Prognostic Significance of ER, PR, Ki67, c-erbB-2, and p53 in Endometrial Carcinoma

Cheepsumon Suthipintawong MD*,
Charnyut Wejaranayang MD**, Chroen Vipupinyo MD**

** Department of Pathology, Rajavithi Hospital, Bangkok*
*** Gynecologic Oncology Division, Department of Obstetrics & Gynecology, Rajavithi Hospital, Bangkok*

Objective: *To better discern the prognostic significance of estrogen-progesterone (ER-PR) receptor, proliferative index, tumor suppressor gene, and over expression of oncogene c-erbB-2 in correlation with survival time and recurrence of tumor.*
Material and Method: *Paraffin blocks from 65 cases of endometrial carcinoma diagnosed and treatment at Rajavithi Hospital, Bangkok, Thailand with a follow-up time of at least 60 months were immunohistochemical studied for ER and PR status, tumor proliferative index (Ki-67), tumor suppressor gene (p53), and overexpression of oncogene c-erbB-2. Survival analysis was performed with the Cox proportional hazards.*
Results: *The mean age of the patients was 54.94 years with a range of 24 to 80 years. The mean follow-up time was 50.35 months. Nine patients (13.8%) had recurrent tumors, 5 years after treatment. Ten patients (15.4%) died of the primary disease during the follow-up period. ER was positive in 50 cases (76.9%) and negative in 15 cases (23.1%). PR was positive in 47 cases (72.3%) and negative in 18 cases (27.7%). Both ER and PR showed significant correlation ($p < 0.01$). Ki-67 showed 27 cases (41.5%) having > 35% positive nuclear staining and 38 cases (58.5%) had ≤ 35% positive nuclear staining. p53 was positive in 31 cases (47.7%) and negative in 34 cases (52.3%). c-erbB-2 was positive in one case (1.5%), equivocal in six cases (9.2%), and negative in 58 cases (89.3%).*
Conclusion: *Survival analysis showed that cases with low-stage, low-grade, no recurrent tumor, ER and PR positive, and Ki-67 ≤ 35% had good survival compared to cases with high-stage, high-grade, presence of recurrent tumor, ER-PR-negative, and Ki-67 > 35% ($p < 0.05$). Cox regression analysis showed ER-PR status and Ki-67 were significant independent prognostic indicators for survival time. Ki-67 expression was also a significant independent prognostic indicator for recurrent tumor. p53 and c-erbB-2 displayed no statistical significance related to survival time.*

Keywords: *Endometrial carcinoma, ER, PR, Ki-67, p53, c-erbB-2*

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Endometrial carcinoma is the third-most common gynecological malignancy in Thailand[1] after cervical carcinoma and ovarian carcinoma. It makes up about 2.2% of all malignant diseases with an incidence of 3.5-4.1: 100,000. The majority of patients have a favorable outcome. Some patients die from their neoplasms within a few years of treatment. These high-risk patients can be identified on the basis of prognostic characteristics.

Correspondence to: Suthipintawong C, Department of Pathology, Rajavithi Hospital, Bangkok 10400, Thailand.

Multiple prognostic factors have been reported for endometrial carcinoma, such as age of the patient[2], histological type[3], histological grade[4,5], vascular invasion[6], FIGO stage[7], estrogen-progesterone receptor[8-12], proliferation index (Ki-67)[13-17], apoptosis indicator bcl-2[17,18], tumor suppressor gene (p53)[18,19], and overexpression/amplification of oncogene c-erbB-2.[20,21]

The purpose of the present study was to better discern the prognostic significance of estrogen-progesterone receptor, tumor proliferative index (Ki-67),

tumor suppressor gene (p53), and overexpression of oncogene c-erbB-2 in correlation with survival time and recurrence of tumor.

Material and Method

Appropriate tissue blocks from 65 cases of endometrial carcinoma were drawn from the files of Department of Pathology, Rajavithi Hospital, Bangkok, Thailand. The inclusion criteria included cases that received complete surgical staging procedures at Rajavithi Hospital and the absence of other malignancy in the 5 years preceding and after the diagnosis of endometrial cancer

Medical records were reviewed for age, FIGO stage, treatment, recurrence, and death. One investigator (C.S) reviewed all slides for the FIGO histologic type and grade of tumors, and the depth of myometrial invasion. The follow-up time was at least 60 months. All cases that were lost to follow-up were contacted directly by telephone, mailing, and/or checking the census records from the city municipality to determine their status.

All surgical staging procedures were completed by gynecologic oncologists. The initial treatment consisted of peritoneal washing for cytologic evaluation, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. Lymphadenectomy was not routinely performed. The pelvic and paraaortic lymphadenectomy were done according to histologic grade, depth of invasion, and presence of extrauterine disease. Cytoreduction of advanced disease was performed when necessary. Omentectomy was done in cases with serous carcinoma, clear cell carcinoma, or presence of extrauterine disease. The patients were staged according to the FIGO 1988 criteria[22] and classified according to World Health Organization criteria[23].

Immunohistochemical procedures

For immunohistochemical study, details of the antibodies used in the present study are provided in Table 1. Consecutive paraffin sections were used for immunostaining with each of the antibodies so that similar areas of the tumor could be assessed. Three-micron thick tissue sections were mounted on aminoalkylsilane-coated slides, deparaffinized with xylene and passed through graded alcohols before successively in deionized water and phosphate-buffered saline (PBS). Endogenous peroxidase was blocked with 0.5% hydrogen peroxide-methanol for 30 minutes. The sections were subjected to epitope retrieval by placing the deparaffinized and rehydrated sections in a closed plastic container (Kartell, Milan, Italy) filled with 10 mmol/L citrate buffer at pH6.0. They were irradiated in a domestic microwave oven with a rotating dish (National, model The Genius, 900W) at 750W for 5 minutes and 500W for 6 minutes. After cooling the sections to room temperature, they were incubated with non-immune horse serum to block non-specific staining. They were then incubated with primary antibodies at room temperature for 1 hour. After rinsing in phosphate-buffered solution, the sections were incubated with DAKO EnVision+TM, peroxidase, mouse (Code No: K4001) for 30 minute. The sections were then incubated with DAB (diaminobenzidine) chromogen. A light Mayer hematoxylin was applied as a counterstain. Positive control slides using breast cancer tissue known to express the antigen, were done at the same time. Negative controls were conducted by omitting the primary antibodies.

Immunohistochemical determination

The percentage of ER, PR, Ki-67, and p53-positive cells was evaluated. Positive cells showed brown staining limited exclusively to the nuclei. In the case of ER and PR counts results were recorded as < 10%, 11-25%, 26-50%, 51-75%, and > 75%. Cases with > 10% positive nuclear staining were considered positive ER and PR. A minimum of 1000 tumor cells were examined per slide with x40 objective and a cross-hatched Whipple grid. Ki-67 and p53 were counted in similar fashion and were recorded as percentage of positive nuclear staining tumor cells to the total number of tumor cells. For p53, a cut off level of $\geq$ 50% positive nuclear staining was used[19]. In determination of Ki-67, > 35% nuclear staining was a cut-off value[24]. The assessment of c-erbB-2 was based on positive membrane staining and recorded as score 0: no staining was observed, score 1+: a faint perceptible

Table 1. Antibodies employed, dilutions, and sources

Antibody	Clone	Dilution	Source[a]
ER	SP1	1:500	Neo Marker
PR	SP2	1:1000	Neo Marker
P53	DO-7	1:500	DAKO
Ki67	MIB-1	1:500	DAKO
c-erbB-2	Poly[b]	1:3000	DAKO

a = Neo Marker, Fremont, CA, USA; DAKO Glostrup, Denmark; b = polyclonal

membrane staining was detected in more than 10% of tumor cells, score 2+: a weak to moderate complete membrane staining was observed in > 10% of the tumor cells, score 3+: a strong complete membrane staining was observed in more than 10% of the tumor cells. Score o and 1+ was negative. Score 2+ was equivocal, and score 3+ was positive.

Statistical analysis

Statistical analysis was performed utilizing SPSS for Windows version 11.5. Survival analysis was performed with the Cox proportional hazards model. This technique was used to examine the relative prognostic significance of the variables in predicting survival. Survival curves were determined by the Kaplan-Meier product-limit method. Multivariate analysis was used to find out the Hazard ratio with 95% confidence interval (95% CI). Statistical significance was considered for $p < 0.05$.

Results

The mean age of the patients was 54.94 years with a range of 24 to 80 years. Sixty-two cases (95.4%) were endometrioid adenocarcinoma and three cases (4.6%) were uterine papillary serous carcinoma. Fifty-three patients (82%) were clinical stage I, four (6%) stage II, six (9%) stage III, and two (3%) stage IV. The 62 endometrioid adenocarcinoma cases, 34 (54.8%) were grade1, 20 (32.2%) were grade 2, and eight (13%) were grade 3. Fifty-two patients (80%) showed no evidence of lymph-vascular invasion, 13 (20%) showed evidence of lymph-vascular invasion. The mean follow-up time was 50.35 months, with a maximum of 100 months. Nine patients (13.8%) had recurrent tumor 5 years after treatment. Ten patients (15.4%) died of the primary disease during the follow-up period. The survival curve is shown in Fig. 1.

ER was positive in 50 cases (76.9%) and negative in 15 cases (23.1%). PR was positive in 47 cases (72.3%) and negative in 18 cases (27.7%). Both ER and PR showed significant correlation ($p < 0.01$). Ki-67 showed 27 cases (41.5%) having > 35% positive nuclear staining and 38 cases (58.5%) had $\leq$ 35% positive nuclear staining. p53 was positive in 31 cases (47.7%) and negative in 34 cases (52.3%). c-erbB-2 was positive in one case (1.5%), equivocal in six cases (9.2%), and negative in 58 cases (89.2%).

Survival analysis of prognostic variables had shown that cases with low-stage, low-grade, no recurrent tumor, ER-PR positive, and Ki-67 $\leq$ 35% have better survival than cases with high-stage, high-grade,

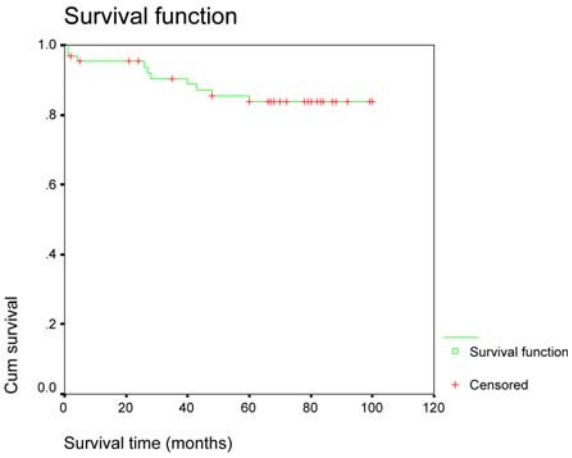

Fig. 1 Kaplan-Meier survival curve for endometrial carcinoma

presence of recurrent tumor, ER-PR-negative, and Ki-67 > 35% ($p < 0.05$) (Table 2).

Cox regression analysis was used to determine independent prognostic factors for survival among the patients. ER-PR status was significant independent prognostic indicators for survival time. Ki-67 expression was significant independent prognostic indicator for survival and recurrent tumor (Table 3-5).

Discussion

The result of the present study showed ER and PR to be independent prognostic factors for survival and recurrent tumor which was similar to many previous studies[8-12] Creasman et al[25] showed that ER-positive, PR-positive, and combined ER- and PR-positive status each implied significantly longer disease free survival times than a negative status. Chambers et al[26] in a multivariate analysis of the ER

Table 2. Survival analysis of prognostic variables

	p-value
Stage	0.0030
Grade	0.0257
Tumor recurrence	0.0000
Lymph-vascular invasion	0.0092
Estrogen receptor	0.0022
Progesterone receptor	0.0022
Ki-67	0.0045
p53	0.8619
c-erbB-2	0.6715

Table 3. Multivariate analysis of Ki-67 and ER-PR status related to stage

Variables	Hazard ratio	95% CI	p-value
Stage 1	0	0	0.990
Stage 2	5.108	1.234-21.147	0.024
Stage 3	1.733	0.173-17.33	0.640
ER-PR status	7.238	1.653-31.681	0.009
Ki-67	9.236	1.716-49.714	0.01

Table 4. Multivariate analysis of Ki-67 and ER-PR status related to grade

Variables	Hazard ratio	95% CI	p-value
Grade 1	2.978	0.522-16.994	0.219
Grade 2	4.909	0.704-34.213	0.108
Grade 3	0.869	0.098-15.554	0.869
ER-PR status	0.154	0.032-0.741	0.020
Ki-67	9.347	1.767-49.450	0.009

Table 5. Multivariate analysis of Ki-67 and ER-PR status related to tumor recurrence

Variables	Hazard ratio	95% CI	p-value
Tumor recurrence	18.780	3.128-112.764	0.01
ER-PR status	3.973	0.694-22.731	0.121
Ki-67	9.251	1-85.560	0.05

status and PR status using various cut-off levels and FIGO grade of the tumor showed that either the ER status or the PR status was the most significant predictor of survival depending on the cut-off level chosen. This is similar to the present finding, the authors found that ER status and PR-status were significant predictors with FIGO staging and grading.

Proliferative index determining with Ki-67 expression also showed independent prognostic significant similar to ER-PR status. This was in line with study of Steansson et al[6] and Geisler et al[15]. Other studies showed correlation with survival in endometrial carcinoma albeit only by univariate analysis[13], or no prognostic significant in determining poor prognosis[27], or associated with high-grade endometrial endometrioid carcinoma[28]. Fanning and associate[29] had found no association between Ki-67 expression and tumor recurrence in high-risk endometrial carcinoma. The authors explained that the lack of association might be due to exclusion of low-risk tumors and the small sample-size.

p53 is a mutation of tumor-suppressor gene leading to accumulation of the mutant protein. The mutant form of p53 is more stable and accumulates to levels detectable by immunohistochemical study in contrast to normal (wild-type) p53 protein which is typically present at levels below the detection of immunohistochemistry. Several reports have shown a close correlation of p53 overexpression and the presence of mutations in the gene[19] and associated with adverse outcome in endometrial carcinoma[18,21,27]. In the present study, p53 showed no statistic significant related to survival time. This may be because p53 is not an independent prognostic factor. It must be related to other significant independent factors such as stage, grade, and histologic type[19].

c-erbB-2 (Her-2/neu) is a proto-oncogene located on the long arm of chromosome 17. It encodes for a 185 kDa transmembane growth factor receptor, p85erb-2. This receptor shares a 40 to 50% homology with the epidermal growth factor that has been shown to induce cell proliferation in tumor cell lines. p185erb-2 is normally expressed in low levels in many adult tissues, including endometrium. In some tissues, amplification leads to protein overexpression, potentially contributing to tumor development or progression. The frequency and clinical significance of c-erbB-2 amplification and/or p185erb-2 overexpression in endometrial carcinoma is less clearly established. A number of previous studies showed a 9-20% frequency of overexpression, and most report that overexpression correlates with poor prognosis[30-33]. Amplification was more frequently observed with high-grade tumor and was associated with clear cell and serous morphology. Overexpression c-erbB-2 was associated with only clear cell carcinoma[21]. Only amplification had predictive value beyond grade, stage, and histologic type, whereas overexpression was not[21]. However, c-erbB-2 (Her-2/neu) determination relied on many factors including preanalytic, analytic, and postanalytic parameters especially the scoring systems[34].

In the present study, c-erbB-2 was negative or equivocal in all cases except one case, which was uterine papillary serous carcinoma that showed c-erbB-2 overexpression. This finding showed that c-erbB-2 displayed no statistic significance related to survival time.

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ความสำคัญในการพยากรณ์โรคของ ER, PR, Ki67, c-erbB-2, และ p53 ในมะเร็งเยื่อบุมดลูก

ชีพสุมน สุทธิพินทะวงศ์, ชาญยุทธ วิจารณาญาณ, เจริญ วิภูภิญโญ

วัตถุประสงค์: *เพื่อศึกษาความสำคัญทางสถิติของ estrogen-progesterone receptor, proliferative index, tumor suppressor gene, และ overexpression of oncogene c-erbB-2 ที่เกี่ยวข้องการรอดชีวิต และการกลับมาเป็นซ้ำของมะเร็ง (tumor recurrence) ในผู้ป่วยมะเร็งเยื่อบุมดลูก*

วัสดุและวิธีการ: *บล็อกพาราฟินจากชิ้นเนื้อของผู้ป่วยมะเร็งเยื่อบุมดลูก 65 ราย ที่ได้รับการวินิจฉัย และรักษาที่โรงพยาบาลราชวิถีในช่วงปี พ.ศ. 2540-2543 และมีการติดตามผู้ป่วยไม่น้อยกว่า 60 เดือน ได้รับการตรวจทาง immunohistochemistry สำหรับ estrogen-progesterone receptor, proliferative index, tumor suppressor gene, และ overexpression of oncogene c-erbB-2 ผลการศึกษาจะถูกวิเคราะห์ด้วย survival analysis และ Cox proportional hazard model*

ผลการศึกษา: *อายุเฉลี่ยของผู้ป่วย 54.94 ปี ซึ่งมีช่วงอายุ 24-80 ปี ค่าเฉลี่ยในการติดตามผู้ป่วย 50.35 เดือน ผู้ป่วย 9 คน (13.8%) มีการกลับมาเป็นซ้ำของมะเร็ง หลังจากรักษามา 5 ปี ผู้ป่วย 10 ราย (15.4%) เสียชีวิตจากโรค การตรวจ immunohistochemistry พบว่า ER ให้ผลบวก 50 ราย (76.9%) และผลลบ 15 ราย (23.1%) PR ให้ผลบวก 47 ราย (72.3%) และผลลบ 18 ราย(17.7%) ผล ER และ PR มีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติ ($p < 0.01$) Ki-67 ให้ผลบวก > 35% 27 ราย (41.5%) และให้ผลบวก ≤ 35% 38 ราย (58.5%) p53 ให้ผลบวก > 50% 31 ราย (47.7%) และให้ผลบวก ≤ 50% 34 ราย (52.3%) c-erbB-2 ให้ผลบวก 1 ราย (1.5%) equivocal 6 ราย (9.2%) และผลลบ 58 ราย (89.3%)*

สรุป: *การศึกษาการรอดชีวิต (survival analysis) พบว่า มะเร็งเยื่อบุมดลูก ที่มี stage และ grade ต่ำ ไม่มีการกลับมาเป็นซ้ำของมะเร็ง ER-PR ให้ผลบวก Ki-67 ให้ผลบวก ≤ 35% จะมีอัตราการรอดชีวิตที่ดี Cox regression analysis พบว่า ER-PR status เป็นตัวแปรอิสระที่มีนัยสำคัญทางสถิติของอัตราการอยู่รอด ในขณะที่ Ki-67 expression จะเป็นตัวแปรที่มีนัยสำคัญทางสถิติของอัตราการอยู่รอดและการกลับมาเป็นซ้ำของมะเร็ง สำหรับ p53 และ c-erbB-2 เป็นตัวแปรที่ไม่มีนัยสำคัญทางสถิติของอัตราการอยู่รอด*