Prediction of Clinical Outcome with Estrogen and Progestin Receptor Concentrations and Their Relationships to Clinical and Histopathological Variables in Endometrial Cancer

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ABSTRACT

Concentrations of cytosol estrogen (ERC) and cytosol progestin (PRC) receptors were assayed in malignant tissue specimens of 230 patients with endometrial cancer, and those of nuclear estrogen and nuclear progestin receptors, and 17β-hydroxysteroid dehydrogenase activities in about 100 specimens. Endometrial cancer was at an early stage in 205 and advanced in 25 patients. As a supplement to surgical and radiation therapy, all patients received p.o. medroxyprogesterone acetate (100 mg a day) for 2 years. The follow-up time varied from 12 to 96 months (median, 42 months).

Concentrations of ERC, PRC, nuclear estrogen, and nuclear progestin receptors in endometrial cancer tissue were significantly lower in clinical stages III-IV than in clinical stage I. In clinical stage I, ERC and PRC appeared in significantly lower concentrations in anaplastic than in moderately and well differentiated malignancies. The concentrations of these receptors were increased in obese patients, and the activity of 17β-hydroxysteroid dehydrogenase was increased in patients younger than 50 years, suggesting that endogenous female steroid hormones modify the pattern of female steroid receptors in malignant endometrium. In clinical stage I, 13 of 153 patients with adequate therapy contracted a recurrent disease. Poor prognosis was predicted by anaplastic structure of the malignancy (P < 0.001), low tissue concentrations (0-30 fmol/mg protein) of ERC alone (P = 0.006), PRC alone (P = 0.010), and ERC and PRC simultaneously (P = 0.004). All 101 patients who simultaneously had ERC and PRC in concentrations higher than 30 fmol/mg protein remained disease free for 2 years, whereas all recurrences in patients with receptor-poor tumors appeared during the 2 years of medroxyprogesterone acetate treatment. In clinical stage II, with 30 patients, no prognosis indicators predicted the clinical outcome, whereas in clinical stages III + IV, with 25 patients, low ERC concentrations were associated with a worsened prognosis (P = 0.045).

Conclusively, cytosol and nuclear estrogen and nuclear progestin receptor concentrations and 17β-hydroxysteroid dehydrogenase activity give valuable information about the endocrine associations in endometrial cancer. Cytosol estrogen and cytosol progestin receptors appeared to be useful predictors of recurrent disease. They also have the potential to distinguish between patients expected to benefit from adjuvant progestin therapy and those expected to be unresponsive to the same treatment.

INTRODUCTION

In endometrial cancer clinical and histopathological indicators of prognosis (1-4) are used in the planning of individual treatment strategies. Because endometrial cancer belongs to the category of hormone-dependent neoplasias, endocrine indicators such as female sex steroid receptors have been expected to serve as a new basis for categorization of patients with endometrial cancer as far as prognosis and treatment modalities are concerned (5-10). In this and other centers, it has been shown that ERC2 and PRC receptors are present in endometrial ade-...
Clinical Stage and Receptors. Concentrations of ERC, PRC, ERN, and PRN were significantly higher in clinical stage I than in clinical stages III + IV (Table 1). In addition, ERC concentration was higher in clinical stage I than in stage II, and PRN concentration in clinical stage II than in stages III–IV.

Histopathological Grade and Receptors. Concentrations of ERC and PRC in grade 1 + 2 tumors were significantly higher than in grade 3 malignancies in clinical stage I (Table 2). In clinical stage II the receptor variables did not differ significantly between these histopathological categories (data not shown). In clinical stages III + IV the concentration of PRC in grades 1 + 2 tumors \( [N = 11; 140 \pm 57 (SE) \text{ fmol/mg protein}] \) was significantly higher \( (P < 0.05) \) than in grade 3 tumors \( (N = 14; \ 7 \pm 2 \text{ fmol/mg protein}) \).

Spearman rank correlation coefficients (Table 3) showed that the histopathological grade of the malignancy and the concentrations of ERC and PRC were significantly \( (P < 0.001) \) negatively correlated with each other. In addition, there was a strong positive correlation between the concentrations of ERC and PRC.

Myometrial Invasion. The concentrations of ERC, PRC, ERN, and PRN and the activity of 17-HSD did not differ significantly between the deeply invasive and superficial tumors in clinical stage I or II. The degree of myometrial invasion had no correlation with histopathological grade of the tumor or the concentrations or ERC and PRC (data not shown).

Age. In clinical stages I + II, 24 patients were younger than 50 years and 181 were 50 years or older. The activity of 17-HSD was higher in the younger than in the older women \( (1.33 \pm 0.53 \text{ versus } 0.41 \pm 0.06 \text{ estradiol to estrone/30 min; } P < 0.006) \).

Weight. In clinical stages I + II, 22 patients weighed more than 90 kg and 180 were less than this. The tumors of overweight women had significantly higher concentrations of ERC \( (233 \pm 41 \text{ versus } 127 \pm 11 \text{ fmol/mg protein}; \ P < 0.02) \) and PRC \( (517 \pm 112 \text{ versus } 278 \pm 29 \text{ fmol/mg protein}; \ P < 0.03) \) than those of the other women.

Other Clinical Parameters. Diabetes, hypertension, or parity had no relationship to any of the other parameters measured (data not shown).

Disease-free Survival in Stages I and II. In clinical stage I, 11 patients died of concurrent disease and 11 patients received radiotherapy alone. They were excluded from the analysis of corrected disease-free survival data. The results from the whole material (175 patients) did not show any basic differences from the data to be presented below for the corrected material (153 patients). Recurrent disease appeared in 13 patients in clinical stage I at 5 to 28 months (mean, 15.7 months) after treatment. At the time of analysis, two patients were alive with recurrent disease while the other patients died of the disease 9 to 36 months after treatment. In two cases recurrent disease appeared simultaneously at pelvic and distant sites whereas in all other cases only distant metastases were found. In clinical stage II, 5 patients contracted distant recurrent disease 2 to 26 months after therapy. Two patients were alive with the disease at the end of follow-up while three patients died of the malignancy 12 to 14 months after therapy. In clinical stages III and IV, 22 of the 25 patients died of the malignant disease 1 to 23 months after therapy. Two patients were disease free, and one patient was alive with the disease at the end of the 60-month follow-up.

The disease-free survival of 153 patients in clinical stage I correlated significantly with the ERC (Fig. 1A), and PRC (Fig. 1B) concentrations when tumors were categorized into receptor-rich and receptor-poor groups and also with the grade of the tumor (Fig. 1E). The combined data of ERC and PRC, categorized as shown in Fig. 1, C and D, also predicted prognosis.

In the categories of patients having receptor-rich tumors, almost all recurrences appeared in close association with the termination of the adjuvant MPA treatment.
Myometrial invasion did not correlate with the prognosis (data not shown). In clinical stage II, the histopathological structure of the malignancy, the myometrial infiltration of the tumor, and the concentration of ERC and PRC separately or together were ineffective for predicting the aggressiveness of the malignancy. Analyses of sensitivity, specificity, and predictive values of the variables recorded were carried out in order to classify stage I and II patients into two categories, patients who contract recurrent disease and patients who remain disease free (Table 4). The main emphasis should be to identify the former group of patients because more intensive therapeutic and follow-up programs should be used and developed for these patients. The histopathological grade appeared to identify most of the patients (sensitivity, 67%) contracting recurrent disease but the predictive value of a positive test was only 41%. The specificity of this test was the highest (89%) of the single variables evaluated. Myometrial invasion was clearly of less value, and cytosol receptor measurements had an intermediate position, ERC appearing to be the more powerful of the two. The combined information of histopathological grade classification and ERC measurements (Table 4) could have resulted in the identification of 9 of the 18 patients who presented with recurrent disease during the follow-up of 12 to 96 months, while 7 patients would have been misclassified in the high risk group.

Lifetime Survival in Stages III + IV. In clinical stages III–IV the data of ERC correlated significantly with the clinical course of the disease (Fig. 2), while the histopathological structure of the malignancy and the PRC data were insensitive indicators of prognosis.

DISCUSSION

Correlation of multiple clinical variables with the receptor data showed that a relatively young age and obesity influence the receptor concentrations and/or 17-HSD activity. The greater activity of 17-HSD in young patients is very probably related to the production of ovarian hormones, and the greater concentrations of ERC and PRC in obesity are probably related to the conversion of adrenal androgens into estrogens by fat tissue (34, 35); hence, endometrial cancer in young and obese patients is characterized by specific receptor patterns which may explain, at least partly, why these patients have a better clinical outcome than other patients (3).

The finding of low concentrations of ERC and PRC in anaplastic tumors in relation to well and moderately differentiated malignancies (6, 14–17) and in advanced or recurrent diseases compared with early ones (6, 23) is in agreement with most previous studies. The response rate to progesterin therapy of endometrial cancer correlated with the ERC and/or PRC content of the tumor (summarized in Ref. 36); hence, the lower sensitivity of anaplastic cancers to the action of female steroid hormones (37–39) seems to be related to the low receptor concentrations of these malignancies. The present new findings of lowered concentrations of ERN and PRN in stages III + IV disease compared to clinical stage I and lowered activity of 17-HSD in anaplastic tumors compared with the others, the latter observed also by Pollow et al. (26), support the view of decreased sensitivity of advanced and anaplastic endometrial malignancies to hormonal therapy. In addition, well-differentiated tumors have responded to progesterin therapy with increased activity of 17-HSD, whereas anaplastic neoplasias were unresponsive (40).

The relatively large number of patients and the long follow-up time make it possible to relate the clinical prognosis indicators and receptor data to prognosis. The two patients surviv-
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Table 4  Predictive values of positive and negative tests, respectively, sensitivity, and specificity of the conventional (histopathological grade, myometrial invasion) and endocrine (ERC, PRC) risk indicators in the detection of recurrent disease in the group of 178 patients with adequately treated stage I or II endometrial cancer. In parentheses, after each variable, the assumed criterion of poor prognosis is indicated (positive when present, negative when absent).

<table>
<thead>
<tr>
<th>Risk indicator</th>
<th>Recurrent disease</th>
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<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Total</td>
<td>Predictive value</td>
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<tr>
<td>ERC (0–30 fmol/mg protein)</td>
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<tr>
<td>Positive</td>
<td>10</td>
<td>39</td>
<td>49</td>
<td>Positive test, 10:49 = 20%</td>
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<tr>
<td>Negative</td>
<td>8</td>
<td>121</td>
<td>129</td>
<td>Negative test, 121:129 = 94%</td>
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<td>PRC (0–30 fmol/mg protein)</td>
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<td>Positive</td>
<td>9</td>
<td>43</td>
<td>52</td>
<td>Positive test, 9:52 = 17%</td>
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<tr>
<td>Negative</td>
<td>9</td>
<td>117</td>
<td>126</td>
<td>Negative test, 117:126 = 93%</td>
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<td></td>
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<td>Histopathological grade (grade 3)</td>
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<tr>
<td>Positive</td>
<td>12</td>
<td>17</td>
<td>29</td>
<td>Positive test, 12:29 = 41%</td>
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<td>Negative</td>
<td>6</td>
<td>141</td>
<td>147</td>
<td>Negative test, 141:149 = 95%</td>
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<td>Myometrial invasion (more than one-half of myometrial depth)</td>
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<tr>
<td>Positive</td>
<td>4</td>
<td>25</td>
<td>29</td>
<td>Positive test, 4:29 = 14%</td>
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<tr>
<td>Negative</td>
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<td>114</td>
<td>126</td>
<td>Negative test, 114:126 = 90%</td>
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<tr>
<td>Histopathological grade (grade 3) plus ERC (0–30 fmol/mg protein)</td>
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<tr>
<td>Positive</td>
<td>9</td>
<td>7</td>
<td>16</td>
<td>Positive test, 9:16 = 56%</td>
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<tr>
<td>Negative</td>
<td>9</td>
<td>151</td>
<td>160</td>
<td>Negative test, 151:160 = 94%</td>
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Other combinations were weaker than "grade + ERC," and are not shown.

Fig. 2. Lifetime analysis of patients with stages III–IV endometrial adenocarcinoma in relation to ERC (ERC) (A) and PRC (PRC) (B) data and histopathological grade (C).

In spite of the fact that an anaplastic malignancy was an indication for more aggressive therapy in the present study, patients with such malignancies have significantly poorer survival figures than patients with well- or moderately differentiated tumors. The potentiation of therapy with pelvic irradiation and adjuvant MPA therapy thus could not eliminate the hazards generally known to be associated with anaplastic endometrial cancers (1–4). Because most of the recurrent lesions appeared outside the pelvic cavity, adjuvant treatment with cytotoxic drugs alone or together with pelvic irradiation might be recommendable in these cases.

It is also clinically important that there was no single case of recurrent disease during the 2-year period of MPA administration if ERC and PRC concentrations were simultaneously higher than 30 fmol/mg protein. All recurrences detected so far in this category appeared soon after termination of adjuvant MPA treatment. Whether this is due to an arresting effect of
progestin or whether the late manifestation of recurrent disease is an inherent property of such cases is not known at present. In addition, all recurrences in patients having receptor-poor tumors appeared during MPA administration. Put together with previous data of the beneficial effect of MPA in advanced endometrial cancer (34, 38, 41), our findings call for studies as to whether adjuvant use of MPA in the form of long-term treatment should be restricted to patients with receptor-rich tumors.

REFERENCES

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