Her-2 Neu Expression in Endometrial Carcinoma

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Abstract

Introduction: Endometrial cancer formed 0.004 of the tumors in Egypt. Detection of high grade tumors from the low-grade ones is mandatory for survival of the patients.

Aim of the Work: The use of immunohistochemical technique to detect the expression of Her-2 neu in endometrial carcinomas.

Material and Methods: Fifty cases of endometrial carcinoma (37 endometrioid, 10 serous, 1 clear cell and 2 undifferentiated carcinomas) were stained with Her-2 neu and its immunoexpression results were evaluated statistically using Chi-square and *t*-test.

Results: Her-2 neu was expressed in (76%) 38/50 cases with statistically significant relation between Her-2 expression and both grade of the tumor $p<0.013$ and stage $p<0.05$. Although Her-2 immunostaining was not correlated with tumor histological type $p<0.088$.

Conclusions: Her-2 neu could be used to detect the low-grade, early-stages, endometrial carcinomas from the more aggressive high-grade endometrial carcinomas for therapy modulation.

Key Words: Her-2 neu – Endometrial carcinoma – Immuno-histochemical expression.

Introduction

ENDOMETRIAL carcinoma (EC) is the fourth most common cancer in women in the developed world. Classification of ECs by histomorphologic criteria has limited reproducibility and better tools are needed to distinguish these tumors and enable a subtype-specific approach to research and clinical care [1].

High-grade carcinomas of the endometrium (ECs) commonly include serous, clear cell, (FIGO) grade 3 endometrioid and undifferentiated endometrial carcinomas. Diagnostic disagreement between pathologists in distinguishing between these tumors is not uncommon owing to overlapping of the morphologic features by routine H&E stain. Immunohistochemistry is helpful as an objective method for a better diagnostic reproducibility, and a reliable prediction of the clinical outcomes [2,3].

Following the successful development of targeted therapy against Her-2 in breast cancer, reports on Her-2 overexpression have sparked considerable interest for a potential novel Her-2-based therapy in endometrial carcinoma (ECs) [4].

The major challenge is in distinguishing the features that comprise low, intermediate, and high risk disease in ECs. Multiple different risk predictive clinical models have been developed to guide treatment [5,6].

Several research teams have defined immuno-histochemical and/or mutation profiles to aid in distinguishing ECs subtypes [7]. In one series, a set of seven immunohistochemical markers was able to improve the distinction between high-grade ECs histeotypes [8]. The most comprehensive molecular study of ECs to date has been The Cancer Genome Atlas (TCGA) project, which included a combination of whole genome sequencing, microsatellite instability (MSI) assays, and copy number analysis. Molecular information was used to classify endometrioid and serous endometrial cancers into four groups: POLE ultramutated, microsatellite instability (MSI) hypermutated, copy-number (CN) low, and CN high that correlate with progression-free survival [9]. Stelloo et al., 2016 used a combination of TP53 mutational status, MSI status, POLE EDM hotspot mutations. Testing ultimately yielded four molecular subgroups: Group 1- p53 (mutation identified), group 2- MSI, group 3- POLE (POLE EDM identified), and finally group 4- NSMP, a group with (no specific molecular profile [10]. It

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had been demonstrated that women within each molecular subgroup have clinic-pathological characteristic that have consistently been shown to be typical of that group [11,12]. It has been shown that a combination of markers, including p53, p16, PTEN, and PR, may be helpful in discriminating uterine serous from endometrioid carcinoma [13], while most Undifferentiated carcinomas (UCs) showed expression of epithelial membrane antigen (EMA), CK8/18 (CAM 5.2), and approximately 50% of the tumors showed loss of at least 1 mismatch repair proteins (MMRs). The typical serous carcinoma is strongly and diffusely positive for p53 and p16, whereas these markers are less commonly positive in clear cell carcinoma [14].

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity. The HER2 receptor is a 1255 amino acid, 185kD transmembrane glycoprotein located at the long arm of human chromosome 17 (17q12) [15]. Homo- or heterodimerization results in the auto-phosphorylation of tyrosine residues within the cytoplasmic domain of the receptors and initiates a variety of signaling pathways, principally the mitogen-activated protein kinase (MAPK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and protein kinase C (PKC) resulting in cell proliferation, survival, differentiation, angiogenesis, and invasion. The introduction of Her-2 directed therapies has dramatically influenced the outcome of patients with Her-2 positive breast and gastric/gastroesophageal cancers; however, the results have been proved disappointing in other Her-2 overexpressing cancers. Both Her-2 overexpression and amplification have been linked to poor prognosis in endometrial carcinoma [16].

Aim of the work:

To study Her-2 neu immunoexpression in endometrial carcinomas and its possible role in differentiating low-grade from high-grade endometrial carcinomas for therapeutic purposes.

Material and Methods

This is a prospective study conducted for a period of 2 years from August 2015 to June 2017, in the Department of Pathology, Sohag University. A total number of 50 cases of endometrial cancers received at the Pathology department were included in the study. All the relevant clinical data were obtained from the patients' medical records. Tissues including hysterectomy and endometrial biopsies were subjected to routine processing and sections were stained with hematoxylin and eosin (H&E).

The histopathological sections were diagnosed based on WHO classification 2014 [17]. Three-4 micron sections were taken from formalin-fixed, paraffin-embedded tissue blocks for immunohistochemistry. The sections were stained by immunohistochemical technique with Her2 neu (Cat #MS-730-R7 (7.0ml) at a dilution of 1/100 for 2 hours at room temperature. Positive control was run with each batch. Positive staining was breast carcinoma sections; the negative control was performed on the same tissue without primary antibody. Her2 neu is a cell membrane marker. Immunohistochemical assessment of Her2 neu overexpression was graded as by ASCO (American society of clinical oncology)/CAP (College of American Pathologists) 2013 guidelines [18]. Data were analyzed statistically using Chi-square and *t*-test using SPSS program [14].

Staining pattern	Score	Her-2 expression assessment
• No staining is observed, or membrane staining is observed in <10% of the tumor cells.	0	Negative
• A faint/barely perceptible membrane staining is detected in >10% of the tumor cells.	+	Negative
• A weak to moderate complete membrane staining is observed in >10% of the tumor cells.	++	Weakly positive/ equivocal
• A strong complete membrane staining is observed in >30% of the tumor cells.	+++	Strongly positive

Staging of all the endometrial carcinomas was done according to FIGO (International federation of Gynaecology and Obstetrics) staging [19,20].

Results

The age range of the 50 studied patients with different histological types of endometrial carcinoma was (40-80) years, mean age was 59.4 years, and median age was 60 years. The patients' clinical and histopathological data were showed in (Table 1). The studied cases were classified in to 37 cases endometrioid carcinoma (25 grade 1, 11 grade 2 and 1 grade 3), 10 cases serous, 1 case clear cell and 2 cases undifferentiated carcinoma (Table 2).

Her-2 neu was positive in 38/50 (76%) of all cases of endometrial carcinoma (31 of them were endometrioid, 6 were serous and 1 was undifferentiated) (Tables 2,3, Graph 1). Her-2 neu was expressed in 31/37 (83.8%) endometrioid carcinomas (92.0% grade I, 82% grade II, in 0% grade III), 6

cases of serous carcinoma and in 1 case of undifferentiated carcinoma. There was a decrease in expression of Her-2 neu with increasing the tumor grade, with a statistically significant difference p-value <0.013 (Table 2, Graph 2). We found significant decrease in Her-2 neu expression with increasing stage of the tumor p-value 0.05 (Table 3, Graph 3).

Table (1): Clinical and histopathological data of studied patients (No=50).

Parameter	Histopathological type			
	Endometrioid ca. (No=37)	Serous (No=10)	Clear cell (No=1)	Undifferentiated (No=2)
Age (years):				
<50	6/37 (16.2%)	3/10 (30%)	1/1 (100%)	0/2 (0%)
≥50	31/37 (83.8%)	7/10 (70%)	0/1 (0%)	2/2 (100%)
Clinical presentation:				
Post-menopausal bleed	20/37 (54.1%)	5/1 0 (50%)	0/1 (0%)	2/2 (100%)
Peri-menopausal bleed	3/37 (1%)	3/10 (30%)	1/1 (1 00%)	0/2 (0%)
Uterine mass or polyp	14/37 (37.8%)	2/10 (120%)	0/1 (0%)	0/2 (0%)
Tumour size:				
≤3cm	9/37 (24.3%)	0/10 (0%)	0/1 (0%)	0/2 (0%)
>3cm	26/37 (70.3%)	3/10 (30%)	0/1 (0%)	1/2 (50%)
D&C "fragments"	2/37 (5.4%)	7/10 (70%)	1/1 (1 00%)	1/2 (50%)
Tumour stage:				
0-1-2	37/37 (100%)	0/10 (0%)	0/1 (0%)	1/2 (50%)
3-4	0/37 (0%)	10/10 (100%)	1/1 (100%)	1/2 (50%)
Lymph node (LN) status:				
Negative	37/37 (100%)	1/10 (10%)		1/2 (50%)
Positive	0/37 (0%)	9/10 (90%)	1/1 (100%)	1/2 (50%)

Table (2): Grading and histological types of Her-2+ve cases.

| Histological type	No	Grade I	Grade II	Grade III	Her-2 +ve	Her-2 −ve
Endometrioid carcinoma	37	25	11	1	31	6
Serous carcinoma	10	—	–	10	6	4
Clear cell carcinoma	1	–	–	1	0	1
Undifferentiated carcinoma	2	–	–	2	1	1
Total	50	25	11	14	38	12

Table (3): Her-2 neu expression in endometrial carcinoma according to the stage and grade.

|	Tumor grading			Tumor stage				Total
	I	II	III	I	II	III	IV	
Her-2 +ve	23	8	7	30	1	3	4	38
Her-2 −ve	2	3	7	5	2	1	4	12
Total	25	11	14	35	3	4	8	50
p-value	0.013*			0.05*				

N.B: grade III including high grade endometrioid, serous, clear cell and undifferentiated carcinoma.
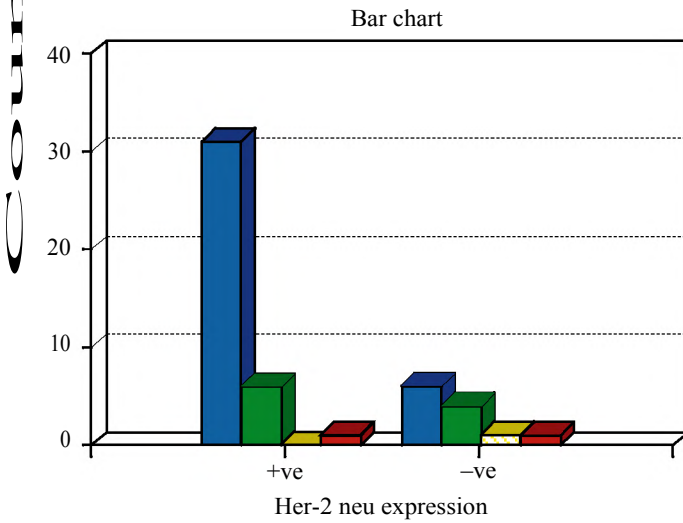Chi square test is used*= significant.
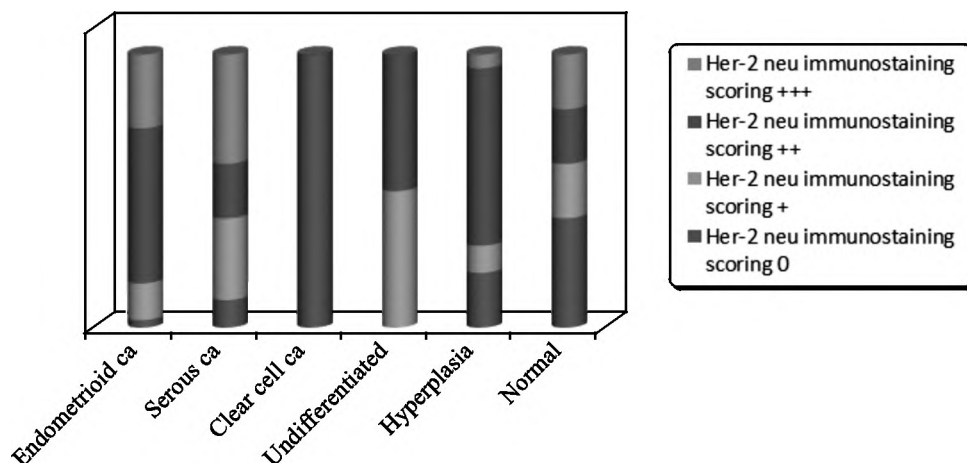
Graph (1): Her-2 scoring in relation to tumor type in the studied cases.
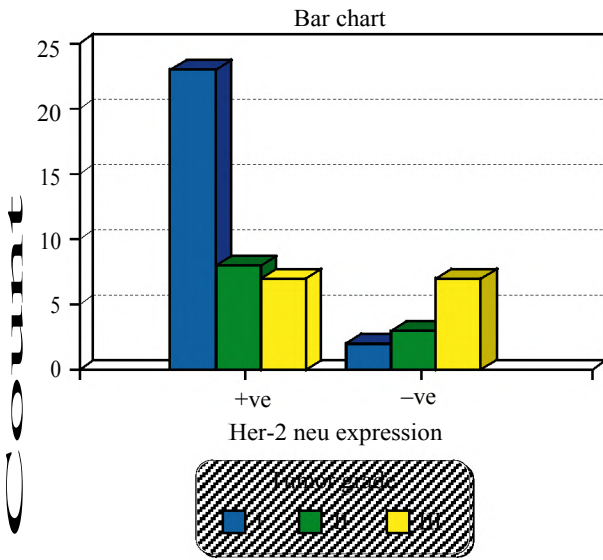
Graph (2): Her-2 expression in relation to tumor grade.
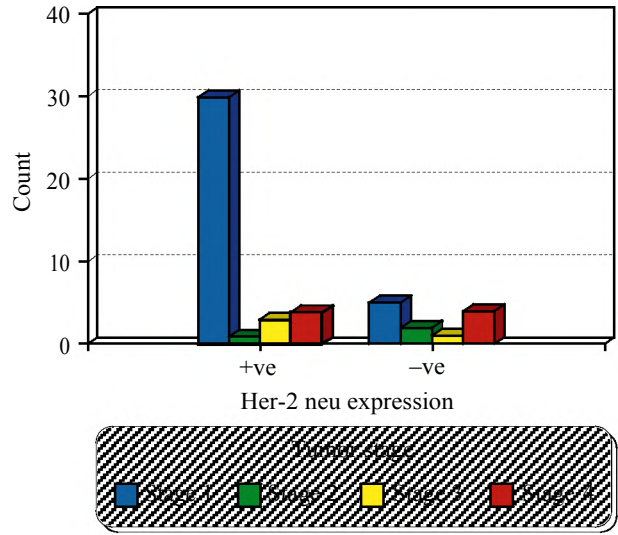
Graph (3): Her-2 expression in relation to tumor stage.

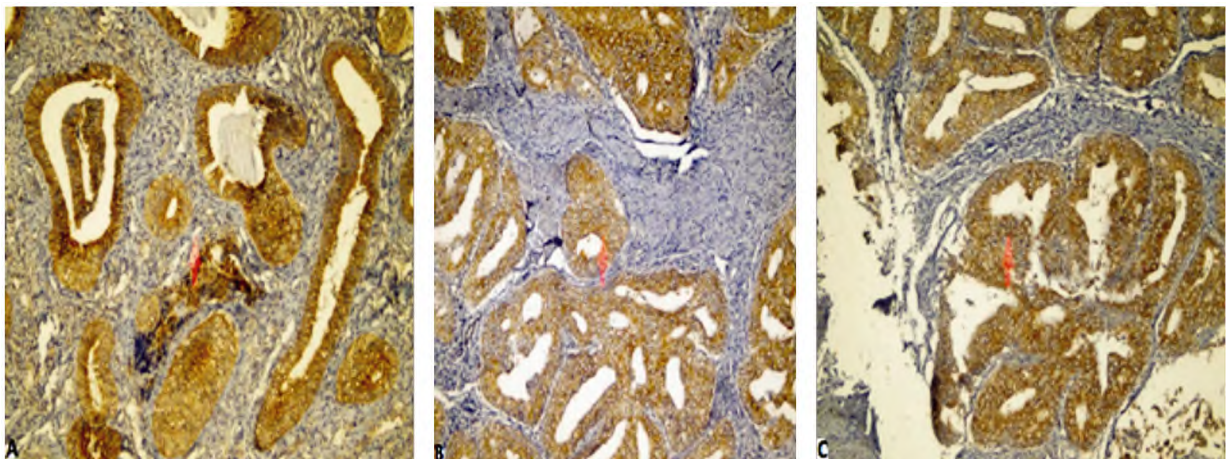Graph (4): Her-2 expression in relation to tumour type.

Fig. (1): Her-2 expression in simple endometrial hyperplasia (A, B&C: X 100).
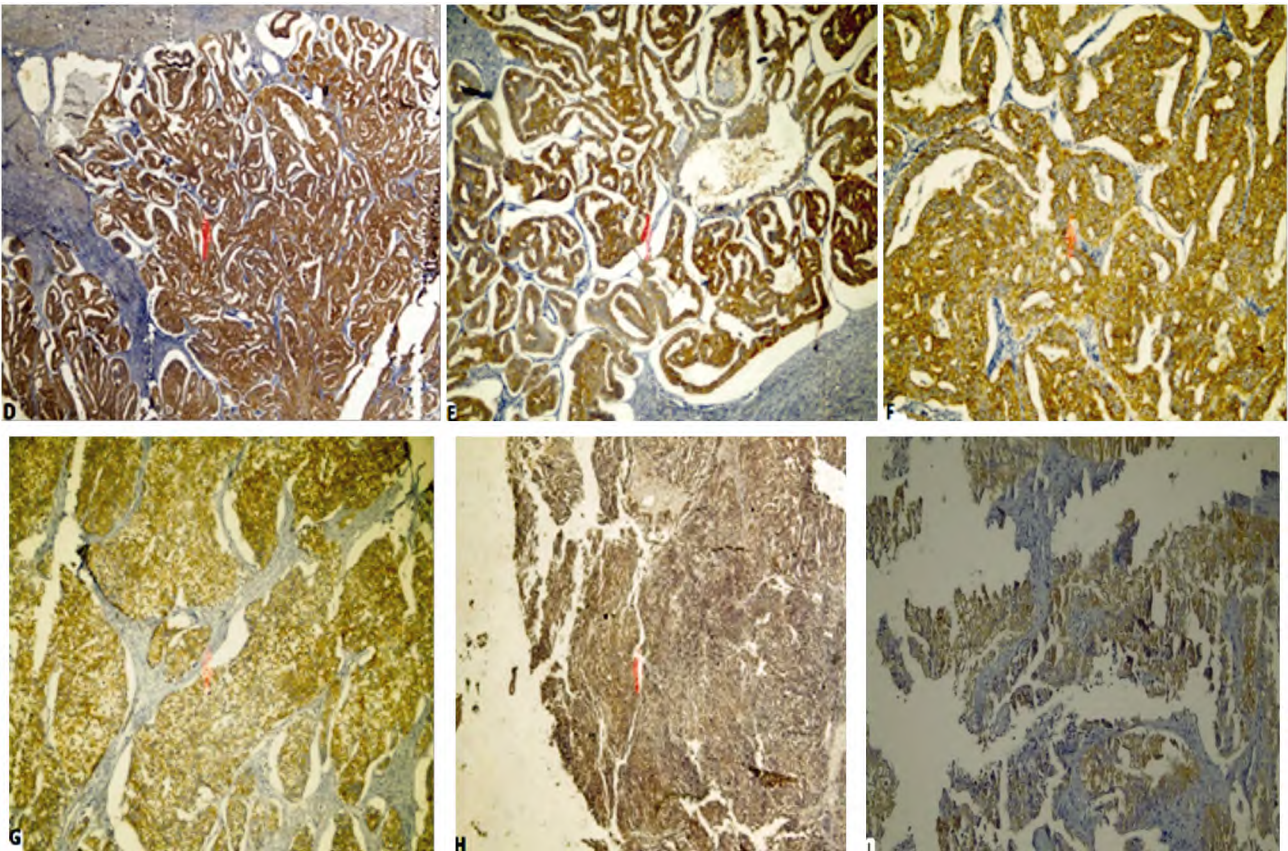
Fig. (1): D: Her-2 immunostaining in endometrioid carcinoma grade I (D: X 40, E: X 100, F: X 200).
G: Her-2 immunostaining in endometrioid carcinoma Grade III (X 100).
H: Her-2 expression in undifferentiated carcinoma (X 40).
I: Her-2 expression in papillary serous carcinoma (X 40).

Discussion

Endometrial carcinoma is the fifth most common cancer of women worldwide [21]. In Egypt, 426/100000 population had uterine cancer at 2014 that will increase to 502/100000 population at 2020 [22].

Her-2 overexpression has been shown to play a key role in the pathogenesis of various different cancer types, including breast, ovarian, gastric, and esophageal carcinomas [23].

Human epidermal growth factor receptor 2 (Her-2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity. Dimerization of the receptor results in the auto-phosphorylation of tyrosine residues within the cytoplasmic domain of the receptors and initiates a variety of signaling pathways leading to cell proliferation and tumorigenesis. Her-2 is expressed in many tissues and its major role in these tissues is to facilitate excessive/uncontrolled cell growth and tumorigenesis [23,25].

In our study Her-2 neu was expressed in 38/50 cases of endometrial carcinomas (76%) with a statistically significant relation between Her-2 immuno-expression and grade of the tumor (increased intensity of the expression with low grade than with high grade tumors) ($p<0.013$). Although the clinical and therapeutic importance of Her-2 in endometrioid type endometrial carcinomas may not be as high as in uterine serous carcinoma, it may have a prognostic value and potential role in the therapy of advanced and/or high-grade endometrioid carcinomas. Her-2 overexpression and amplification in endometrioid carcinomas have been reported in the range of 1% to 47% [26]. Direct correlation between tumor grade and Her-2 overexpression/amplification has been observed in some studies [27,28] whereas others have not confirmed such an association [29].

In the current study, Her-2 was expressed in low-grade tumors 63% and in 37% of the high grade tumors with a statistically significant relation ($p<0.013$). Growdon et al., 2015 studied the ex-

pression of Her-2 on 86 high-grade endometrial carcinomas and they identified high Her-2 expression in 59% of the tumors. They mentioned that high-grade endometrial carcinomas expressed higher levels of p95Her-2 (a mutant variant of Her-2/neu) possibly providing rationale for the trastuzumab resistance observed in endometrial carcinoma [30]. Benevolo et al., 2007 found Her-2 to be expressed in 31.5% of the study cases (200 cases) with the highest rate of expression in papillary carcinoma [31].

In contrast to our results, Srijaipracharoen et al., found that Her-2 neu expression was identified in only 2.8% of 108 studied cases. They found that all three cases which expressed Her-2 neu were of the endometrioid type [32], while another study of Suthipinthawong et al., reported that Her-2 neu was expressed in only 1.5% of the studied cases with no statistically significant relation to survival time [33]. Both studies showed low Her-2 immunostaining in endometrial carcinoma and this could be explained by a racial and ethical background of the Asian population.

Coronado et al., 2001 have reported Her-2 neu expression rate of 17% of 114 cases and its expression had a limited significance on survival [34], similarly, Jongen et al., in a large cohort of 315 endometrioid endometrial carcinomas, concluded that there was no significant correlation between Her-2 neu overexpression and patients' survival [35], which was also the finding of Engelsen et al., in a cohort consisting of similarly large sample of endometrioid cases (316 cases) where Her-2 was expressed in 23% of the cases [36]. Gul et al., detected a positive staining with Her-2 in 18.1% of the 72 casess of endometrial adenocarcinomas. They didn't find a statistically significant difference between Her-2 and histological grade, myometrial invasion, lymph node status, stage and survival [37].

In the present study Her-2 was expressed in 83% (3 1/38 cases) at stages I & II and in 7/38 cases at stages III& IV with a statistically significant relation $p<0.05$. Kalogiannidis et al., 2014, Her-2 neu expression was detected in 14 of 77 cases (18.2 %) and rate was significantly increased in patients with high FIGO stage ($p<0.001$) and tumor diameter >2cm ($p<0.04$) [38].

Grushko et al., 2008 had examined prospectively collected tumors from women with stage III-IV endometrial cancer, and identified Her-2 overexpression in 44% of the cases by IHC with increased positivity seen in the serous subtype [28]. Morrison

et al., concluded in their study that the expression of Her-2 was significantly correlated with higher grade ($p<.0001$) and stage ($p<.0001$), non endometrioid histology type ($p<.0001$), positive lymph node status ($p<.0107$), and greater than 50% myometrial invasion ($p<.0002$) [27]. These conflicting results could be explained by the smaller number of cases in our study (50 cases) in comparison to the Morrison study which is considered the largest study to date including 484 cases with Her-2 overexpression/amplification detection using both immunohistochemistry and fluorescent in situ hybridization techniques.

Conclusions:

Her-2 is an important factor particularly in low-risk tumors. Unfortunately the role that Her-2 plays in the vast majority of endometrial cancer may be diminished in comparison with breast cancer due to the relatively low incidence of expression in high-grade and stage endometrial cancer.

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تعبير هير-٢ نيو فى سرطان بطانة الرحم

يشكل سرطان بطانة الرحم ٠.٠٠٤ من الأورام في مصر. الكشف عن الأورام عالية الدرجة من تلك ذات الدرجة المنخفضة أمر حتمى ومنطقى لبقاء المرضى. يهدف هذا البحث الى معرفة تعبير هير -٢ نيو فى سرطان بطانة الرحم.

الطريقة:درسنا تعبير هير-٢ نيو عن طريق الصباغة المناعية الهستوكيميائية ل ٥٠ حالة من سرطان بطانة الرحم (٣٧ عينة سرطان شبيهة بطانة الرحم، ١٠ عينات سرطان مصلية، ١ عينة سرطان الخلايا الشفافة و ٢ عينة سرطان غير متمايزة) و قيمت النتائج احصائيا .

النتائج: قد تم التعبير عن الهير-٢ نيو فى (٥٠/٣٨) ٧٦٪ من الحالات و قد كان هناك ارتباط ذو دلالة احصائية بين التعبير عن هير -٢ نيو و درجة و مرحلة الورم بينما لم يكن هناك علاقة ذو دلالة احصائية بين تعبير هير -٢ نيو و نوع الورم.

الخلاصة:يمكن أن يستخدم هير -٢ نيو للكشف عن الأورام ذات الدرجة المنخفضة، و ايضا المراحل المبكرة، و تمييزها من سرطان بطانة الرحم ذات الدرجة العالية و الأكثر عدوانية لتشكيل العلاج.