RESEARCH COMMUNICATION

Expression of ER, PR, and Her-2/neu in Endometrial Cancer: A Clinicopathological Study

Sunamchok Srijaipracharoen[1]*, Siriwan Tangjitgamol[1,2], Sujitra Tanvanich[2], Sumonmal Manusirivithaya[1], Jakkapan Khunnarong[1], Thaovalai Thavaramara[1], Surawute Leelahakorn[1], Kamol Pataradool[1]

Abstract

Objective: To determine any association between expression of estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu and clinicopathological features, including survival, of endometrial carcinoma (EMC) patients. Methods: Samples of formalin-fixed, paraffin-embedded tissue of 108 patients with EMC treated at our institution between January 1994 and December 2007 were immunohistochemically studied. Results: ER, PR, and Her-2/neu expression were positive in 59.3%, 65.7% and 2.8% of cases, respectively. Positive ER expression was significantly associated with grade I-II tumor while PR expression was linked with endometrioid histology, grade I-II tumor, less myometrial invasion (MI) and negative lymph node involvement. Her-2/neu expression was significantly associated with deep MI, while positive ER and negative Her-2/neu expression in combination was significantly associated with longer disease-free and overall survival. Conclusion: ER expression is a good prognostic factor while Her-2/neu expression appears to be a poor indicator for both disease-free and overall survival, while PR tended to show favorable influence for only disease-free survival of Thai EMCs.

Key Words: Endometrial carcinoma - ER and PR expression - Her-2/neu status

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Introduction

Endometrial carcinoma (EMC) is the third most common gynecological malignancy in South-Eastern Asia following cervical and ovarian carcinomas. The majority of patients have favorable outcomes because they frequently present at early stage. The overall 5-year survival is approximately 80% (Parkin et al., 2005).

Primary treatment of EMC is surgery. Adjuvant therapy is given to the patients based on various clinical and surgico-pathological risk factors. Most of the patients with advanced stage and high-risk early stage disease will have additional treatment with radiation, either alone or in combination with chemotherapy (Creutzberg et al., 2000; Keys et al., 2004; Kodama et al., 2007). Aside from stage, other features which serve as prognostic factors are age, histopathological type, tumor grade, lymph-vascular space involvement (LVSI), depth of myometrial invasion (MI), cervical invasion, and extrauterine involvement including lymph node (LN) status (Gal et al., 1991; Wolfson et al., 1992; Creutzberg et al., 2000). Being a hormone-related cancer like breast cancer, estrogen receptor (ER) and progesterone receptor (PR) are also identified as specific prognostic factors for EMC (Carcangiu et al., 1990; Kleine et al.,1990; Nyholm et al.,1993; Fukuda et al., 1998; Iwai et al.,1999).

The expression of hormonal receptors in EMC is reported to range from 32-77% for ER and 54-72% for PR (Fukuda et al., 1998; Jeon et al., 2006; Suthipinthawong et al., 2008). Their expressions are associated with other good prognostic factors, such as early stage of disease, less myometrial invasion, low tumor grade, and absence of LVSI (Creasman et al., 1985; Nyhlom et al., 1992; Hanekamp et al., 2003; Miyamoto et al., 2004; Jeon et al., 2006; Jongen et al., 2009). Regarding an impact of ER and PR expression on survival, controversial data exist. Some authors reported PR and/or ER positivity as the independent good prognostic factors for survival (Palmer et al., 1988; Kleine et al., 1990; Morris et al., 1995) while others could not demonstrate such findings (Luke et al., 1994; Iversen et al., 1998; Sivridis et al., 2001).

In breast carcinoma, Her-2/neu is another important protein receptor being studied as a marker together with ER and PR. Her-2/neu expression in breast cancer was reported ranging from 5-55% with a mean of 26% (Revillion et al., 1998; Klijanienko et al., 1999). Its expression was found to be inversely correlated to ER and PR expression (Heintz et al., 1990; Todd et al., 1992). Additionally, Her-2/neu was identified as an important poor prognostic factor associated with clinical aggressiveness in breast cancer (Klijanienko et al., 1999). In EMC, a few studies reported 9-30% Her-2/neu expression (Saffari et al., 1995; Niederacher et al., 1999;

*[1]Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, [2]Department of Anatomical Pathology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, Bangkok, Thailand *For Correspondence: handsomejoob@hotmail.com*

Coronado et al., 2001; Engelsen et al., 2008). Many authors attempted to study an association between Her-2/neu expression and the clinicopathological features in EMC, but the results were inconclusive. Some authors reported association between the Her-2/neu expression and other poor prognostic factors, such as advanced stage, high tumor grade (Berchuck et al., 1991; Coronado et al., 2001), deep myometrial invasion (Khalifa et al., 1994), and as an independent prognostic factor for survival (Engelsen et al., 2008). However, others could not demonstrate such findings (Luke et al., 1994; Pisani et al., 1995).

The purposes of this study were to determine the association between the expression of ER, PR, and Her-2/neu and clinicopathological features including survival of EMC patients.

Materials and Methods

The study had obtained an approval from the Ethics Committee for Research involving Human Subjects of Bangkok Metropolitan Administration. We searched the archives of the Department of Anatomical Pathology and the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology of Bangkok Metropolitan Administration Medical College and Vajira Hospital to identify patients with EMC treated at the institution between January 1994 and December 2007. Inclusion criteria were patients with EMC who were operated on in the institution and had follow-up data. Exclusion criteria were patients whose medical records were not available, had no available paraffin blocks or inadequate pathological tumor tissue for immunohistochemical (IHC) processing. Pathological data collected were: tumor histologic subtype, tumor grade, depth of myometrial invasion, cervical involvement, LVSI, and lymph node metastasis. Clinical data abstracted from the patients' charts included: age, menopausal status, FIGO stage, date of recurrence and date of last visit or death.

Immunohistochemistry

The IHC staining for ER, PR, and Her-2/neu of the endometrial tissue in the paraffin blocks of 108 patients were performed. Expression of immunostaining slides were interpreted independently by two authors (S.S. and S.T.) who were blinded to the clinical information. Nuclear staining for ER and PR and membrane staining for Her-2/neu were considered as positive when the extent of immunostaining was >10%, regardless of the intensity. The results of positive or negative immunostaining among the first 30 cases were compared between the two authors (S.S. and S.T.) for inter-observer and intra-observer reliability. For any discordant interpretation, the two authors would study the immunostaining slides together for the adjustment. After this, all cases studied would be interpreted independently. Inter-observer reliability of both observers was analyzed again. Cases with discordant results were studied together and discussed to reach consensus on the positive or negative results of each stain.

Statistical analysis

The association between the expression of ER, PR, and Her-2/neu and the following clinicopathological factors were studied: age, menopausal status, FIGO stage, tumor grade, depth of myometrial invasion, cervical involvement, lymph node metastasis, disease-free survival (DFS), and overall survival (OS). DFS was defined as interval from the end of treatment to the time of recurrence or progression of disease. Patients who were lost to follow-up, DFS data were right-censored at the time of the last evaluation or contact when the patients were known to be disease-free. OS was defined as the time from the date of diagnosis to date of death. For patients who were still alive at the time of the study or dead from other causes, OS data were right-censored at the date of last follow-up visit.

Data were analyzed using SPSS statistical software, version 11.5. Association between ER and PR expression and clinicopathological characteristics were compared by Chi square test. OS and DFS of each group were analyzed by the Kaplan-Meier method and were compared between groups with log-rank test. P-values of < 0.05 were considered statistically significant.

Results

During the study period, 108 EMC patients met all clinical and pathological inclusion criteria were included in the study. The Kappa values of intra-observer reliability of the first 30 cases were: 0.730 and 0.933 for ER expression, 0.860 and 0.933 for PR expression, and 1.000 from both researchers for Her-2/neu expression. The corresponding inter-observer Kappa values were 0.800, 0.791, and 1.000. From the total 108 cases studied, the Kappa values of inter-observer were 0.732 for ER expression, 0.857 for PR expression, and 1.000 for Her-2/neu expression. A few cases with discordant result were studied together until reaching a consensus for a final result of each stain.

Mean age of all 108 patients was 56.3 ± 10.2 years. Seventy five patients (69.4%) were age ≤ 60 years old. Eighty seven patients (80.6%) were in postmenopausal period. The most common histopathology was endometrioid carcinoma (93 patients or 86.1%). Sixty one patients (56.5%) had grade I-II tumors while 47 (43.5%) had grade III tumor. The majority of patients had early stage disease (85 patients or 78.7%). Among 102 patients with available clinical data, 60 patients had no further treatment after primary surgery while 42 patients had adjuvant treatment as radiation therapy (n=39), radiation and chemotherapy (n=1), or chemotherapy (n=2). Clinicopathological features of the patients are shown in Table 1.

From IHC study, 64/108 patients (59.3%) showed positive ER expression, 71 patients (65.7%) for PR expression, and three patients (2.8%) for Her-2/neu expression. From all 108 patients, 57 patients were positive for both ER and PR expression, seven and 14 patients had isolated ER and PR positive respectively while 30 patients showed no expression of the two markers. From the only three cases of positive Her-2/neu, one case showed ER expression and no case had PR co-expression. We studied the association of ER, PR, and Her-2/neu with the clinicopathological features of age, stage, histology,

Table 1. Expression of Estrogen, Progesterone, and Her-2/neu Receptors according to the Characteristics of Endometrial Cancer Patients (N=108)

Patient characteristic	ER		p-value	PR		p-value	Her-2/neu		p-value
	Neg (%)	Pos (%)		Neg (%)	Pos (%)		Neg (%)	Pos (%)	
Age									
≤ 60 yrs (n= 74, 69.4%)	29 (39.2)	45 (60.8)	0.628	22 (29.7)	52 (70.3)	0.143	72 (97.3)	2 (2.7)	0.944
> 60 yrs (n= 34, 30.6%)	15 (44.1)	19 (55.9)		15 (44.1)	19 (55.9)		33 (97.1)	1 (2.9)	
Myometrial invasion									
< 1/2 (n= 69, 63.9%)	24 (34.8)	45 (65.2)	0.094	18 (26.1)	51 (73.9)	0.017	69 (100)	0	0.045
> 1/2 (n= 39, 36.1%)	20 (51.3)	19 (48.7)		19 (48.7)	20 (51.3)		36 (92.3)	3 (7.7)	
LVSI									
No (n=85, 78.7%)	34 (40.0)	51 (60.0)	0.763	29 (34.1)	56 (65.9)	0.952	82 (96.5)	3 (3.5)	0.484
Yes (n=23, 21.3%)	10 (43.5)	13 (56.5)		8 (34.8)	15 (65.2)		23 (100)	0	
Cervical involvement									
No (n=84, 71.3%)	31 (36.9)	53 (63.1)	0.129	26 (34.8)	58 (65.2)	0.175	81 (96.4)	3 (3.6)	0.467
Yes (n=34, 28.7%)	13 (54.2)	11 (45.8)		11 (45.8)	13 (54.2)		24 (100)	0	
LN involvement									
No (n=88, 81.5%)	33 (37.5)	55 (62.5)	0.150	26 (29.5)	62 (70.5)	0.030	87 (98.9)	1 (1.1)	0.087
Yes (n=20, 18.5%)	11 (55.0)	9 (45.0)		11 (55.0)	9 (45.0)		18(90.0)	2 (10.0)	
Stage									
I-II (n=85, 78.7%)	32 (37.6)	53 (62.4)	0.208	26 (30.6)	59 (69.4)	0.122	84 (98.8)	1 (1.2)	0.114
III-IV (n=23, 21.3%)	12 (52.2)	11 (47.8)		11 (47.8)	12 (52.2)		21 (91.3)	2 (8.7)	
Grade									
I-II (n=61, 56.5%)	14 (23.0)	47 (77.0)	0.001	11 (18.0)	50 (82.0)	0.001	60 (98.4)	1 (1.6)	0.538
III (n=47, 43.5%)	30 (63.8)	17 (36.2)		26 (55.3)	21 (44.7)		45 (95.7)	2 (4.3)	
Histology									
Endometrioid (n=93, 86.1%)	35 (37.6)	58 (62.4)	0.102	27 (29.0)	66 (71.0)	0.004	90 (96.8)	3 (3.2)	0.636
Non-endometrioid (n=15, 13.9%)	9 (60.0)	6 (40.0)		10 (66.7)	5 (33.3)		15 (100)	0	

LVSI, lymph vascular space involvement; LN, lymph node

Table 2. Univariable Analysis of Survival according to Clinicopathological Characteristics (N=108)

Characteristic		5 yrs DFS (%)	95%CI	p-value	5 yrs OS (%)	95%CI	p-value
Age	≤ 60 yrs (n=74, 69.4%)	73.1	59.6-86.8	0.250	77.6	64.6-90.6	0.470
	> 60 yrs (n=34, 30.6%)	77.1	61.9 -92.3		84.9	70.2-99.5	
Histology	Endometrioid(n=93, 86.1%)	79.5	69.5-89.6	0.197	81.9	71.9-92.4	0.131
	Non-endometrioid (n=15, 13.9%)	71.5	47.7-95.3		72.2	49.0-95.4	
Grade	I-II (n=61, 56.5%)	88.1	77.7-98.4	0.003	90.2	80.2-100	0.015
	III (n=47, 43.5%)	60.8	54.6-85.0		69.8	54.6-85.0	
Myometrial invasion	<1/2 (n=69, 63.9%)	88.0	79.5-96.5	0.012	89.5	81.6-97.5	0.037
	>1/2 (n=39, 36.1%)	64.4	47.1-81.7		69.2	52.2-86.2	
Cervical involvement	No (n=84, 71.3%)	81.5	70.2-92.8	0.036	82.0	70.3-93.7	0.188
	Yes (n=34, 28.7%)	65.8	46.5-85.1		73.5	55.0-92.0	
LVSI	No (n=85, 78.7%)	74.5	63.0-86.1	0.195	76.2	64.4-87.9	0.115
	Yes (n=23, 21.3%)	91.1	79.3-100.0		95.7	87.3-100.0	
Stage	I-II (n=85, 78.7%)	93.4	87.0-99.8	<0.001	94.0	87.1-100.8	<0.001
	III-IV (n=23, 21.3%)	18.6	0-46.2		31.1	2.6-59.6	
LN involvement	No (n=88, 81.5%)	92.6	86.1-99.0	<0.001	92.9	85.9-99.9	<0.001
	Yes (n=20, 18.5%)	16.0	0-40.7		29.6	1.4-56.4	
ER expression	Negative (n=64, 59.3%)	65.5	49.6-81.5	0.006	69.3	53.2-85.3	0.012
	Positive (n=44, 40.7%)	86.4	74.9-98.0		92.9	86.0-99.7	
PR expression	Negative (n=71, 65.7%)	69.0	52.6-85.4	0.083	75.4	60.1-90.6	0.193
	Positive (n=37, 34.3%)	83.1	71.5-94.8		83.2	70.9-95.4	
Her-2/neu expression	-ve (n=105, 97.2%)	81.0	71.8-90.3	<0.001	83.5	74.3-92.7	<0.001
	+ve (n=3, 2.8%)	0	-		0	-	

DFS, disease-free survival; OS, overall survival; LVSI, lymph vascular space involvement; LN, lymph node

tumor grade, MI, LVSI, cervical involvement, and lymph node status. There was a significant association between grade I-II tumor and positive expression of ER and PR (p=0.001 both). Only positive PR expression was significantly associated with less myometrial invasion (p=0.017), endometrioid type (p=0.004), and negative nodal involvement (p=0.030). Positive Her-2/neu expression showed marginal significant association with deep MI (p=0.045) (Table 1)

At the time of this report, 19 patients had recurrences and had salvage treatment. Twenty-two patients were dead; six were dead of unrelated causes while 16 patients were dead of EMC. The 5-year DFS and 5-year OS (see table 2) were 77.8% (95% confidence interval [CI], 68.1%-

87.5%) and 80.5% (95% CI, 70.8%-90.1%), respectively. We studied the impact of various prognostic factors to survival and found that grade I-II tumor, less myometrial invasion, early stage diseases, negative nodal involvement, positive ER expression, and negative Her-2/neu expression were associated with longer DFS and OS (see Table 2). Absence of cervical involvement was associated only with longer DFS but not OS. Although the patients with positive PR expression tended to have longer DFS and OS, but it did not reach statistical significance.

Discussion

In carcinoma of breast, expression of ER and PR is generally associated with better prognosis. It is contrary to Her-2/neu expression which carries poor prognosis (Slamon et al., 1989; Ravdin et al., 1995). These basic knowledges lead to a standard adjuvant treatment in breast cancer to use hormonal therapy in patients whose tumors showed positive ER or PR expression or to use anti- Her-2/neu in patients with positive Her-2/neu expression (Goldhirsch et al., 2009). Thus, it is mandatory in current practice to know the status of ER, PR, and Her-2/neu at the time of primary diagnosis from surgical treatment of breast cancer.

In EMC, the main adjuvant therapy after surgery is radiation therapy while hormonal therapy has more important role for advanced or recurrent diseases. The response of EMC to hormone correlates directly to degree of tumor differentiation, which is in turn linked to hormonal receptor status particularly progesterone receptor levels (Decruze and Green, 2007). Thus, knowing the status of these hormonal receptors would be certainly helpful in selecting treatment options.

We used IHC technique to evaluate steroid hormonal receptors rather than biochemical method due to the false positive results of the latter technique as a result of contamination by PR-rich normal endometrial tissue (Mutch et al., 1987; Snijders et al., 1990). Although some authors also reported inaccuracy of IHC method in quantitation and inter-observer variability of positive receptor status (Gehrig et al., 1999), this technique is generally used in clinical practice nowadays. We minimized these variations by adjusting the criteria of positivity between two authors. Any differences in the interpretation were resolved by the consensus of two researchers together.

We found 59.3% of ER and 65.7% of PR expression. Our findings were in the ranges as reported by other studies: 32-77% for ER and 54-72% for PR expression (Fukuda et al., 1998; Jeon et al., 2006; Suthipinthawong et al., 2008). Different rates of hormonal receptors expression from various studies certainly depend on many factors, such as, proportion of low and high grade tumor which were reported to have higher and lower degree of hormonal receptors expression, respectively.

Her-2/neu expression was identified in only 2.8% in our study. This result was close to another study in Thai endometrial cancer patients (Suthipinthawong et al., 2008), that reported the incidence of Her-2/neu expression in only 1.5%. These figures were much lower than 9-30% as reported in other previous studies (Berchuck et al., 1991; Hetzel et al., 1992; Khalifa et al., 1994; Luke et al., 1994; Hamel et al., 1996; Coronado et al., 2001; Engelsen et al., 2008). The lower rates of Her-2/neu expression in EMC of Thai population comparing to the others were similar to that found in breast cancer. One study in breast cancer of Thai women also found lower rate of Her-2/neu expression (Chearskul et al., 2000) compared to the study of Western patients (Revillion et al.,1998), 13% versus 21% respectively. We do not know whether there was any racial influence on Her-2/ neu expression. A definite conclusion cannot be made until the results from more number of studies with a larger number of patients would support our findings.

Regarding their association with other clinicopathological factors, ER was found to be significantly associated with grade I-II tumor while positive PR expression showed significant association with other good prognostic factors including less myometrial invasion, endometrioid histology, grade I-II tumor and the absence of LN involvement. Most studies reported the association of ER and PR with other favorable clinicopathological features: endometrioid histopathology, well differentiated tumor, or less myometrial invasion (Creasman et al., 1985; Nyhlom et al.,1992; Hanekamp et al., 2003; Miyamoto et al., 2004; Jeon et al., 2006; Jongen et al., 2009). However, our study and another study (Fukuda et al., 1998) could not demonstrate the association of ER expression and other good prognostic factors. This might be due to the small number of patients in both studies. For Her-2/neu expression, we found that all three cases which expressed Her-2/neu were endometrioid type, and had more than half of myometrial invasion. Only two had advanced stage, grade III tumor, LVSI and LN involvement. Because of a limited number of positive Her-2/neu cases in our study, we could not support or refute the controversial findings from various studies regarding its association with other poor prognostic factors (Berchuck et al, 1991; Khalifa et al., 1994; Luke et al., 1994; Hamel et al., 1996; Coronado et al., 2001) or no such association (Bigsby et al., 1992; Hetzel et al., 1992; Gassel et al., 1998).

Many prognostic factors were reported to impact both DFS and OS in EMC patients such as histopathological type, stage of disease, tumor grade, LVSI, depth of myometrial invasion, cervical invasion, and extrauterine involvement including lymph node (LN) status (Gal et al., 1991; Wolfson et al., 1992; Fukuda et al., 1998; Creutzberg et al., 2000; Sivridis et al., 2001). In our study, we found that stage of disease, tumor grade, LVSI, depth of myometrial invasion, and cervical invasion were prognostic factors to DFS and/or OS as shown in Table II.

Regarding the prognostic role of ER, PR and HER-2/neu expression, we found that ER expression had significantly positive association with both DFS and OS. This was consistent with some studies (Palmer et al., 1988; Suthipinthawong et al., 2008). However, other studies could not demonstrate such association (Sivridis et al., 2001; Jeon et al., 2006). For PR expression, we could not

demonstrate the association between the positive PR expression and DFS or OS, although the figure of DFS tended to reach the statistical significant (p=0.083). The reports from other studies were also conflicting; some showed positive influence to survival of PR expression (Ehrlich et al.,1988; Palmer et al., 1988; Fukuda et al., 1998) while others could not demonstrate such finding (Morris et al., 1995; Sivridis et al., 2001). We also found that Her-2/neu showed significant negative impact for DFS and OS similar to another study (Engelsen et al., 2008). However, we could not make a definite conclusion due to limited number of positive Her-2/neu expressions in our study.

Aside from being an indicator for adjuvant treatment, IHC evaluation of steroid hormone receptors may be useful in a pre-operative setting as the predictor of tumor behavior. With the low reproducibility for tumor grading from the small fragmented curettage specimens and the suboptimal performance of imaging to predict the myometrial invasion preoperatively, the data of ER, PR expression in the curettage specimens may aid to identify the patients who are less likely to have other poor features (Iwai et al., 1999). This may facilitate decision-making whether a patient should undergo complete surgical staging procedure especially when the therapeutic role of lymph node resection in early stage EMC appeared disputable (Chan et al., 2006; Benedetti et al., 2008; Kitchener et al., 2009).

In conclusion, our study showed 59.3% of ER, 65.7% of PR, and 2.8% of Her-2/neu expression. ER was found to be significantly associated with grade I-II tumor while positive PR expression showed significant association with other good prognostic factors including less myometrial invasion, endometrioid type, grade I-II tumor and the absence of LN involvement. ER expression was a good prognostic factor while Her-2/neu expression appeared to be a poor indicator for both disease-free and overall survivals and PR tended to show favorable influence for only disease-free survival.

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