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# Correlation of estrogen and progesterone receptors ER and PR expression with the growth of endometrial cancer

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ABSTRACT

**Objective:** To study the correlation of estrogen and progesterone receptors ER and PR expression with the growth of endometrial cancer. **Methods:** A total of 80 patients with endometrial cancer who were treated collected in the Fourth People's Hospital of Shaanxi and the First Affiliated Hospital of Xi'an Jiaotong University between January 2013 and January 2017 were collected, endometrial cancer tissue and para-carcinoma normal tissue were collected, immunohistochemical method was used to detect positive expression of ER and PR, and fluorescence quantitative PCR was used to detect the mRNA expression of proliferation and apoptosis genes. **Results:** The positive expression of ER and PR in tumor tissue were significantly lower than those in para-carcinoma tissue; proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in tumor tissue of ER-positive group and PR-positive group were lower than those of ER-negative group and PR-negative group; anti-apoptosis genes Wip-1 and Bcl-2 mRNA expression were lower than those of ER-negative group and PR-negative group respectively while pro-apoptosis genes Bid, Bax and Fas mRNA expression were higher than those of ER-negative group and PR-negative group respectively. **Conclusion:** Patients with positive expression of endometrial estrogen and progesterone receptors ER and PR are with lower tumor proliferation activity, higher apoptosis activity and lower malignant degree than patients with negative ER and PR expression.

## 1. Introduction

Endometrial cancer is the most common reproductive system malignancy in women, and choosing a reasonable therapy is the key to optimize the patient's treatment outcome[1,2]. Studies in recent years have discovered that there are significant differences in hormone sensitivity among patients with endometrial cancer, resulting in different treatment options and treatment outcomes. Hormone-dependent endometrial cancer is produced under sustained high hormone stimulation, it is with endometrial hyperplasia and endometrial intraepithelial neoplasia in early stage, the occurrence of non-hormone-dependent cancer has nothing to do with estrogen and progesterone stimulation, and the disease progresses fast in such patients, easily causes myometrial invasion and lymphatic metastasis and is with poor prognosis[3,4]. So early judgment of hormone sensitivity in patients with endometrial carcinoma is the precondition for the clinical therapy formulation, and the positive expression of estrogen and progesterone receptors ER and PR in diseased tissue can objectively reflect the patient's disease type. In the study, ER and PR protein expression in endometrial carcinoma tissue were detected, and the positive protein expression of ER and PR as well as the effect on the activity of tumor cell growth and apoptosis were further explored, now reported as follows.

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## 2. Information and methods

### 2.1 Case information

A total of 80 patients with endometrial cancer who were treated collected in the Fourth People′s Hospital of Shaanxi and the First Affiliated Hospital of Xi'an Jiaotong University between January 2013 and January 2017 were selected as the research subjects, and the patients themselves and families sign the consent form. The patients were 48-79 years old and weighed 47-72 kg. The inclusion criteria were as follows: (1) diagnosed with primary endometrial carcinoma by tissue biopsy; (2) diagnosed for the first time, and not receiving systematic treatment before; (3) cooperating with the whole related inspection and with complete clinical data. Exclusion criteria: (1) associated with primary malignant tumor of other tissue organs; (2) combined with systemic infectious diseases; (3) with application history of estrogen and progesterone half a year before admission.

### 2.2 Estrogen and progesterone receptor expression

Endometrial cancer tissues and para-carcinoma normal tissues were collected, and immunohistochemical method was used to detect positive expression of ER and PR. According to the expression of ER and PR in tumor tissues, the tissues were divided into ER-positive group and ER-negative group as well as PR-positive group and PR-negative group.

### 2.3 Proliferation and apoptosis gene expression

Endometrial cancer tissue and para-carcinoma normal tissue samples were taken, the upper water phase was obtained after cell splitting and high-speed centrifuge, same volume of isopropanol (Shanghai Gaochuang Chemical Technology Co., Ltd., the article number of 0918) was added to precipitate total RNA gel block, and it was cleaned by 75% ethanol ( Shanghai Zeye Biological Technology Co., Ltd., the article number of XW-RS-028) and then air-dried at room temperature for 5-10 min. Reverse transcription kit (Shanghai Kalang Biological Technology Co., Ltd., the article number KL266) instructions were followed to synthesize sample cDNA, and fluorescence quantitative PCR kit (Beijing Huaxia Yuanyang Technology Co., Ltd., the article number RT0411-03) instructions were followed for mRNA amplification of proliferation genes: KCC1, RRM2, SRPX2 and Snail as well as apoptosis genes: Wip-1, Bid, Bcl-2, Bax and Fas. The corresponding PCR amplification curves were obtained, and then the mRNA expression of the above target gene were calculated.

### 2.4 Statistical processing

Statistical software was SPSS 21.0. ER and PR expression belong to count data and were in terms of percentage, and comparison between groups was by chi-square test; proliferation gene and apoptosis gene expression belong to measurement data and were in terms of mean ± standard deviation, and comparison between groups was by t test. Statistics $P<0.05$ was the standard of statistical significance in differences.

## 3. Results

### 3.1 ER and PR expression in tumor tissue and para-carcinoma tissue

The positive expression of ER in para-carcinoma tissue was 97.50% (78/80), the positive expression of PR in para-carcinoma tissue was 98.75% (79/80), the positive expression of ER in tumor tissue was 42.5%(34/80), and the positive expression of PR in tumor tissue was 46.25%(37/80). The positive expression of ER and PR in tumor tissue were significantly lower than those in para-carcinoma tissue, and differences were statistically significant ($P<0.01$). According to the positive expression of ER and PR in tumor tissue, the enrolled patients were divided into ER-positive group ($n=34$) and ER-negative group ($n=46$) as well as PR-positive group ($n=37$) and PR-negative group ($n=43$).

### 3.2 ER expression and proliferation gene expression

Comparison of proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in endometrial cancer tissue with different ER expression was as follows: proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in tumor tissue of ER-positive group were significantly lower than those of ER-negative group, and differences were statistically significant in KCC1, RRM2, SRPX2 and Snail mRNA expression in endometrial cancer tissue with different ER expression ($P<0.01$), shown in Table 1.

**Table 1.**

Comparison of proliferation gene expression in endometrial cancer tissue with different ER expression.

| Groups | *n* | KCC1 | RRM2 | SRPX2 | Snail |
|---|---|---|---|---|---|
| ER-negative group | 46 | 98.72±10.49 | 102.37±14.82 | 99.54±10.83 | 101.76±14.38 |
| ER-positive group | 34 | 50.18±6.37 | 71.46±8.52 | 65.16±9.46 | 58.25±7.19 |
| *T* | | 11.283 | 10.938 | 13.264 | 15.382 |
| *P* | | <0.01 | <0.01 | <0.01 | <0.01 |

**Table 2.**

Comparison of apoptosis gene expression in endometrial cancer tissue with different ER expression.

| Groups | *n* | Wip-1 | Bid | Bcl-2 | Bax | Fas |
|---|---|---|---|---|---|---|
| ER-negative group | 46 | 95.37±10.27 | 102.48±15.94 | 99.37±10.28 | 101.55±14.68 | 97.23±10.54 |
| ER-positive group | 34 | 41.24±5.68 | 175.33±21.54 | 30.41±4.52 | 163.47±18.55 | 147.48±16.93 |
| *T* | | 13.284 | 17.382 | 15.662 | 9.309 | 11.261 |
| *P* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |

### *3.3 ER expression and apoptosis gene expression*

Comparison of apoptosis genes Wip-1, Bid, Bcl-2, Bax and Fas mRNA expression in endometrial cancer tissue with different ER expression was as follows: anti-apoptosis genes Wip-1 and Bcl-2 mRNA expression in the tumor tissue of ER-positive group were lower than those of ER-negative group while pro-apoptosis genes Bid, Bax and Fas mRNA expression were higher than those of ER-negative group, and differences were statistically significant in Wip-1, Bid, Bcl-2, Bax and Fas mRNA expression in endometrial cancer tissue with different ER expression ($P$<0.01), shown in Table 2.

### *3.4 PR expression and proliferation gene expression*

Comparison of proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in endometrial cancer tissue with different PR expression was as follows: proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in tumor tissue of PR-positive group were significantly lower than those of PR-negative group, and differences were statistically significant in KCC1, RRM2, SRPX2 and Snail mRNA expression in endometrial cancer tissue with different PR expression ($P$<0.01), shown in Table 3.

**Table 3.**

Comparison of proliferation gene expression in endometrial cancer tissue with different PR expression.

| Groups | *n* | KCC1 | RRM2 | SRPX2 | Snail |
|---|---|---|---|---|---|
| PR-negative group | 43 | 102.37±13.25 | 99.16±11.53 | 105.77±14.93 | 102.64±13.28 |
| PR-positive group | 37 | 63.21±7.04 | 51.93±6.32 | 58.62±7.18 | 46.81±5.79 |
| *T* | | 13.281 | 10.983 | 11.726 | 15.438 |
| *P* | | <0.01 | <0.01 | <0.01 | <0.01 |

### *3.5 PR expression and apoptosis gene expression*

Comparison of apoptosis genes Wip-1, Bid, Bcl-2, Bax and Fas mRNA expression in endometrial cancer tissue with different PR expression was as follows: anti-apoptosis genes Wip-1 and Bcl-2 mRNA expression in the tumor tissue of PR-positive group were lower than those of PR-negative group while pro-apoptosis genes Bid, Bax and Fas mRNA expression were higher than those of PR-negative group, and differences were statistically significant in Wip-1, Bid, Bcl-2, Bax and Fas mRNA expression in endometrial cancer tissue with different PR expression ($P$<0.01), shown in Table 4.

## 4. Discussion

Endometrium is the target organ tissue of hormone, ER and PR exist in most hormone-dependent endometrial cancer lesions, but they are mostly less expressed and even not expressed in the serous carcinoma and clear cell carcinoma[5,6]. Studies both at home and abroad have confirmed that ER and PR expression are directly related to tumor stage and tumor differentiation, the positive expression of ER and PR in patients with lymph node metastasis is significantly lower than that in patients without metastasis, and the ER and PR expression deletion is a sign of high tumor malignancy[7,8]. In the study, the positive expression of ER and PR in tumor tissue and para-carcinoma tissue were compared at first, and it was found that the positive expression of ER and PR in tumor tissue were lower than those in para-carcinoma tissue. The positive expression of ER and PR in tumor tissue as well as the effect on the tumor cell malignancy is to be confirmed in the study below.

Tumor cell proliferation activity directly determines its malignant degree, and the abnormal expression of the proliferation genes is the most direct reason that decides the tumor proliferation state, and detection of endometrial cancer-related proliferation gene expression can objectively reflect the disease severity[9]. KCC1 is a transport protein on cell membrane, it has been found that its expression in endometrial cancer tissue is higher than that in normal endometrial tissue, and KCC1 expression increases with the increase of the tumor histology grading. RRM2 is a key rate-limiting enzyme for DNA synthesis and repair, and it is found that cell proliferation activity declines after cell experiment interferes with the expression of RRM2 in endometrial cancer tissue[10]. It has been confirmed that the expression of SRPX2 in endometrial carcinoma is significantly

**Table 4.**

Comparison of apoptosis gene expression in endometrial cancer tissue with different PR expression.

| Groups | *n* | Wip-1 | Bid | Bcl-2 | Bax | Fas |
|---|---|---|---|---|---|---|
| PR-negative group | 43 | 93.26±9.84 | 100.73±11.62 | 104.58±15.29 | 99.63±10.72 | 95.46±10.71 |
| PR-positive group | 37 | 69.23±7.12 | 147.95±15.83 | 58.63±6.24 | 137.48±15.79 | 156.92±18.77 |
| *T* | | 12.387 | 11.647 | 15.398 | 13.261 | 17.293 |
| *P* | | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |

increased, and it is closely related to the increase of tumor diameter, tumor staging and so on[11]. Snail is a transcription factor that plays an important role in tumor proliferation and invasion, which accelerates tumor progression by activating the expression of its downstream target genes[12]. In the study, comparison of the proliferation gene expression in endometrial carcinoma tissue with different ER and PR protein expression showed that proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in tumor tissue of ER-positive group were lower than those of ER-negative group; proliferation genes KCC1, RRM2, SRPX2 and Snail mRNA expression in tumor tissue of PR-positive group were lower than those of PR-negative group, confirming that negative ER and PR expression are the signs of higher endometrial cancer proliferation activity, in other words, those with positive ER and PR expression are with lower malignant degree.

Apoptosis is a programmed death process, normal cells will enter into apoptosis stage after their function declines, but the apoptosis process of malignant tumor cells is in disorder, persistent escape from apoptosis make them obtain continuous proliferation ability, and it is the important material basis to lead to increased tumor volume, distant metastasis, and others[13,14]. Wip-1 is a gene that is closely related to the apoptosis of endometrial cancer cells, which may make tumor suppressor gene p53 inactivated through direct/ indirect pathways, and lead to tumor cell apoptosis disorder and progression. Both Bid and Bax are the pro-apoptosis genes of Bcl-2 family, and their expression reduction or deletion is the important cause of many malignancies. Bcl-2 is an anti-apoptosis gene of Bcl-2 family, which can induce tumor cells to escape apoptosis and prompt their infinite proliferation[15,16]. Studies have shown that the positive expression rate of Fas in endometrial cancer tissue is lower than that in endometrial hyperplasia tissue, and its low expression can enhance the expression of FasL accordingly and make tumor cell apoptosis blocked. In the study, comparison of the apoptosis gene expression in endometrial carcinoma tissue with different ER and PR protein expression showed that anti-apoptosis genes Wip-1 and Bcl-2 mRNA expression in the tumor tissue of ER-positive group were lower than those of ER-negative group while pro-apoptosis genes Bid, Bax and Fas mRNA expression were higher than those of ER-negative group; anti-apoptosis genes Wip-1 and Bcl-2 mRNA expression in the tumor tissue of PR-positive group were lower than those of PR-negative group while pro-apoptosis genes Bid, Bax and Fas mRNA expression were higher than those of PR-negative group, confirming that the negative ER and PR expression are the signs of endometrial carcinoma apoptosis inhibition.

To sum up, it can be concluded that positive ER and PR protein expression in endometrial carcinoma tissues are the signs of lower proliferation activity and higher apoptosis activity of tumor cells, and different treatments should be taken for patients with different ER and PR protein expression.

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