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HER-2/Neu Oncogene in Endometrial Cancer

Maather Baqer Hussein Al-Harmooshee

Department of Pathology, College of Medicine, University of Al-Qadisiyah, Iraq.
Email: maather.hussein@qu.edu.iq

ABSTRACT

This analytical study was performed to estimate the overexpression and potential associations between the HER-2\neu oncoprotein in endometrial carcinoma of Middle Iraq and estrogen and progesterone, as well as the relevant pathological parameters. We analyzed the available tissue paraffin blocks of 60 patients with endometrial carcinoma who referred between January 2016 and December 2018 to hospitals of central Iraq governorates / pathology departments. The age ranges from 50 to 78 years (47 cases 78.3% was up to 60 & 13 cases 21.7 was more than 60) with mean of 64. most of the cases was postmenapousal in 80.4% and 16.6% was perimenapousal. 80% of cases was by hysterectomy & 20% of cases was by curettage. The cases were classified into grade I, II and III according to the grading system in 12, 38 and 10 cases respectively & out of 48 cases of hysterectomy, 36 cases were in stage I, 4 cases were in stage II & 8 cases were in stage III. A total of 19 (32 per cent) cases were positive for ER oncogene overexpression, 36 (60 per cent) positive for PR oncogene overexpression and 40 (66.6 per cent) positive for HER-2\neu oncoprotein overexpression. Low age groups of the endometrial carcinoma studied cases were linked to increased expression of PR & ER, 12 (63.1%) cases with ER positive & 23 cases (63.8%) with PR positive with age group less than 60 years old while high age groups of the endometrial carcinoma studied cases were linked to increased expression of HER-2/neu, 25 (62.5%) cases were positive. Postmenopausal cases of the endometrial carcinoma studied cases were linked to high expression of HER-2/neu, ER & PR, 13 (68.4%) ER cases, 28 (77.7%) PR cases & 34 (85%) HER-2/neu cases were positive. High histological grades of the endometrial carcinoma studied cases were linked to over expression of HER-2/neu & ER. 9 (22.5%) HER-2/neu cases & 2 (10.5%) ER cases were positive with a grade I tumor, 25 (62.5%) HER-2/neu cases & 11 (57.8%) ER cases were positive with grade II, and 6 (15%) HER-2/neu cases & 6 cases(31.5%) ER cases were positive with grade III.

While low histological grades of the endometrial carcinoma studied cases were associated with increased expression of PR receptors, 9 cases (25%) of positive cases in grade I, 22 cases (61.1%) in grade II & 5 cases (13.8%) in grade III. Low stages of the 48 hysterectomies endometrial carcinoma studied cases had increased expression of HER-2/neu, ER& PR. 30 (81%) HER-2/neu cases, 12 cases (63.1%) ER cases & 20 (17.4%) PR cases were positive with stage I tumor, 3 (8.1%) of HER-2/neu cases, 1 (5.2%) of ER cases & 2 (7.1%) cases of PR cases were positive with stage II tumor, and 4 (10.9%) of HER-2/neu cases, 6 cases (31.5%) of ER cases & 6 (21.5%) of PR cases were positive with stage three tumor. The expression of ER&PR, ER & HER- 2 / new & PR & HER-2 / new respectively, have no significant relationship

Keywords: HER-2\ne oncoprotein, Endometrial carcinoma, Estrogen, Progesterone, Post & peri menopousal

Correspondence:
Maather Baqer Hussein Al-Harmooshee
Department of pathology, college of Medicine, University of Al-Qadisiyah, Iraq.
Email: maather.hussein@qu.edu.iq

INTRODUCTION

In developed countries, endometrial cancer (EC) is the most prevalent cancer in females, accounting for about 7 percent and fifth leading cancer among women worldwide [1&2]. It's the third common gynecological malignancy after cervical and ovarian cancer in South East Asian, accounting for 6-9% of all cancers in women [3-5]. Endometrial cancer is often detectable in the early stages due to the nature of the disease and incidence of uterine and/or vaginal bleeding, with the 5-year survival rate of 85-91% 6. Most patients have good prognosis because they mostly presented early. The average 5 years' survival rate is around 80% [6]. It is representing the 4th cause of death after breast, colon and pulmonary ca and the 7th death cause due to female's cancer [6]. In addition to stage, age, histopathological type, tumor grade, lymph-vascular space involvement (LVSI), depth of myometrium invasion (MI), cervical invasion, and extra uterine involvement including lymph node (LN) status serve as prognostic factors [7,8]. Also, estrogen receptor (ER) and progesterone receptor (PR) do [9,10]. Most risk factors of endometrial cancer are associated with long stimulation by estrogen action not antagonized by progesterone, such factors being nuliparity (50% of cancers), late menopauses, obesity by converting adrenal androstendion in estrone in adipose tissue, polycystic ovary syndrome or functional ovarian tumors and estrogen substitution in postmenopausal treatment [11].

In EMC, expression of hormonal receptors is ranged from 32-77% for ER and 54-72% for PR [12,13]. They are associated with other good prognostic factor, including early disease stage, less invasion of myometrium, low grade, and absence of LVSI. [12,14-16]. In perimeopausal / postmenopausal age endometrial cancers are the commonest. However, in premenopausal patients it accounts up to 10% to 15%, with up to 2% to 5% under the age of 40 years [17]. Most endometrial cancers nearly (90%) still are sporadic and hereditary in less than 10% [18] and usually associated with hereditary non-polyposis colonic cancer [18]. The Her-2 / neu gene (c-erb B-2) is a chromosome 17q protooncogen that codes the 185 kd transmembrane glycoprotein with tyrosine kinase activity and structural homology for the human epidermal growth factor receptor [20].

HER-2/neu overexpression has been detected in some different types of human cancers**;** in one study it is

overexpressed in 13/59 cases of breast carcinoma, 8/29 cases of pulmonary adenocarcinomas , 10/58 cases of colorectal carcinoma , 6/56 cases of pulmonary squamous carcinoma and 7/62 cases of gastric adenocarcinoma [20].15/112 cases of endomaterial carcinoma [21] in other study 101/177 of transitional cell carcinoma of the urinary bladder showed overexpression of HER2 oncoprotein [22].

Also Her-2 expression ranged between 4% to 69% of endometrial malignancy [23,24], However, 4 to 69 percent of endometrial carcinoma have been reported to have HER-2 amplification, and some series have shown high expression in serous histology tumors [24]. In several studies on ovarian, breast and endometrial cancer, reported that over expression of this gene is linked to resistance to treatment and poor survival, this indicates that more offensive biological actions can occur with over express of HER2 / neu [25].

MATERIAL AND METHOD

We analyzed the available tissue blocks of 60 patients with endometrial cancer who had referred between January 2016 and December 2018 to hospitals of central Iraq governorates / pathology departments. Clinical factors, including age,stage, grade, treatment, recurrence and survival rate, have been collected from patients data. Both molecular analyzes were performed on formalin-fixed and paraffin-embedded (FFPE) diagnostic specimens. From paraffin-embedded tissue blocks, sections of 3 micrometer thickness were prepared and stained by hematoxylin-eosin stain. By using the International Federation of Gynecology and Obstetrics (FIGO) system, tumor grade was then determined [10] by a single pathologist blinded to the records of the patients.

Then IHC staining for ER, PR, and Her-2/neu were performed. Regardless of the intensity, nuclear staining for ER and PR assumed as positive when the immuno-staining extent >10%. The intensity and pattern of the HER2 membrane immuno-staining were evaluated, and all samples were scored on a 0 to 3+ scale with 0 means no staining, 1+ means >10% of invasive tumor cells with faint weak staining with only apportion of the membrane is positive (incomplete), 2+ representing weak - moderate intensity in more than 10% of cells with complete membrane immunoreactivity and 3+ representing an intense circumferential membranous staining in more than 10% of the invasive carcinoma.

Data were analyzed by SPSS software (24v, USA). P value < 0.05 was considered significant.

RESULT

60 Endometrial carcinoma cases have been included in our study. Mean age was 57.3 years (ranged from 50 - 78 years). Most of the studied cases (80.4%) were menopausal. 48 cases obtained by hysterectomy and 12 cases by curettage. The cases were classified into grade I, II, and III in 12 (20%), 38 (63%), and 10 (17%) cases, respectively. A total of 48 hysterectomy cases classified into stage I, II, and III, in 36 (60%). 4 (6.6%) & 8 (13.4), respectively (table 1).

A total of 19 (32%) cases were positive for over expression of *estrogen* & 36 cases (60%) were positive for over expression of *progesterone*.

Over expression of *HER-2/neu* were 19 (31.6%) cases, which classified into score 0, 1, 2 & 3 in 32, 9 ,11 & 8 cases respectively (table 2).

Low age groups of the endometrial carcinoma studied cases were correlated with over expression of PR & ER, there have been 12 (63.1%) cases of ER positive & 23 cases (63.8%) of PR positive with age group less than 60 years old with no significant relationship while high age groups of the endometrial carcinoma studied cases have been correlated with over expression of HER-2/neu, where 12(63%) cases of positive HER-2/neu with highly significant relationship (table 3).

Postmenopausal cases of the endometrial carcinoma studied cases were highly expressed of HER-2/neu, ER & PR, there have been 13 (68.4%) positive cases of ER & 28(77.7%) positive cases of PR & 16 (85%) cases were positive of HER-2/neu (table 4).

High histological grades of the endometrial carcinoma studied cases were with high expression of HER-2/neu & ER , There have been 4 (22.5%) positive cases of HER-2/neu & 2 positive cases (10.5%) of ER with a grade I tumor, 12 (62.5%) positive cases of HER-2/neu & 11 (57.8%) positive cases of ER with grade II, and 3(15%) of positive cases HER-2/neu & 6 positive cases (31.5%) of ER with grade III. While low histological grades of the endometrial carcinoma studied cases were associated with increased expression of PR receptors, 9 cases (25%) of positive cases in grade I, 22 cases (61.1%) in grade II & 5 cases (13.8%) in grade III (table 5).

Low stages of the 48 hysterectomies endometrial carcinoma studied cases were correlated with high expression of HER-2/neu , ER& PR , There have been 10 (76.9%) positive cases of HER-2/neu , 12 (63.1%) positive cases of ER & 20 (17.4%) positive cases of PR with stage I tumor, 1 (7.7%) positive cases of HER-2/neu, 1 (5.2%) positive cases of ER & 2 (7.1%) positive cases of PR positive with stage II tumor, and 2 (15.4%) positive cases of HER-2/neu, 6 (31.5%) positive cases of ER & 6 (21.5%) positive cases of PR with stage III tumor (table 6).

The relationship between ER & PR, ER&HER-2neu, and & PR & HER-2 neu was **non-significant**.

Table 1: Clinicopathologic characteristics of endometrial carcinoma cases.

Clinicopathological characteristic		
Age	**≥ 60**	**47**
	< 60	**13**
Menopausal status	**Perimenopausal**	**10**
	Postmenopausal	**50**
Grade	**I**	**12**
	II	**38**
	III	**10**
Stages	**I**	**36**
	II	**4**
	III	**8**

Table 2: HER-2/neu, ER& PR expression in analytical cases.

ER	**Positive**	**19 (32%)**
	Negative	**41 (68? %)**
PR	**Positive**	**36 (60%)**
	Negative	**24 (40%)**
HER-2/neu	**0**	**32 (53.4%)**
	+1	**9 (15%)**
	+2	**11 (18.3%)**
	+3	**8 (13.3%)**

Table 3: HER-2/neu, ER& PR expression in analytical cases in relation to the age.

		< 60	**≥ 60**	**Total**	**P value**
ER	**Positive**	12 (63.1%)	7 (36.8%)	41(68.3%)	**0.22**
	Negative	19 (46.3%)	22 (53.7%)	19(31.7%)	
PR	**Positive**	23(63.8%)	13 (36.2%)	36(60%)	**0.09**
	Negative	10 (41.6%)	14 (58.6%)	24(40%)	
HER-2/neu	**Positive**	7(37%)	12(63%)	19(31.6%)	**0.11**
	Negative	24(60%)	17(40%)	41(68.4%)	

Table 4: HER-2/neu, ER & PR, expression in endometrial carcinoma cases in relation to the menopausal state.

		Perimenopausal	**Postmenopausal**	**Total**	**P value**
ER	**Positive**	6 (31.6%)	12(68.4%)	19 (31.7%)	**0.03**
	Negative	4 (9.8%)	37 (90.2%)	41(68.3%)	
PR	**Positive**	8(22.3%)	28 (77.7%)	36 (60%)	**0.15**
	Negative	2 (8.4%)	22 (91.6%)	24 (40%)	
HER-2/neu	**Positive**	3 (15%)	16 (85%)	19 (31.6%)	**0.7**
	Negative	8 (20%)	33 (80%)	41(68.4%)	

Table 5: HER-2/neu, ER & PR, expression in endometrial carcinoma cases in relation to the grades.

		Grade I	**Grade II**	**Grade III**	**Total**	**P value**
ER	**Positive**	2 (10.5%)	11 (57.8%)	6 (31.5%)	19 (31.7%)	**0.7**
	Negative	10 (24.3%)	27 (65.8%)	4 (9.7%)	41 (68.3%)	
PR	**Positive**	3 (12.5%)	16 (66.6%)	5 (20.9%)	24 (40%)	**0.44**
	Negative	9 (25%)	22 (61.1%)	5 (13.8%)	36 (60%)	
HER-2/neu	**Positive**	4 (22.5%)	12 (62.5%)	3(15%)	19 (31.6%)	**0.8**
	Negative	6 (15%)	27 (65%)	8 (20%)	41(68.4%)	

Table 6: HER-2/neu, ER & PR, expression in endometrial carcinoma cases in relation to the stages.

	Stage I	**Stage II**	**Stage III**	**Total**	**P value**

ER	Positive	12 (63.1%)	1 (5.2%)	6 (31.5%)	19 (39.6%)	**0.76**
	Negative	3 (12.5%)	16 (66.6%)	5 (20.9%)	29 (60.4%)	
PR	Positive	20 (17.4%)	2 (7.1%)	6 (21.5%)	28 (58.4%)	**0.56**
	Negative	16 (80%)	2 (10%)	2 (10%)	20 (41.6%)	
HER-2/neu	Positive	10 (76.9%)	1 (7.7%)	2(15.4%)	13 (27%)	**0.32**
	Negative	19(54.5%)	3(9%)	13 (36.3%)	35 (73%)	

Table 7: ER & PR expression in endometrial carcinoma cases.

		PR		**Total**	**P value**
		Positive	**Negative**		
ER	**Positive**	15 (41.6%)	4(16.6%)	19(31.6%)	**0.04 S**
	Negative	21(58.4%)	20 (83.4%)	41(68.3%)	
Total		36(40%)	24(60%)	60(100%)	

Table 8: HER-2/neu & ER, expression in endometrial carcinoma cases.

		HER-2/neu		**Total**	**P value**
		Positive	**Negative**		
ER	Positive	7 (37.5%)	12 (29.2%)	19(31.6%)	**0.5 NS**
	Negative	12(62.5%)	29 (70.8%)	41(68.3%)	
Total		19 (31.6%)	41(68.4%)	60(100%)	

Table 9: HER-2/neu &PR, expression in endometrial carcinoma cases.

		HER-2/neu		**Total**	**P value**
		Positive	**Negative**		
PR	**Positive**	15 (78.9%)	21(51.2%)	36(60%)	**0.07 NS**
	Negative	4(21.1%)	20(48.8%)	24(40%)	
Total		19 (31.6%)	41(68.4%)	60(100%)	

A&B: Strong HER2 immunohistochemistry: deep, full membrane stains in approximately 90% of tumor cells, 3score, C&D: Moderate degree of ER stains, E&F: Strong &Moderate PR stains.

DISCUSSION

To improve cancer treatment, identification of molecular markers that provide an insight into the tumors' potential behavior or aggressiveness is necessary., Slamon et al on breast cancer in 1987 was the first who's determined the linked between HER-2 / new gene amplifying and bad prognosis [25]. Expression of ER and PR was usually linked to better prognosis of breast carcinomas, while her-2 neu has poor prognosis [24, 25]. This basic information leads to standard adjuvant therapy in breast cancer for the use of hormonal therapy in cases whose tumors displayed positive expression of ER or PR or for the use of anti-her2 / neu in cases with positive Her-2 / neu expression [26]. Thus, recognizing the status of ER, PR, and Her-2 / neu at the time of primary diagnosis from surgical breast cancer care is mandatory in clinical practice. In EMC, radiation therapy is the main adjuvant therapy after surgery. For advanced or recurrent disease, the hormone therapy plays a greater role. EMC reacts directly to the degree of tumor differentiation, which, in turn, is associated with hormonal receptor status, especially the levels of the progesterone receptor [27]. So, it will definitely be important to know the status of these hormonal receptors when considering care choices.

Our analytical study found ER and PR expression in 32% & 60% respectively, with highly significant relationship. Our results were in the ranges of other studies results

(32-77% for ER and 54-72% for PR expression) [12-14]. While lower than other studies as Bassma M. El Sabaa and Iman M. Talaat, 2017 which was in 94% of studied cases and Caifeng Wang1et al 2020 which was in 59.8% & 75.0% for ER & PR respectively [28-30]. Obviously, different levels of hormonal receptor expression from various studies depend on several factors, such as the proportion of low- and high-grade tumors reported to have higher and lower expression of hormonal receptors, respectively. The growth factor HER2 / new plays a significant role in controlling cell proliferation and differentiation [31]. It is one of the human epidermal growth factors receptors for human development. These include EGFR (ER1, ErbB1), HER2 / Neu (ErbB2, HER3 (ErbB3), HER4 (ErbB4) transmembrane tyrosine kinase families [32-34]. Many studies have shown that increased HER2/neu expression in ovarian and breast cancer is an independent factor predicting a poor prognosis. It is found that her-2 / neu oncogene is overexpressed in approximately 20 % to 40% of endometrial carcinomas [35-38]. We found expression of her-2 in endometrial carcinoma was in (32.6) %. Grushko, et al report that 44% positive cases of her2/neu among the endometrial carcinoma [32], which is slightly higher than our study, this most likely due to lower number of patients in our study. Khalifa and Mohammed found that 59% & 58.8% positivity of her-2/neu expression respectively [39,40].

High histological grades of the endometrial carcinoma studied cases have been linked to increased expression of HER-2 neu & ER, while low histological grades studied cases have been linked to high expression of PR receptors, with no significant relationship, this is disagree with Sunamchok Srijaipracharoenet al 2010 , Kaustav Mohapatra & Sheela devi C. Shivalingaiah 2019 & Samina Waqar et al,2018 where their expression is statistically significantly related to tumor grades [41-43]. Low stages of the 48 hysterectomies endometrial carcinoma studied cases have been associated with high expression of HER-2 neu , ER& PR, with no significant relationship , this is disagree with Sunamchok Srijaipracharoenet al 2010 , Kaustav Mohapatra & Sheela devi C. Shivalingaiah 2019 & Samina Waqar et al,2018 where their expression is statistically significantly related to tumor stages [41-43].

CONCLUSION

Diagnosis of endometrial carcinoma 's molecular subtype with minimal markers, including ER / PR, HER2 / neu-related breast cancer, may be helpful for evaluating treatment and prognosis, particularly in developing countries. Studies with larger samples could clarify their role, which was the constraint in this study. And in order to further elucidate the function of HER-2 / neu oncogenes, extensive research with longer follow-up periods and larger sample sizes is needed.

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