)**	**5 (10%)**			
I	2 (6%)	1 (50%)	1 (50%)	3.578	-0.100	0.167
II	7 (22%)	7 (100%)	0 (0%)			
III	23 (72%)	20 (87%)	3 (13%)			
Myometrial invasion	**44 (100%)**	**45 (90%)**	**5 (10%)**			
<50%	21 (48%)	18 (86%)	3 (14%)	0.385	-0.173	0.269
>50%	23 (52%)	22 (96%)	1 (4%)			
Lymphovascular invasion	**37 (100%)**	**45 (90%)**	**5 (10%)**			
Present	17 (46%)	14 (82%)	3 (18%)	0.495	-0.203	0.242
Absent	20 (54%)	19 (95%)	1 (5%)			
Lymphnodes status	**40 (100%)**	**45 (90%)**	**5 (10%)**			
Positive	10 (25%)	8 (80%)	2 (20%)	0.495	-0.203	0.242
Negative	30 (75%)	28 (93%)	2 (7%)			

χ2 = Chi Square, r = Correlation Coefficient, p = p value ≤ 0.05 is significant

Correlation of Her-2neu expression with diagnostic immunohistochemistry panel

Her-2neu expression was correlated with the diagnostic immunohistochemistry panel. Higher Her-2neu expression was observed in ER-negative 22% (2/9) as compared to ER-positive 8% (3/38) tumors, but was not statistically significant. In relation to the Progesterone Receptor (PR), only 15 patients had known PR status. Similar Her-2neu expression was observed in PR positive 10% (1/10) and PR negative 0% (0/5) tumors. Her-2neu expression was higher in p53 mutant type 17% (4/24) tumors compared to p53 wild-type 5% (1/19) tumors, but was not statistically significant. Similar Her-2neu expression was observed in patients with p16-positive 11% (3/27) and p16-negative 20% (1/5) tumors. Though not statistically significant, higher Her-2neu expression was observed in WT1-positive 25% (1/4) tumors compared to WT1-negative 9% (2/22) tumors. Concerning Vimentin, only four patients, 12% (4/34) expressed Her-2neu and were all Vimentin positive. Regarding PAX8, similar Her-2neu expression was found in PAX8-positive 7% (1/14) and PAX8-negative 0% (0/3) tumors. (Table 2)

Univariate survival analysis

According to Kaplan and Meier univariate survival analysis, concerning DFS, a higher incidence of relapse/metastasis was found in patients with Her-2neu positive 40% (2/5) as compared to Her-2neu negative 24% (11/45) tumors. Only one patient died during the study period; therefore, overall survival was not evaluated. (Table 3)

Table 2. Correlation of Her-2neu expression with diagnostic immunohistochemistry panel

IHC marker		Her-2neu expression				
	No of patients (% of the parameters available)	**Negative**	**Positive**	**χ2**	**r**	**p**
ER	**47 (100%)**	**45 (90%)**	**5 (10%)**			
Negative	9 (19%)	7 (78%)	2 (22%)	0.426	-0.183	0.240
Positive	38 (81%)	35 (92%)	3 (8%)			
PR	**15 (100%)**	**45 (90%)**	**5 (10%)**			
Negative	5 (33%)	5 (100%)	0 (0%)	0.536	0.189	0.667
Positive	10 (67%)	9 (90%)	1 (10%)			
P53	**42 (100%)**	**45 (90%)**	**5 (10%)**			
Wild type	19 (44%)	18 (95%)	1 (5%)	0.462	0.177	0.254
Mutant	24 (56%)	20 (83%)	4 (17%)			
P16	**32 (100%)**	**45 (90%)**	**5 (10%)**			
Negative	5 (16%)	4 (80%)	1 (20%)	0.228	0.116	0.824
Positive	27 (8%)	24 (89%)	3 (11%)			
WT1	**26 (100%)**	**45 (90%)**	**5 (10%)**			
Negative	22 (85%)	20 (91%)	2 (9%)	0.839	0.180	0.408
Positive	4 (15%)	3 (75%)	1 (25%)			
Vimentin	**43 (100%)**	**45 (90%)**	**5 (10%)**			
Negative	9 (21%)	9 (100%)	0 (0%)	0.189	0.165	0.376
Positive	34 (79%)	30 (88%)	4 (12%)			

$\chi 2$ = Chi Square, r = Correlation Coefficient, p = p value ≤ 0.05 is significant

Table 3. Univariate survival analysis of Her-2neu expression

Her-2neu expression	No of patients (% of the parameters available)	Remission N (%)	Relapse N (%)
Negative	45 (90%)	34 (76%)	11 (24%)
Positive	5 (10%)	3 (60%)	2 (40%)
		(χ2=1.305, df=1,p=0.253)	

χ2 = Chi Square, p = p value ≤ 0.05 is significant

DISCUSSION:

In endometrial cancer, Her-2neu is linked to other prognostic factors that may predict worse outcomes. Her-2neu overexpression or amplification is more common in type 2 endometrial cancer than in type 1. Research has shown that Her-2neu amplification and overexpression occur in endometrial cancer, with overexpression rates between 2% and 36% according to immunohistochemistry (IHC) [7].

In the present study, Her-2neu expression was observed in 10% of patients and was absent in 90% of patients. Similar results were observed by different study groups on Her-2neu expression by IHC in the range of 9% to 18% in 78 to 247 endometrial carcinoma cases, as mentioned in the study of Saffari B etal.,1995[8]. Similar Her-2neu expression was noted in patients aged ≤58 years (11%) or >58 years (8%). All patients expressing Her-2neu were postmenopausal, and this was observed in 10% of the patients. These results were concordant with the study of Morrison et al.,2006, who found higher Her-2neu expression in postmenopausal women with endometrial carcinoma [9]. Regarding tumor size, 12% of T1 tumors showed Her-2neu expression, while no expression was noted in T2 and T3 tumors. The results were discordant with the findings of Morrison C et al.,2006, who found higher Her-2neu expression in larger tumors of patients with endometrial carcinoma [9]. Her-2neu expression was observed in 33% of clear cell carcinomas, 14% of serous carcinomas, and 6% of endometrial adenocarcinomas, while no expression was observed in mixed endometrial carcinomas. Other studies using FISH have indicated Her-2neu amplification observed in the serous histological subtype of endometrial carcinoma in the range of 14% to 80%, suggesting a strong relationship of Her-2neu expression and serous subtypes, but this was not observed in our study [10]. In terms of histological grade, grade III tumors (13%) had higher Her-2neu expression as compared to grade II tumors (0%). Grade I tumor patients showed 50% Her-2neu expression; however, there were only two patients with grade I tumors, and hence Her-2neu positivity was noted in 50% of patients. The results were similar to the study of Morrison et al.,2006, who reported a higher prevalence of Her-2neu expression in grade III endometrial carcinoma tumors, suggesting that Her-2neu overexpression may be associated with more aggressive tumor behavior[9]. Her-2neu expression was more frequent in cases with <50% invasion (14%) than in those with >50% invasion (4%). The reasons for this need to be evaluated. These results were discordant with those of Grushko et al.,2008, who reported a significant correlation between Her-2neu expression and deeper myometrial invasion in endometrial carcinoma [11]. Her-2neu expression was higher in patients with lymphovascular invasion (18%) than in those without lymphovascular invasion (5%). Similar findings were reported by Morrison et al. (2006, who found that Her-2neu amplification was significantly associated with lymphovascular invasion and worse clinical outcomes in patients with endometrial carcinoma, indicating its probable role in metastatic processes and tumor spread [9]. Her-2neu expression was higher in patients with lymph node positivity (20%) than in those with lymph node negativity (7%). Similar Her-2neu expression was observed by Mori N et al.,2010[12].

Further, Her-2neu was correlated with the diagnostic immunohistochemistry panel, such as estrogen receptors (ER), progesterone receptor (PR), p53, p16, WT1, Vimentin, and PAX8. The findings indicated that Her-2neu expression was more frequent in ER-negative tumors (22%) than in ER-positive tumors (8%). A Similar finding was observed in various studies, which reported that Her-2neu overexpression was more common in ER-negative endometrial carcinomas [13]. With respect to PR, PR status was only available in 15 patients, of whom one showed Her-2neu positivity. Study of Srijaipracharoen S et al., 2010 reported higher rates

of Her-2neu expression in PR-negative endometrial carcinomas [13]. Her-2neu expression was higher in p53 mutant tumors (17%) than in wild-type tumors (5%). This result is concordant with the study by Ross et al.,2022, who reported that Her-2neu overexpression was more frequently associated with p53 mutations, which are more aggressive in endometrial carcinoma [14]. Similar Her-2neu expression was found in 11% of p16-positive tumors and 20% of p16-negative tumors. In various studies, p16 expression in endometrioid adenocarcinoma ranged between 26% and 34% but did not show any correlation with Her-2neu expression [15,16]. Higher Her-2neu expression was found in WT1-positive tumors (25%) than in WT1-negative tumors (9%). A study by Tuna M et al.,2005, reported that Her-2neu enhances WT1 expression in breast cancer [17]. Her-2neu expression was only noted in 12% of Vimentin-positive tumors, suggesting that vimentin is a marker for epithelial-mesenchymal transition (EMT), which is associated with cancer progression and metastasis. Similar results were found in the study by Khillare CD et al.,2019, who found vimentin positivity in Her-2neu-positive breast cancer [18].

Furthermore, survival was assessed using Kaplan-Meier univariate survival analysis. A higher incidence of disease relapse/metastasis was observed in Her-2neu positive cases (40%) than in Her-2neu negative cases (24%). Only one patient died during the study period; therefore, the overall survival was not evaluated.

CONCLUSION:

In the present study, higher expression of Her-2neu was observed in patients with lymphovascular invasion, lymph node positivity, ER negative, p53 mutant tumors, WT1 positive, Vimentin positive patients, and those with reduced DFS. These findings suggest that Her-2neu is associated with disease spread, aggressiveness, proliferation in a hormone-independent manner, its role in the EMT process, and negative prognostic implications. The success of treatments in breast cancers suggests that targeting Her-2neu in endometrial cancer could represent a plausible and attractive treatment strategy that could spare the patient from currently available cytotoxic chemotherapies that yield short-lived responses with significant systemic toxicities. However, as the study was conducted in a small sample size, this needs to be confirmed in larger patient cohorts.

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