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Expression of estrogen receptor, progesterone receptor, and Her-2/ neu in primary and extra-corporeal endometrial cancer

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Summary. Objective: To compare immunohistochemical (IHC) expression of estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu in the primary tumors of endometrial cancer (EMC) and their extra-corporeal lesions.

Methods: Paraffin-embedded tissues of the primary and extra-corporeal tumors of EMC were retrieved for IHC study. Expression of ER, PR, and Her-2/ neu in the primary tumors and extra-corporeal lesions were compared.

Results: From 72 EMC patients with 87 extra-corporeal lesions, positive PR expression was significantly lower in the extra-corporeal lesions than that in the primary sites: 42.5% vs. 63.9%, respectively (p=0.007). No statistically significant differences of ER and Her-2/ neu expressions in the extra-corporeal and the primary sites were found: 42.5% and 55.6% for ER (p=0.102) and 20.7% vs. 13.9% for Her-2/ neu (p=0.262), respectively. The expression of extra-corporeal lesions were concordant to the primary tumor in 65.5% of ER (k=0.319), 71.2% of PR (k=0.445), and 83.9% of Her-2/ neu (k=0.413). From 15 cases wherein IHC from two extra-corporeal sites were studied, 73% had concordant ER expression between the two extra-corporeal lesions (k=0.412) while 93.3% had concordant PR and concordant Her-2/ neu expression (k=0.842 for PR and 0.634 for Her-2/ neu)

Conclusion: PR expression was significantly higher in the primary tumors than the extra-corporeal sites. Higher ER and lower Her-2/ neu expressions in the primary tumors were also observed but the differences were not significant. The tumors heterogeneity suggests it may be important to study tumor tissues from both primary and extra-corporeal sites when planning treatment, especially by hormonal or targeted therapies.

Key words: Estrogen receptor, Progesterone receptor, Her- 2/neu, Primary endometrial cancer, Extra-corporeal lesion

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Introduction

Endometrial carcinoma (EMC) is the third-most common gynecologic malignancy following breast and cervical carcinomas in both more or less developed areas of the world (Jemal et al., 2011). EMC, particularly of type I, is a hormone-related cancer with a well recognized pathogenesis of a high estrogen milieu surfeiting progesterone, which controls cellular proliferation. The expression of hormonal as well as target receptors, particularly estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu is identified in both normal and cancer tissue, and has been studied as prognostic factors for cancer (Saffari et al., 1995; Fukuda et al., 1998; Niederacher et al., 1999; Coronado et al., 2001; Jeon et al., 2006; Engelson et al., 2008; Srijaipracharoen et al, 2010; Suthipintawong et al., 2008). Well differentiated tumors and ER- or PR-positive disease are important factors predicting good response of EMC to hormonal treatment. The response rates were higher in ER- or PR-positive tumors compared to PR-negative tumors: 26-89% and 8-17% respectively (Thigpen et al., 1999; Decruze and Green, 2007). The decision of hormonal treatment for EMC is theoretically based on tumor grade and expression of ER and PR.

Despite having a role in selecting therapy for advanced, metastatic, or recurrent EMC, most studies focused the expression of ER, PR, and Her-2/ neu only

in the primary tumor (Saffari et al., 1995; Fukuda et al., 1998; Niederacher et al., 1999; Coronado et al., 2001; Jeon et al., 2006; Engelson et al., 2008; Srijaipracharoen et al, 2010; Suthipintawong et al., 2008), with only few reports in metastatic or extrauterine lesions (Runowicz et al., 1990; Ma et al., 2004; Singh et al., 2007; Vandenput et al., 2011). Immunohistochemical (IHC) expression in the primary endometrial tumor ranged from 32-77% for ER, 54-72% for PR (Fukuda et al., 1998; Jeon et al., 2006; Srijaipracharoen et al, 2010; Suthipintawong et al., 2008) and 3-30% for Her-2/ neu (Saffari et al., 1995; Niederacher et al., 1999; Coronado et al., 2001; Engelson et al., 2008; Srijaipracharoen et al, 2010; Suthipintawong et al., 2008). Among studies which evaluated the expression of ER and PR in metastatic EMC (Runowicz et al., 1990; Ma et al., 2004; Singh et al., 2007; Vandenput et al., 2011), different findings were observed regarding the expression rate of ER or PR in metastatic lesions which ranged from 40-86% (Ma et al., 2004; Singh et al., 2007), the concordant rates of expression between metastatic or recurrent lesions and the primary tumor which varied from 20-90% (Runowicz et al. 1990; Vandenput et al., 2011), or the inconsistent results regarding a relationship of ER or PR expression and response or survival after hormonal treatment (Ma et al., 2004; Singh et al., 2007; Vandenput et al., 2011). These dissimilar findings from a limited number of studies indicated that more data are needed.

The purpose of this study was to compare the expression of ER, PR, and Her-2/neu in extra-corporeal EMC lesions and primary tumors, and to evaluate the association of these markers expression with some clinico- pathological features.

Material and methods

The study obtained the approval of the Ethics Committee for Research involving Human Subjects of the institution. We searched the archives of the Department of Anatomical Pathology and Department of Obstetrics and Gynecology to identify EMC patients treated between January 1994 and December 2010. Inclusion criteria were: patients who had an operation in the institution and had extra-corporeal lesions including cervical stroma, adnexa, lymph node, bowel, etc. Exclusion criteria were cases with inadequate tumor tissue in paraffin blocks for IHC processing. Patients with synchronous endometrial and ovarian cancers were also excluded.

Data collected were: age, the International Federation of Gynecology and Obstetrics (FIGO) 2009 stage, tumor histopathology, grade, and sites of extra-corporeal lesions. For patients who had an operation prior to 2009, clinical and surgico-pathological data was used to re-allocate their stage.

Immunohistochemistry

All H &E slides of primary endometrial tumors and extra-corporeal lesions of the EMC patients who met inclusion criteria were reviewed to select appropriate slides to process their paraffin-embedded tissue for an IHC study for ER, PR, and Her-2/neu. Histology and grade of the extra-corporeal lesions were also reviewed in comparison to their primary tumor. In cases with more than one available tissue block of extra-corporeal lesions, we processed another block with adequate tissue for IHC.

Immunoperoxidase staining was performed on 5-μm sections of formalin-fixed, paraffin-embedded tissue section. In brief, the paraffin-embedded sections were mounted on slides and dried by microwave for 15 minutes. The tissues were deparaffinized and rehydrated with xylene and ethanol, blocked endogenous peroxidase with 3% H_2O_2 for 20 minutes. The sections were pretreated with citrate buffer, pH 6.0 in a microwave for 13 minutes and incubated in protein blocking solution for 10 minutes. All slides were incubated with a 1:40 dilution of primary anti-ER of · subtype (Novocastra, Newcastle, UK), 1:100 dilution of primary anti-PR of A subtype (Novocastra, Newcastle, UK), and 1:700 dilution of primary anti-Her-2/ neu (Dako, Glostrup, Denmark) for 120 minutes at room temperature followed by secondary antibody (Envision kit, Novocastra, Newcastle, UK) for 30 minutes and finally with diaminobenzidine for 6 minutes. All samples were counterstained with Mayer's hematoxylin for 2 minutes and mounted in coated glass. Positive staining of ER and PR was controlled by immunostaining of normal endometrial tissue. Positive staining of Her-2/ neu was controlled by immunostaining of known positive breast cancer samples. The negative control performed in the same tissue consisted of non-immune immunoglobulin of the same isotype substituted for primary antibody.

Expression of immunostaining slides was interpreted independently by two authors specialized in gynecologic cancer under a transmission light microscope. The readers were double blinded as to primary vs. extra-corporal sites of each case and to each other's findings. Nuclear staining in the tumor cells was considered positive for ER and PR and membrane staining for Her-2/ neu. Positive staining was defined when the area 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 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 would be interpreted independently. Inter-observer reliability of both observers was analyzed again.

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 cases studied, the Kappa values of inter-observer were 0.740 for ER expression, 0.859 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.

Statistical analysis

Data were analyzed using SPSS statistical software, version 11.5. Expressions of ER, PR, and Her-2/neu of the primary tumors and extra-corporeal lesions were studied. The overall expressions of the primary tumors and extra-corporeal lesions were compared by Pearson's chi-square. The expressions of extra-corporeal lesions in each individual were compared to the expression of their primary tumors and presented as percentage of agreement or concordant expression. Kappa values ≥0.7 were considered as good agreement, 0.3-0.6 as moderate agreement, and ≤0.3 as poor. Each expression was also studied according to the histopathology, tumor grade, and the sites of metastases. Data were compared by Pearson's chi-square or Fisher's Exact Test as appropriate. P values of <0.05 were considered statistically significant.

Results

During the study period, 332 EMC patients were identified. Amongst these, 241 patients with stage I diseases without any extra-corporeal lesions were excluded (four of them also had two independent primary cancers of endometrium and ovary). An additional 19 cases with inadequate extra-corporeal tissue blocks for IHC processing were also excluded. Mean age of the 72 patients who met inclusion criteria and were included in the study was 54.0±9.9 years. Fifteen cases had second extra-corporeal tissue blocks processed for IHC study, making up a total of 87 extra-corporeal lesions. Characteristic features of all 72 EMC patients and their sites of extra-corporeal lesions are shown in Table 1. No discrepancy of histopathology and grade between primary EMC and extra-corporeal lesions was found.

The IHC expressions in 72 primary EMC and 87 extra-corporeal lesions are shown Table 2. We found overall lower expression of ER and PR in the extra-corporeal lesions than in the primary sites. On the contrary, extra-corporeal lesions had higher percentages of Her-2/ neu expression. However, the difference was significant only for PR expression.

When we compared marker expression of 87 extra-corporeal lesions to their primary tumor in each individual, we found a moderate degree of agreement. The concordant expression was 65.5% for ER (k=0.319), 71.2% for PR (k=0.445), and 83.9% for Her-2/ neu expression (k=0.413). On the other hand, the discordance rates were 34.5%, 29.8%, and 16.1% respectively. Among the discordant pairs, a larger number of extra-uterine lesions lost their ER and PR expression rather than gained. The opposite finding was found for Her-2/ neu expression. Numbers and percentages of cases with concordant and discordant expression of ER, PR, and Her-2/ neu between the extra-corporeal lesions and the primary tumor are demonstrated in Table 3. Notably, a majority of the concordant cases were negative cases. Findings of the marker expression among 15 cases with available tissue blocks of second extra-corporeal lesion are also shown in Table 3. Good agreement between the two extra-corporeal lesions was found with PR expression

Table 1. Characteristic features of endometrial cancer patients with extrauterine metastasis (n=72).

Surgico-pathological features	n (%)
FIGO stage	
Stage II	21 (29.2)
Stage III	45 (62.5)
Stage IV	6 (8.3)
Histopathology	
Endometrioid carcinoma	53 (73.6)
Endometrioid carcinoma with other components[a]	13 (18.1)
Others[b]	6 (8.3)
Tumor grade	
Grade I	10 (13.9)
Grade II	26 (36.1)
Grade III	36 (50.0)
Sites of extra-corporeal lesions (n=87[c])	
Pelvic or para-aortic lymph node	47 (54.0)
Cervix	25 (28.7)
Ovary	11 (12.7)
Others[d]	4 (4.6)

[a]: Other components mixed with endometrioid were: squamous (n=10), serous (n=2), clear (n=2), mucinous (n=1), neuroendocrine (n=1); [b]: Other histopathologies were: clear cell carcinoma (n=2), serous carcinoma (n=2), carcinosarcoma (n=2); [c]: Fifteen cases had two tissue blocks of extra-corporeal lesions for immunohistochemical study (13 cases had additional pelvic or para-aortic metastatic nodal tissue and two cases had contralateral ovarian metastatic tissues); [d]: Other sites of metastasis were: omentum (n=2), peritoneum (n=1), or bowel serosa (n=1).

Table 2. Overall expression of estrogen receptor, progesterone receptor, Her-2/ neu of the primary tumors and extra- corporeal lesions.

	Positive immunohistochemical expression n (%)	P values
ER expression		0.102
Primary tumors (n=72)	40 (55.6)	
Extra-corporeal lesions (n=87[a])	37 (42.5)	
PR expression		0.007
Primary tumors (n=72)	46 (63.9)	
Extra-corporeal lesions (n=87[a])	37 (42.5)	
Her-2/ neu		0.262
Primary tumors (n=72)	10 (13.9)	
Extra-corporeal lesions (n=87[a])	18 (20.7)	

[a]: Fifteen cases had two tissue blocks of extra-corporeal lesions processed for immunohistochemical study.

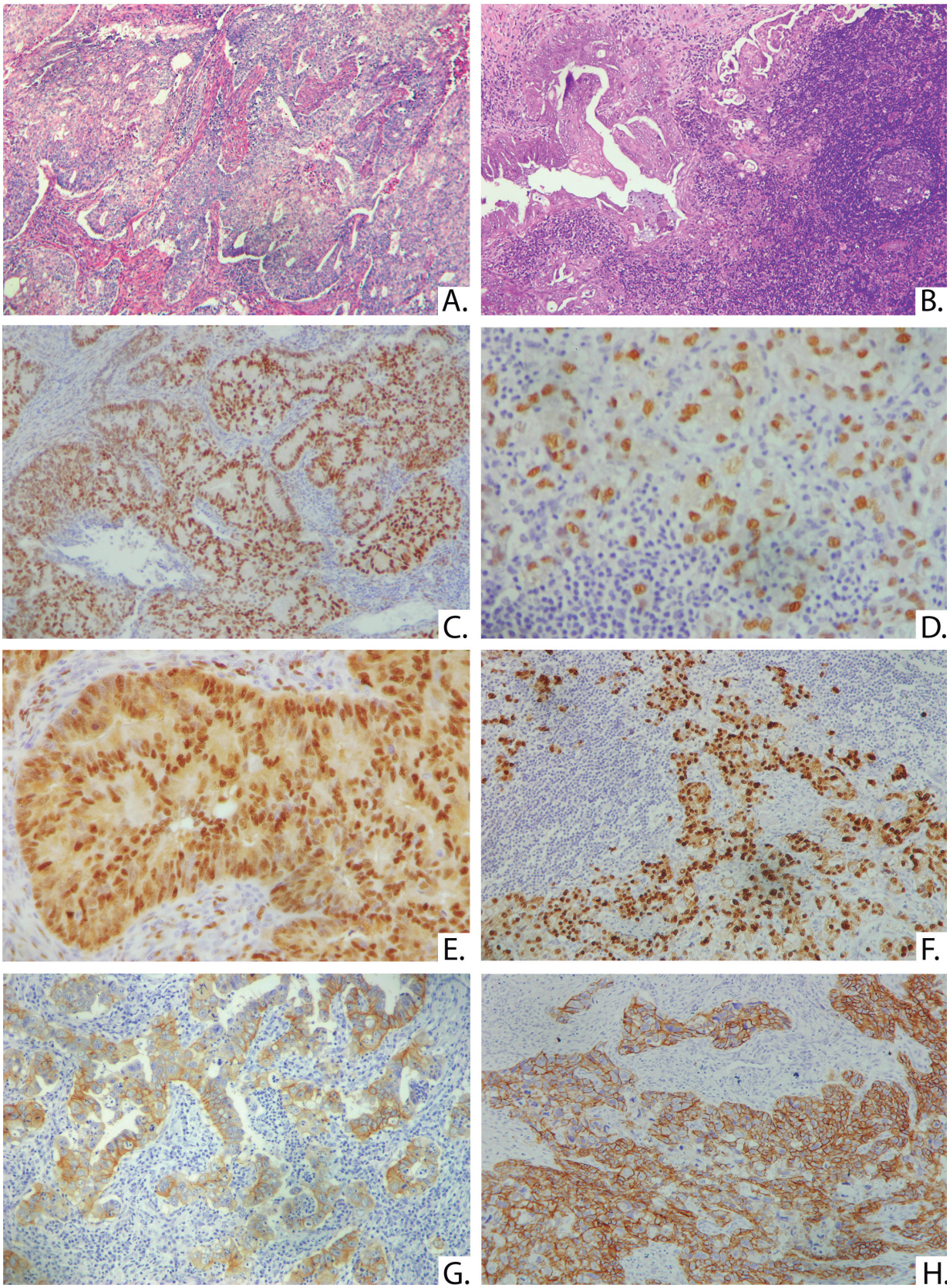

Fig. 1. A, B. Hematoxylin & Eosin stain of the primary tumor in the uterus shows endometrioid carcinoma with tumor cells arranged in sheets and glands infiltrating into myometrium. Metastatic lesion is evidenced in lymph node. **C-H.** Immunohistochemical study shows positive nuclear stain of ER in the primary tumor and metastatic lesions in lymph nodes. Positive nuclear stain of PR is also demonstrated in the primary tumor and metastatic lesion in lymph nodes. For Her-2/ neu, membranous stain is shown in the primary tumor and metastatic lesion. A-C, F-H, x 40; D, E, x 100

Table 3. Agreement of estrogen receptor, progesterone receptor, Her-2/ neu expression between various sites of endometrial cancer in an individual patient.

	ER n (%)	K value	PR n (%)	K value	Her-2/ neu n (%)	K value
Comparing extra-corporeal lesions to primary tumor (N=87[a])		0.319		0.445		0.413
Concordant	57 (65.5)		62 (71.2)		73 (83.9)	
Negative	30 (34.5)		29 (33.3)		66 (75.9)	
Positive	27 (31.0)		33 (37.9)		7 (8.0)	
Discordant	30 (34.5)		25 (28.8)		14 (16.1)	
Gain	10 (11.5)		4 (4.6)		11 (12.6)	
Loss	20 (23.0)		21 (24.2)		3 (3.5)	
Comparing between the two extra-corporeal lesions (N=15)		0.412		0.842		0.634
Concordant	11 (73.3)		14 (93.3)		14 (93.3)	
Negative	8 (53.3)		10 (66.7)		13 (86.6)	
Positive	3 (20.0)		4 (26.6)		1 (6.7)	
Discordant	4 (26.7)		1 (6.7)		1 (6.7)	

[a]: Fifteen cases had two tissue blocks of extra-corporeal lesions processed for immunohistochemical study.

Table 4. Expression of estrogen, progesterone, and Her-2/neu receptors according to the characteristics of endometrial cancer patients.

Sites and characteristic features of tumor	Positive immunohistochemical expressions of receptors					
	ER n (%)	P values	PR n (%)	P values	Her-2/neu n (%)	P values
A. Primary tumor of endometrial carcinoma (n=72)						
I. *Histopathology*		0.173		0.009		0.343
Endometrioid CA (n=66)	37 (58.7)		44 (69.8)		10 (15.9)	
Non-endometrioid CA[a] (n=6)	3 (33.3)		2 (22.2)		0	
II. *Grade*		1.000		0.011		0.338
I (n=10)	6 (60.0)		10 (100.0)		0	
II-III (n=62)	34 (54.8)		36 (58.1)		10 (16.1)	
B. Extra-corporeal lesions (n=87[b])						
I. *Histopathology*		0.124		0.006		0.727
Endometrioid CA (n=74)	34 (45.9)		36 (48.6)		15 (20.3)	
Non-endometrioid CA[c] (n=13)	3 (23.1)		1 (7.7)		3 (23.1)	
II. *Grade*		0.517		0.192		1.000
I (n=11)	6 (54.5)		7 (63.6)		2 (18.2)	
II-III (n=76)	31 (40.8)		30 (39.5)		16 (21.1)	
III. *Sites of extra-corporeal lesions*		0.212		0.010		0.036
Cervix (n=25)	13 (52.0)		15 (60.0)		7 (28.0)	
Pelvic/ para-aortic LN (n=47)	16 (34.0)		14 (29.8)		8 (17.0)	
Ovary (n=11)	7 (63.6)		8 (72.7)		1 (9.1)	
Others[d] (n=4)	1 (25.0)		0		2 (50.0)	

[a]: Non-endometrioid CA of the primary tumor included clear cell carcinoma (n=2), serous carcinoma (n=2), carcinosarcoma (n=2); [b]: Fifteen cases had two tissue blocks of extra-corporeal lesions processed for immunohistochemical study; [c]: Extra-corporeal lesions which were non-endometrioid CA were clear cell carcinoma (n=5), serous carcinoma (n=4), carcinosarcoma (n=4); [d]: Other sites of metastasis were: metastasis were: omentum (n=2), peritoneum (n=1), or bowel serosa (n=1).

Table 5. Estrogen receptor, progesterone receptor, Her-2/ neu in the primary and metastatic or extra-uterine lesions of endometrial cancer from our study and previous reports.

First author, year	Reference	Primary tumor			Metastatic or extra-uterine tumors		
		ER	PR	Her-2/ neu	ER	PR	Her-2/ neu
Runowicz[a] et al., 1990	13	70	65	-	63	25	-
Singh et al., 2007	14	-	-	-	40	45	-
Ma et al., 2004	15	-	-	-	86	86	0
Vandenput et al., 2011	16	38	44	6	34	31	8
Our study[b]	-	56	64	14	43	43	21

[a]: This study used the radioligand biochemical assay technique while the other studies used immunohistochemical technique; [b]: The rates of marker expression in our study were rounded up as whole figures.

(k=0.842), however, only modest agreements for ER (k=0.412) and Her-2/ neu (k=0.634) was found.

We also studied the expression of these markers at the primary tumor and the extra-corporeal lesions according to tumor histopathology and grade, and to the sites of extra-corporeal lesions (Table 4). Tumors with endometrioid histology showed significantly higher PR expression than non-endometrioid tumors: 69.8% vs. 22.2% (p=0.009) in primary tumors and 48.6% vs. 7.7% (p=0.006) in extra-corporeal lesions. Higher PR expression was also found in low grade than higher grades in tumors of both sites but the difference was significant only in the primary tumor: 100% vs. 58.1% (p=0.011). Regarding the sites of extra-corporeal lesions, metastatic ovarian lesions showed significantly higher PR expression (p=0.010) while metastatic non-pelvic viscera showed significantly higher Her-2/ neu expression than any other sites (p=0.036).

Discussion

Because extra-corporeal EMC may have a different tumor biology than the primary lesion, knowing the biological status of each tumor may be important to estimate the responses to hormonal or possible anti-Her-2/ neu agents.

Our study included 72 primary tumors with 87 extra-corporeal lesions, a relatively large sample compared to previously published studies. The latter included from 10 to 85 cases (Runowicz et al., 1990; Ma et al., 2004; Singh et al., 2007; Vandenput et al., 2011). By IHC technique, we interpreted slides with areas of immunostaining >10% as positive regardless of the intensity because the staining intensity varied in different areas of tumor. Possible subjective bias was minimized by a double blinded interpretation of the slides by two pathologists. Inter- and intra-observer reliability testing was done with high Kappa values of all markers.

Our study demonstrated 56% ER, 64% PR, and 14% Her-2/neu expression in the primary EMC. One previous study (Runowicz et al., 1990) reported higher ER expression and similar PR expression compared to our study. This must be interpreted with caution because only ten patients and 16 metastatic lesions were included in that study (Runowicz et al., 1990). Furthermore, the authors used radioligand biochemical assay technique to measure the cytosol steroid receptor content of tissue samples. Normal endometrial tissue and surrounding stroma components in their samples can lead to erroneously high values of hormonal receptors in the primary tumor compared to the metastatic site. Subsequent reports used IHC technique to study the expression of ER, PR, and Her-2/ neu in either the metastatic or recurrent EMC (Ma et al., 2004; Singh et al., 2007) or the primary EMC tumor in comparison to metastatic or recurrent EMC (Vandenput et al., 2011). The latter study by Vandenput et al. (2011) reported lower rates of marker expression in the primary tumor than our study. Different expression rates of these receptors in each study may be due to the possibility of different tumor grade and histology. Their study had 74% high grade tumors and 27% with aggressive histopathology (Vandenput et al., 2011) while our study had 86% high grade tumors but less than 10% aggressive tumor subtypes.

Regarding marker expression in extra-uterine or metastatic lesions, the 43% ER and PR expression rates found in our study were in the ranges of previous reports: 34-86% of ER and 31-86% of PR (Runowicz et al., 1990; Ma et al., 2004; Singh et al., 2007). However, we reported higher Her-2/ neu expression than previous reports (Ma et al., 2004; Vandenput et al., 2011). A possible influencing factor for the differences, in addition to grade or histology, was the tumor setting. Two studies (Singh et al., 2007; Vandenput et al., 2011) evaluated the recurrent metastatic lesions while our study focused on the extra-corporeal lesions during the primary treatment. Taking the extra-corporeal tumors from the primary surgery, we excluded two possibilities: 1) change in tumor biology over a period of time and 2) exposure of occult tumor cells to local or systemic adjuvant therapy modifying the tumor biology.

In comparing overall rates of marker expression between the primary tumor and extra-corporeal lesions, we found lower expression of ER or PR and higher Her-2/ neu in the metastatic lesions than primary tumors. However, the difference was significant only with PR expression. These findings were also found in the other two studies (Runowicz et al., 1990; Vandenput et al., 2011) using either radioligand biochemical assay (Runowicz et al., 1990) or IHC techniques (Vandenput et al., 2011). We summarized the IHC expression of these markers in both primary EMC and extra-uterine or metastatic sites from our study and other reports in Table 5.

Our analysis of each individual also showed differences of marker expression in the extra-corporeal lesions and the primary tumors. The concordance rates were only modest with kappa values of only 0.319-0.445. The primary and extra-corporeal lesions had concordant rates of approximately 66% for ER, 71% for PR, and 84% for Her-2/ neu expressions. On the other hand, the discordance rates were approximately 34%, 29%, and 16%. Another study using IHC technique found a moderate to high degree of agreement between the primary and recurrent tumors (Vandenput et al., 2011). Their study showed that the primary and recurrent tumors had 82%, 78%, and 93% concordant rates of expression of ER, PR, and Her-2/neu while the corresponding discordant rates were 18%, 22%, and 7%, respectively. Their study had one finding in common with our study, that the majority of the discordance was the loss of ER and PR and the gain of Her-2/ neu expression in the recurrent or extra-corporeal lesions. Our study showed approximately 25% of an individual lost their ER or PR expression in the extra-corporeal lesions while slightly more than 10% gained Her-2/ neu expression, while their study demonstrated 11% of the

recurrent lesions lost ER, 18% lost PR expression, and 5% gain Her-2/ neu expression (Vandenput et al., 2011). The discordant rates of marker expression between the primary tumor and metastatic lesions in the same individual may be explained by the following reason. The metastatic or recurrent lesions may have different tumor grade and/ or histology from the primary tumors. This was evidenced in previous studies that histopathology and grade between the primary and metastatic or recurrent tumors were dissimilar in 8%-20% (Runowicz et al., 1990; Vandenput et al., 2011). This event may result from selective clones of tumor cells with a higher grade and more aggressive clinical behavior. Our study did not find any discrepancy of tumor grades or histology of the extra-corporeal lesions from the primary tumor during the slide review for tissue block selection for IHC study. Hence, we presumed that the reduction rates of hormone receptor expression could be related to the genuine increase of tumor biology aggressiveness. This was indirectly supported by our finding of increased Her-2/ neu expression in the extra-corporeal lesions. Nevertheless, we do not know whether the environmental factor of the extra-corporeal sites themselves may contribute to modification of tumor biology or expression of these markers.

We would like to emphasize the different expressions between the two extra-corporeal lesions in each patient (Table 3). Although a moderate to high degree of agreement for marker expression was found between two different metastatic lesions, the majority of the concordance was in negative cases. This should alert clinicians that marker expression in the extra-corporeal lesions was not homogeneous. Positive expression at one site did not absolutely reflect positivity at other sites.

Some findings from our study are to be noted. We found endometrioid histopathology and low grade tumors had higher ER and PR expression than the non-endometrioid or higher grade tumors in all sites of primary and extra-corporeal sites. However, this was significant only for PR expression. This was also found in the study of Singh et al. who reported that the expression of ER and PR in their metastatic tumors was inversely related to tumor grade (Singh et al., 2007). Among various extra-corporeal lesions, we found that metastatic ovarian lesions had significantly higher PR expression than the other sites while Her-2/ neu expression was significantly higher in extra-pelvic viscera. On the other hand, lymph node appeared to have lower expression of these markers than the other sites. Although the small number of cases in each extra-corporeal site was limited, these findings might serve as basic data for clinical application in selecting adjuvant or salvage treatment. We also collected data concerning cervical stromal tissue invasion. Such patients may be considered for conservative hormonal therapy. Unfortunately, only 50-60% of our cases with cervical lesions had ER or PR expression. This data provokes caution on the use of such an approach.

The clinician should be aware of possible different responses to hormonal and anti-Her-2/ neu targeted therapy between primary tumor, recurrent and metastatic disease. Immunohistochemical analysis of different sites may be needed. In a clinical setting, extensive IHC is probably not functional. Our findings demonstrated higher ER and PR expression in endometrioid histopathology and low grade tumor and higher Her-2/ neu in high grade tumors in both primary tumor and extra-corporeal sites. These may provide some clinical guidance for selection of therapies.

Conclusion

Our study found lower ER and PR, and higher Her-2/ neu expressions in extra-corporeal endometrial cancer lesions, although the difference was significant only for PR expression. Discordant expression between the primary and recurrent or metastatic endometrial cancer and between various metastatic sites was found in 16-35%. These data should be kept in mind for physicians selecting treatment for endometrial cancer patients with metastatic diseases.

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