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Progesterone receptor negativity is an independent risk factor for relapse in patients with early stage endometrioid endometrial adenocarcinoma

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HIGHLIGHTS

- Approximately 10% of patients with stages I–II endometrioid endometrial adenocarcinoma experience a relapse.
- Negative progesterone receptor expression was associated with relapse risk in multivariate analysis.
- Presence of LVI, tumor size >2cm or negative estrogen receptor expression was not associated with relapse risk.

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ABSTRACT

Objective. In endometrioid endometrial adenocarcinoma (EEA), the currently established prognostic factors in clinical guidelines are stage and grade. Many guidelines include lymphovascular invasion (LVI) and tumor size as prognostic factors. Although several studies have associated lack of estrogen (ER) and progesterone receptor (PR) expression with reduced outcome, the prognostic use of these markers is uncommon. Better prognostication of clinical behavior would be useful in patients with early stage (I–II) disease. In this study we evaluated ER and PR as prognostic factors in EEA, and compared their expression with other potential biomarkers and clinical parameters.

Methods. Tissue microarrays were constructed from 182 patients with stages I–II EEA. ER, PR, p53, Ki-67, PTEN, MLH and HER-2 expression were assessed by immunohistochemical staining and HER-2 was confirmed with SISH. The results were correlated with clinicopathologic parameters and to disease-free survival.

Results. Eleven patients (6%) developed recurrent disease during a median follow up time of 62.8 months. In univariate analysis FIGO grade ($p = 0.019$), positive expression of p53 ($p = 0.010$) and negative PR expression ($p = 0.001$) were associated with a shorter disease-free survival. In multivariate analysis only negative PR expression ($p = 0.019$) was significantly associated with a shorter disease-free survival. LVI and tumor size where not of prognostic value.

Conclusions. Lack of PR expression is a strong, independent risk factor for tumor recurrence in patients with stages I–II endometrioid endometrial cancer. The use of this easily measurable biomarker as a prognostic factor in the clinical context should be considered and tested in a larger patient population.

Introduction

Endometrial cancer is the most common gynecologic cancer in industrialized countries. The incidence is on the rise, which is proposed to be related to an increase in life expectancy and the epidemic of obesity [1]. Approximately 80% of endometrial cancers are of endometrioid adenocarcinoma (EEA) histology and the majority of endometrial cancers are detected at an early stage when the disease is restricted to the uterus. Although the prognosis is generally favorable, approximately 15% of cancers relapse [2].

EEA is usually categorized into three groups according to the relapse risk: low risk (stage IA grades 1–2), intermediate risk (stage IB

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grades 1–2, stage IA grade 3) and high risk (stage IB grade 3, stages II–IV). Besides stage and grade, several clinical guidelines recommend the use of additional prognostic factors such as tumor size >2 cm and lymphovascular invasion (LVI) [3–5].

Already in 1985 Creasman et al. reported that hormone receptor expression correlates with disease-free survival in stages I and II endometrial carcinoma [6]. Thereafter the prognostic value of PR status has been confirmed in several studies [7–11]. Lack of PR expression by immunohistochemistry has been shown to be strongly related to reduced disease-free survival (DFS) and to be an independent predictor of the clinical course of endometrial cancer [8]. The value of PR negativity as an independent prognostic factor has been challenged because it is usually associated with a more aggressive phenotype [12]. The National Cancer Institute recommends the incorporation of ER and PR into the evaluation of endometrial cancer patients with stages I and II disease [13]. However, evaluation of hormone receptors and the use of this information in risk assessment are currently not included in any of the treatment guidelines that we were able to retrieve from databases [3–5].

The purpose of our study was to evaluate the usefulness of hormone receptor status in risk assessment of patients with EEA limited to the uterus (stages I–II). Specifically we wanted to compare hormone receptor status as a prognostic factor with the two commonly used parameters: LVI and tumor size. We included assessment of p53, Ki-67, PTEN and MLH1 in our analysis, since these factors have also been described to have a prognostic effect in endometrial cancer [14–19]. In addition, we evaluated the role on HER-2, since it has been shown to be associated with aggressive phenotype of endometrial cancer [20].

Table 1
Clinicopathologic characteristics of 182 patients with EEA.

Variable	n (%)	Median (range)
Age		67 (35–93)
BMI*		27.3 (18.4–58.3)
Menopausal status		
Pre-menopausal	13 (7.1)	
Post-menopausal	169 (92.9)	
CA12-5 <35 U/ml**		
Yes	145 (84.3)	
No	27 (15.7)	
Stage (FIGO 2009)		
Ia	136 (74.7)	
Ib	42 (23.1)	
II	4 (2.2)	
Grade		
G1	107 (58.8)	
G2	48 (26.4)	
G3	27 (14.8)	
MI		
≤50%	138 (75.8)	
>50%	44 (24.2)	
LVI		
No	169 (92.9)	
Yes	13 (7.1)	
Tumor size		
≤2 cm	74 (40.7)	
>2 cm	108 (59.3)	
Risk group		
Low risk	121 (66.5)	
Intermediate risk	45 (24.7)	
High risk	16 (8.8)	

* n = 181.
** n = 172.

Material and methods

This study was conducted at the Department of Obstetrics and Gynecology and the Department of Pathology of Turku University Hospital (Finland). Turku University Hospital is the referral hospital for operative treatment of gynecologic cancer surgeries in Southwestern Finland. As the patients were originally staged according to the FIGO 1988 guidelines, the patients were restaged by AA and JH to comply with the FIGO 2009 staging guidelines. The current study was approved by the Ethical Committee of the Southwestern Finland Hospital District and the Finnish National Authority for Medicolegal Affairs.

Between 1 September 2004 and 31 December 2007, 244 women with EEA underwent surgery at the Department of Obstetrics and Gynecology of Turku University Hospital. Twenty-seven patients were excluded from the study, 3 because they had received pre-operative radiotherapy or chemotherapy, 23 because there was an insufficient amount of cancerous tissue in the surgical specimen and one because of a carcinosarcomatous component in the preoperative sample. Thirty-five cases were stage IIIa or higher, and they were excluded from the analysis. Thus, the final study group consisted of 182 patients with stages I–II EEA. Operative treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy for patients with grade 1 or 2 disease; moreover, para-aortic lymphadenectomy was performed on patients with grade 3 disease. Post-operative adjuvant treatment was determined based on the final stage and grade of the tumor and was performed according to the hospital guidelines.

The histopathologic classification of each tumor was re-evaluated according to the International Federation of Gynecology and Obstetrics (FIGO 1988) guidelines (LT). Demographic, clinical, and pathologic information and follow-up data for relapse was obtained from hospital records. Survival data were obtained from the Population Registry, and the cause of death from Statistics Finland. All patients were followed until death or 31 October 2011.

The clinical and pathologic features of the 182 patients with EEA included in this study are summarized in Table 1. Of the patients 142 (78%) underwent either pelvic 123 (67.6%), or pelvic and para-aortic 19 (10.4%) lymphadenectomy. Adjuvant therapy was primarily given according to the hospital guidelines provided that there was no patient-related impairment. Sixteen patients (8.8%) received no adjuvant treatment. Vaginal brachytherapy was given to 100 (54.9%) patients, external beam radiotherapy (EBRT) to 35 (19.2%) patients, and 8 (4.4%) patients received both vaginal brachytherapy and EBRT. Finally, 23 (12.6%) patients received both chemotherapy and radiation therapy.

The median follow-up time was 62.8 months (4.2–84.4 months). No patients were lost to follow-up. During follow-up, a relapse was diagnosed in 11 (6%) patients, as follows: 5 in the pelvis (3 peritoneal and 2 vaginal) and 4 distant (1 in the para-aortic lymph nodes and 3 in the lungs). In two cases, relapses occurred in multiple anatomical sites. The median disease-free time for all patients was 62.2 months (4.2–84.4 months) and 11.3 months (5.2–68.5 months) for relapsed cases. By the end of follow-up, 25 (13.7%) deaths had occurred, 7 (3.8%) of which were due to EEA.

Tissue microarrays (TMAs) and immunohistochemistry (IHC)

Generation of TMAs, IHC, and slide scanning was performed on TMAs from the Swedish Science for Life Laboratory (SciLifeLab) facilities in the Department of Immunology, Genetics, and Pathology at the Rudbeck Laboratory of Uppsala University (Sweden), in accordance with strategies used in The Human Protein Atlas project (www.proteinatlas.org). In brief, formalin-fixed, paraffin-embedded tumor samples were selected and corresponding hematoxylin-eosin stained histologic slides were reviewed by a pathologist (LT) to select representative areas for TMA production of TMAs representing the 182 EEA specimens. To construct the TMAs, two 1.0-mm diameter cores from each donor block (duplicate samples) were taken and assembled in an array format in a recipient TMA block using TMArrayer™ (Pathology Devices, Westminster, MD, USA) or the Beecher Instruments Manual Tissue Arrayer MTA-1 (Estigen OÜ, Tartu, Estonia).