

Overexpression of Her-2/neu oncogene in 51 cases of endometrial carcinoma

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Abstract

Background: Endometrial cancer is a common malignancy of the female genital tract. Her-2 overexpression is strongly correlated with tumor grade, type, and stage and this association complicate the issue of response of Her-2 positive endometrial carcinoma to chemotherapy. The aims of the current study are; to estimate the overexpression of Her-2 in endometrial carcinoma in our patients, to correlate the results with other known clinicopathologic markers and to compare our results with others.

Material and Methods: This is a cross-sectional retrospective study of 51 cases of endometrial carcinoma collected with their clinical data from Al-Batool Teaching Hospital and Al-Khansa'a Maternity Teaching Hospital in Mosul-Iraq from January 2007 to January 2010. All cases were revised histologically. Forty-three cases were total abdominal hysterectomy and 8 were curetting material. Tumors were classified into two main types, endometrioid and non-endometrioid carcinomas. Immunoperoxidase stains for Her-2/neu were performed on representative formalin-fixed paraffin embedded blocks.

Results: Majority of the endometrial carcinoma were in the 6th decade (50.9%) with a mean of 56.5 year. Her-2/ neu overexpression was observed in 58.8% of cases. The most frequent association was with non-endometrioid carcinoma (100%). Expression of Her-2/neu increased with increasing grade reaching 89.47% in grade III tumors. The highest expression was detected in tumors invading deep into the myometrium (77.77%).

Conclusion: HER-2/neu appears to play an important role in the biologic behavior of endometrial cancers. It was overexpressed in non-endometrioid carcinoma, especially papillary-serous type, high grade tumors, and among the higher stages. Therefore, targeted therapies directed against HER-2, could be effective in some patients with endometrial cancer.

Keywords: Endometrial carcinoma, Her-2/neu overexpression.

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Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract in the developed countries; it accounts for about 7% of all malignancies occurring in women^(1&2). In USA there were about 39,080 thousands estimated new cases of EC for the year 2007 representing the fourth most common cancer in women and ranks the first one in cancers of the female genital tract⁽³⁾. In Iraq according to the results of Iraqi Cancer Registry 2004-2008, uterine cancer was not included within the ten commonest cancer in woman, while malignant tumors of the ovary and the cervix ranked the fourth and tenth respectively⁽⁴⁾.

According to WHO/International Society of Gynecological Pathologists, there are several histological types of endometrial cancer. These include: 1- endometrioid and variants, such as ciliated cell adenocarcinoma, secretory adenocarcinoma, villoglandular, and adenocarcinoma with squamous differentiation, accounting for 75-80%; 2- mixed accounting for 10%; 3- uterine papillary serous accounting for <10%; 4- clear cell accounting for 4%; 5- mucinous accounting for 1%; 6- squamous cell accounting for <1%; and 7- undifferentiated carcinoma⁽⁵⁾. About 10% of endometrial carcinoma are hereditary and usually associated with hereditary non-polyposis colonic cancer, whereas the remaining 90% cases are sporadic⁽⁶⁾. Endometrial carcinoma occurs mostly in postmenopausal women especially in sixth decade. However, 20-25% of cases are diagnosed before menopause, particularly familial cases^(1,7).

The Her-2/neu (c-erb B-2) gene is protooncogen localized to chromosome 17q

that encodes a 185 kd transmembrane glycoprotein with tyrosine kinase activity and structural homology to the human epidermal growth factor receptor. Tyrosine kinase receptor family is involved in cell-cell and cell-stromal interaction⁽⁸⁾. Overexpression of Her-2 oncogene occurs in about 20-40% of endometrial carcinomas^(8,9). However; HER-2 amplification or overexpression has been reported in 4% to 69% of endometrial carcinomas, and some series note that, overexpression are more often in tumors of serous histology⁽¹⁰⁾. Her-2 overexpression is strongly correlated with other independent prognostic markers, including tumor grade, type, and stage and this association complicate the issue of response of Her-2 positive endometrial carcinoma to chemotherapy⁽¹¹⁾. Studies also showed there is a decline in survival curves of the Her-2 positive cases^(11,12).

The aims of this study were; to estimate the overexpression of Her-2 in endometrial carcinoma; to correlate that status with other known clinicopathologic markers; and to compare our results with others.

Material and Methods:

This is a cross-sectional study. A retrospective collection of 51 cases of endometrial carcinoma were collected from Al-Batool Teaching Hospital and Al-Khansa'a Maternity Teaching Hospital in Mosul-Iraq from January 2007 to January 2010. Forty-three cases were total abdominal hysterectomy and 8 cases were curetting material.

According to FIGO classification tumors were classified into two main categories: endometrioid (with its variants), and non-endometrioid carcinomas (includes papillary

serous and clear cell carcinoma), and were graded into architectural grade 1 (tumors composed of well-formed glands), architectural grade 2 (tumors show combination of glands and masses of solid epithelium), or architectural grade 3 (tumors composed predominantly of solid epithelial proliferations, papillary serous and clear cell carcinomas), including the nuclear grading, and were staged into no myometrial invasion, invasion within 1/2 of myometrial thickness, and invasion of > 1/2 of the thickness of the myometrium^(13,14).

Hematoxylin-eosin stained sections were reviewed for histological type, grade and depth of invasion of the myometrium. Clinical data were obtained from archival histopathological reports.

Immunohistochemistry

Immunoperoxidase stain for Her-2/neu was performed on representative formalin-fixed paraffin embedded blocks and was scored from

0 to 3 score according to the recent criteria set by ASCO/CAP, in which the cut-off positivity is changed from the previous 10% membrane staining cells to 30%. In final analysis score 0 and 1+ were considered negative, score 2+ was considered weakly positive and score 3+ was considered as strongly positive^(15,16,17).

Statistical Analysis

A chi square (X^2) statistic was used to test for correlations. Statistical significance was considered achieved when the p-value was less than or equal to 0.05.

Results

Clinical Finding

Fifty-one cases of endometrial carcinoma were collected. The patient age ranging from 30-70 years with a mean of 56.5, half of them were in the 6th decade of life. Thirty-three (64.7%) were above the age of menopause (>50 years), (Figure 1).

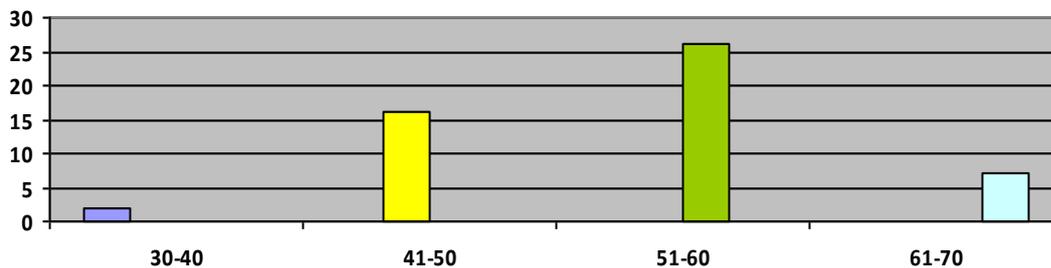


Figure 1: The age distribution of endometrial carcinoma

Histological finding:

Endometroid carcinoma (with its variants) was the predominant type encountered in 43 (84.31%) cases, while the non endometroid carcinoma was diagnosed in 7 (13.72%) cases. From endometroid cases, there was 31 (60.7%)

conventional type, 3 (5.88%) adenoacanthoma, 5 (9.8%) adenosquamous, 2 (3.92%) secretory type, 2 (3.92%) villoglandular and 1 (1.96%) mucinous type. Whereas the non-endometroid carcinoma, papillary serous carcinoma were 4 (7.84%) cases and clear cell carcinoma 3 (5.88%) cases.

Regarding the histological grading: there were 10 (19.6%) grade I, 22 (43.13%) grade II, and 19 (37.25%) grade III. From the 43 hysterectomy specimens, non-invasive tumor was identified in 13 (30.23%) cases, invasion to less than half of myometrial thickness present in 21 (48.83%) of cases and invasion to more than half of wall thickness identified in 9 (20.93%) hysterectomy specimen.

Her-2/ neu status

Overexpression of Her-2 was identified in 30 (58.8%) cases. Eleven of which scored 2+ (21.56%), and the remaining scored 3+ (37.25%). In relation to the age: Her-2 expression failed to show a statistically significant correlation. Although the highest reading (65.38%) was found in the age group 51-60 years (Table 1).

Table (1): Her-2 status and the age groups

Age group	Her-2 positivity	Her-2 negativity	Total number	Percentage of Positivity	P-Value
30 - 40	1	1	2	50.0%	0.894 (non-significant)
41 - 50	8	8	16	50.0%	
51 - 60	17	9	26	65.38%	
61 - 70	4	3	7	57.14%	
Total	30	21	51	58.8%	

Her-2 overexpression in correlation with the type of the tumor: Her-2/neu was overexpressed in 23/44 (52.27%) of endometroid carcinoma (including all its variants), and in all of non-endometroid carcinoma, 7/7 (100%). All of adenosquamous, papillary-serous

carcinoma and clear cell carcinomas were Her-2 positive (Figure 2). Therefore; Her-2 positivity and the types of endometrial carcinoma is statically significant with a p-value= 0.017 (Table 2).

Table (2): Correlation between the types of tumor and Her-2 positivity

Types of tumor	Her-2 positivity	Her-2 negativity	Total number	Percentage of Positivity	P-Value
Endometroid					0.017 (significant)
Classical	16	15	31	51.61%	
Adenoacanthoma	1	2	3	33.3%	
Adenosquamous	5	0	5	100%	
Villoglandular	0	2	2	0.0%	
Secretory	0	2	2	0.0%	
Mucinous	1	0	1	100%	
Non-endometroid					
Papillary-serous	4	0	4	100%	
Clear cell ca.	3	0	3	100%	
Total	30	21	51	58.8%	

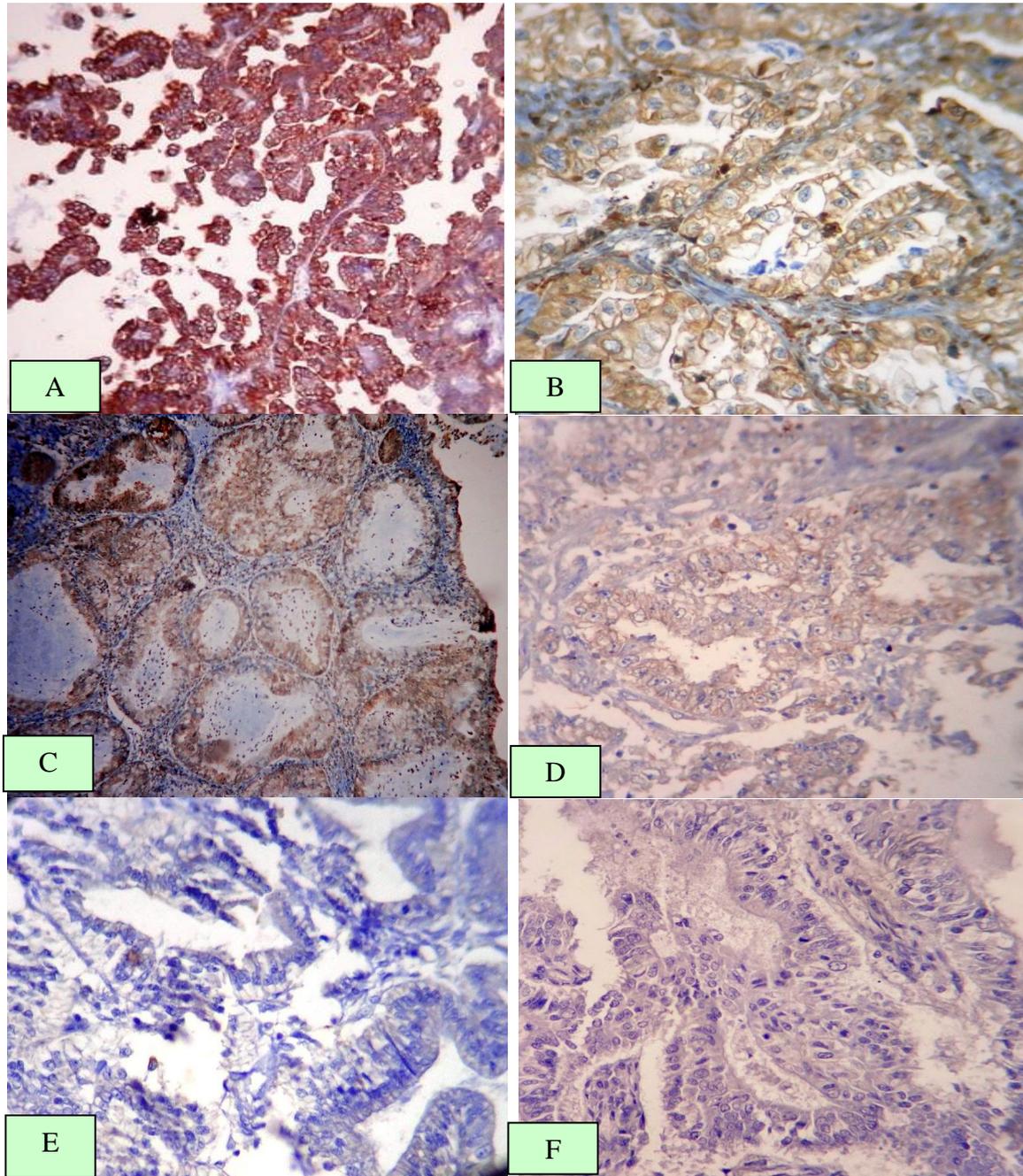


Figure 2: A- Papillary (3+, IHC x100), B- Clear cell (3+, IHC x400), C- Mucinous (2+, IHC x100), D- Classical endometroid, well-differentiated (1+, IHC x400), E- Secretory (0, IHC x400), F- Classical endometroid (0, IHC x400).

Regarding the grade of the tumors: Her-2 was over-expressed in 2/10 (20%) of grade I tumor, in 11/22 (50%) of grade II carcinoma, and in 17/19 (89.47%) of grade III cases. There was a

direct relationship between Her-2 overexpression and the grade of the tumor with a p-value = 0.005 (Table 3).

Table (3): The relationship between grade of the tumor and Her-2 overexpression

Grade	Her-2 positivity	Her-2 negativity	Total number	Percentage of Positivity	P-Value
I	2	8	10	20.0%	0.005 (significant)
II	11	11	22	50.0%	
III	17	2	19	89.47%	
Total	30	21	51	58.8%	

In correlation with the stage: Her-2 expression was in 1/13 (7.69%) of non-invasive tumors, 14/21 (66.66%) of tumor invading less than half of myometrial thickness, and 7/9 (77.77%)

of carcinomas invading more than half of the wall thickness. So the relationship is statistically significant (p-value = 0.000) (Table 4).

Table (4): Her-2 expression and the stage of the tumor

Myometrium invasion	Her-2 positivity	Her-2 negativity	Total number	Percentage of Positivity	P-value
No invasion	1	12	13	7.69%	0.000 (significant)
Less than half	14	7	21	66.66%	
More than half	7	2	9	77.77%	
Total	22	21	43	51.16%	

Discussion:

Her-2 overexpression and c-erbB-2 gene amplification are frequently associated with a more aggressive and chemo-resistant cancers⁽¹⁸⁾.

Overexpression of Her-2/neu oncogene occurs in about 20-40% of endometrial carcinomas^(1,8,9,12). However; Her-2/neu amplification or overexpression has been reported in 4% to 69% of endometrial carcinomas, and some series noted that, overexpression is more often in tumors of papillary-serous histology⁽¹⁰⁾. In the current study overexpression of Her-2 was observed in a relatively higher percentage (58.8%). This

might be explained by: First, the above percentage includes both 3+ and 2+ scores, and the 2+ score need further analysis by FISH technique. And secondly, by the high percentage of grade II and III tumors, presence of non-endometrioid carcinomas and the advanced tumors. Khalifa et al report a 59% positivity of Her-2/neu and many other studies correlate with our findings^(8,10,19,20). However; some other studies showed lower positivity of Her-2 status^(21,22).

In relation to age; no significant relationship has been found with Her-2 expression. This is similar to the majority of the other studies^(8,17,20).

Concerning the histological types; Her-2/neu expression was detected in a high percentage of non-endometroid carcinoma (100%). Santin et al, found that 80% of uterine papillary-serous carcinoma overexpressed Her-2/neu, and Prat et al, evaluated 10 cases of papillary-serous carcinoma and found protein overexpression in 40% of the tumors^(23,24). While other studies like Berchuck and Brian reported lower percentage of positivity (25% and 18% respectively) among uterine papillary-serous carcinoma^(25,26). So it is obvious that the present study is mildly higher than the majority of other similar studies which reported positivity ranging between 40-80% of non-endometrial carcinoma⁽²⁷⁾. However, this may be due to the fact that 2 out of the 7 cases of the positive non-endometroid carcinoma were 2+ score and these may need further gene amplification evaluation, as well as the 4 cases of papillary-serous carcinoma were of pure papillary.

In our study Her-2 overexpression was observed in 52.27% of endometroid carcinoma. Again this was higher than other related studies, probably because all of the adenosquamous cases were positive for Her-2/neu whereas some studies categorized them with non-endometroid carcinoma⁽²⁸⁾. Grushko et al identified 44% positivity of Her-2/neu among the endometroid carcinoma⁽⁸⁾. However, there was discrepancy with other researches, which reported lower percentage of positivity ranging between 18.1% to 21%^(10,21,29,30).

In regarding to the grade of tumor, Her-2/neu overexpression shows direct correlation with the increasing grade, reaching 89.47% in grade III tumors. This also explained the higher positivity of Her-2/neu in the current

endometroid carcinoma as the majority of which were grade II and grade III. These findings correlate with many similar studies^(8, 11,29).

With increasing depth of invasion of the myometrium, higher positivity of Her-2/neu was identified. Her-2 expression increased from 7.69% in non-invasive tumors, to 66.66% in less than half of myometrial thickness invasion, to 77.77% in tumor invades more than half of the wall thickness. Results from similar studies were concordant with ours^(11,20) or discordant⁽²⁹⁾.

Her-2 expression is considered as a independent bad prognostic factor and the overall survival was significantly shorter in patients who overexpressed and/or showed amplification of Her-2 versus those that did not^(11, 25,31,32,33).

Studies similar to ours have concluded that, Her-2 positive endometrial carcinoma cases may well respond to target therapeutic agents like Iressa (ZD1839), Herceptin (trastuzumab), and Lapatinib (GW572016). Moreover, other selective inhibitors like TK inhibitors have been explored for their therapeutic potential in the treatment of endometrial cancer^(11,24,34,35,36,37).

Conclusion:

Her-2/neu appears to play an important role in the biologic behavior of an, endometrial cancers and holds potential as a target for oncogene-directed therapies. HER-2 amplification was more common in non-endometroid carcinoma, especially papillary-serous type, relative to other histologic types, (100% versus 52.27%) and, among non-serous tumors, was more common in grade 3 tumors

(89.47%) than in grade 1 or 2 tumors (20.0% and 50.0%), and was associated with higher stages. Therefore, it is logical to assume that targeted therapies directed against Her-2/neu may be effective in some patients with endometrial carcinoma.

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فرط إظهار Her-2/neu في 51 من حالات الإصابة بسرطان بطانة الرحم

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الملخص

الخلفية: سرطان بطانة الرحم هو الورم الخبيث الشائع في المسالك التناسلية للإناث. وفرط إظهار Her-2 يرتبط بقوة مع علامات النذير المستقلة الأخرى، بما في ذلك درجة الورم، نوعه، ومرحلة انتشاره. وبالتعاون مع علامات أخرى سريرية مرضية تعقد مسألة استجابة سرطان بطانة الرحم ذات Her-2 إيجابي للعلاج الكيميائي. أهداف هذه الدراسة: تقدير فرط إظهار Her-2 في سرطانات بطانة الرحم، وربط هذه النتيجة مع علامات أخرى سريرية مرضية معروفة، وأخيراً مقارنة النتائج التي توصلنا إليها مع الآخرين.

المواد والأساليب: هذه دراسة مستعرضة بأثر رجعي لـ 51 حالة من سرطانات بطانة الرحم مع بياناتها السريرية بما في ذلك السن، والنوع النسيجية والرتبة ومرحلة انتشار الورم من مستشفى البتول التعليمي و مستشفى الخنساء للنسائية والأطفال التعليمي في مدينة الموصل-العراق من يناير 2007 إلى يناير 2010. تم تنقيح جميع الحالات نسيجياً. وكانت ثلاث وأربعون منها حالة استئصال كامل للرحم، و 8 حالات قشط لغشاع بطانة الرحم. تم تصنيف الأورام إلى نوعين رئيسيين، سرطانات شبيهةً ببطانة الرحم، وسرطانات غير شبيهةً ببطانة الرحم. وأجريت صبغة بيروكسيداز المناعي لها Her-2/neu على القوالب الممتلئة للورم من الفورمالين المثابتة، البارافين المدججة.

النتائج: كانت غالبية الحالات في العقد السادس (50.9%) وبمتوسط 56,5 سنة. سجلت فرط اظهار جين السرطاني Her-2/neu في 58.8% من سرطانات بطانة الرحم. وقد لوحظ أنه أكثر شيوعاً بالمقارنة مع سرطانات غير شبيهةً ببطانة الرحم ونسبة 100%. ووجدت زيادة التعبير عن Her-2/neu مع ازدياد فقدان درجة التميز، حيث تصل إلى 89,47% في أورام الدرجة الثالثة. وكذلك وجدت أعلى قراءة لـ Her-2/neu في الأورام الغازية عمقا في جدار عضلة الرحم (77.77%).

الخلاصة: Her-2/neu يبدو أنه يؤدي دوراً مهماً في السلوك البيولوجي لسرطانات بطانة الرحم. وكان فرط اظهار Her-2 أكثر شيوعاً في سرطانات غير شبيهةً ببطانة الرحم، خصوصاً نوع حلبي-مصلي، وكان أكثر شيوعاً مع الدرجات العالية والمرحلة المتقدمة من الورم. إن تلك العلاجات المستهدفة والموجهة ضد Her-2 قد تكون فعالة في جزء من المرضى الذين يعانون من الإصابة بسرطان الرحم.

الكلمات الدالة: سرطان بطانة الرحم، فرط إظهار Her-2، المسالك التناسلية للنساء.