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The expression of stanniocalcin-1, estrogen receptor and progesterone receptor in endometrioid endometrial cancer

Endometrioid endometrial kanserde staniokalsin-1, östrojen reseptörü ve progesteron reseptörü ekspresyonu

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Abstract

Objective: To evaluate the expression of stanniocalcin-1 (STC-1) and to investigate the correlation of STC-1 with expression of estrogen receptor (ER), progesterone receptor (PR) and clinical parameters, histopathological findings and prognostic factors in endometrioid endometrial cancer (EEC).

Materials and Methods: In this retrospective study, STC-1 (cytoplasmic), ER (nuclear), and PR (nuclear) stainings were applied to tissue microarray sections of 89 EEC, 27 endometrial intraepithelial neoplasia (EIN), and 21 normal endometrium (NE). Prognostic factors such as age, tumor size, depth of myometrial invasion, lymphovascular invasion, perineural invasion, and lymph node metastasis were compared with the expression of these markers.

Results: ER showed significantly higher positivity in grade 1 EEC. PR expression was also higher in grade 1 EEC, but these findings were not statistically significant. Strong expression of STC-1 was observed in EIN and EECs compared with NE. STC-1 showed low staining in the NE, and high staining was also noted in the EIN foci adjacent to the NE. STC-1 expression was positively correlated with grade 1 EECs.

Conclusion: STC-1 expression was positively correlated with low histologic grade in EECs. STC-1 can be used for distinguishing low-grade endometrioid tumors and high -grade endometrioid tumors in curretage specimens. Since STC-1 is related to well differentiated tumors, it can also be regarded as a good prognostic factor in EECs.

Keywords: Stanniocalcin-1, estrogen receptor, progesterone receptor, endometrioid endometrial cancer

Öz

Amaç: Bu çalışmanın amacı stanniokalsin-1 (STC-1) ekspresyonunu değerlendirmek ve endometrioid endometrial kanserde (EEK) STC-1 ile östrojen reseptörü (ER), progesteron reseptörü (PR) ekspresyonları ile, klinik parametreler, histopatolojik bulgular ve prognostik faktörlerin korelasyonunu araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmada 89 EEK, 27 endometrial intraepitelyal neoplazi (EİN) ve 21 normal endometriumun (NE) doku mikroarray kesitlerine STC-1 (sitoplazmik), ER (nükleer), PR (nükleer) boyamaları uygulandı. Yaş, tümör boyutu, myometriyal invazyonun derinliği, lenfovasküler invazyon, perinöral invazyon ve lenf nodu metastazı gibi prognostik faktörler bu belirteçlerin ekspresyonu ile karşılaştırıldı.

PRECIS: Stanniocalcin-1 (STC-1) expression was associated with well differantiated endometriod endometrial cancer. Decreased expression of STC-1 was observed in poor differentiated endometriod endometrial cancer.

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Bulgular: ER, grade 1 EEK'de anlamlı olarak daha yüksek pozitiflik gösterdi. PR ekspresyonu da grade 1 EEK'de daha yüksekti, ancak bu bulgu istatistiksel olarak anlamlı değildi. EİN ve EEK'de NE'ye kıyasla güçlü STC-1 ekspresyonu gözlendi. STC-1, NE'de zayıf boyanma gösterdi ve NE komşuluğundaki EİN odaklarında yüksek boyanma kaydedildi. STC-1 ekspresyonu, grade 1 EEK'ler ile pozitif korelasyon gösterdi.

Sonuç: STC-1 ekspresyonu, EEK'de düşük histolojik derece ile pozitif korelasyon gösterdi. STC-1, küretaj örneklerinde düşük dereceli ve yüksek dereceli endometrioid tümörleri ayırt etmek için kullanılabilir. STC-1, iyi diferansiye tümörlerle ilişkili olduğu için EEK'de iyi bir prognostik faktör olarak kabul edilebilir.

Anahtar Kelimeler: Staniokalsin-1, östrojen reseptörü, progesteron reseptörü, endometrioid endometrial kanser

Introduction

Endometrial cancer (EC) is mostly seen in peri-postmenopausal women. The incidence and mortality rates increase with age[1]. Hormone receptor status has a prognostic role in EC that estrogen receptor (ER) or progesterone receptor (PR) positivity are good prognostic markers[2].

Endometrioid endometrial cancer (EEC) and serous/clear cell endometrial cancers (SEC), show significantly different clinicopathological features[2]. Endometrioid type is mostly associated with overexposure to the estrogen. There are 2 forms of estrogen hormone, alpha and beta. The alpha form was associated with poor survival. Progesterone hormone is used to treat early-stage PR -positive ECs. The progesterone response is low in advanced and recurrent ECs. Progesterone response is an important prognostic indicator in ECs[3]. SECs have a worse prognosis. They are unrelated to estrogen exposure[4].

Increasing the incidence of EC makes it important to forecast the likelihood of recurrence and prognosis after diagnosis to reduce mortality and morbidity. Studies have shown that tumor stage, histological grade, histopathological type, invasion depth, and lymphovascular space involvement status are crucial parameters in predicting recurrence[5,6]. However, it is critical to search for more indicators in predicting prognosis and recurrence.

Stanniocalcin-1 (STC-1), is regarded as a prognostic marker, in predicting the grade and size of tumor and risk of metastasis[7]. STC-1 is a glycoprotein hormone that has a role in cell proliferation, calcium metabolism, programmed cell death, and oxidative stress responses[8].

STC-1 was first detected in humans in 1995[9]. It was determined that ovarian cancers showed higher STC-1 expression than other cancer types[10]. High expression of STC-1 has been detected in hepatocellular carcinoma, thyroid cancer, colon cancer, and lung adenocarcinoma. Conversely, downregulation of STC-1 was shown in cervical cancer[11].

The expression of STC-1 in gynecological cancers has not yet been clarified. In our study, we evaluated the expression of ER, PR and STC-1 expression, which are important in ECs, and clinical, prognostic parameters, histopathological findings.

Materials and Methods

Patients and Tissue Samples

In this retrospective study, tissue samples from 89 EECs, 27 EIN, and 21 normal endometrium (NE) diagnosed between 2011 and 2020 were used. The date of patient age, tumor size, myometrial invasion depth, lymphovascular invasion (LVI), perineural invasion, distant organ metastasis, and lymph node metastasis were obtained from the hospital records.

Since deep myometrial invasion ≥50%[12] and tumor diameter ≥2 cm were previously reported as poor prognostic markers[13], patients were divided into groups using these indicators. Histological grades of EEC, and hematoxylin and eosin (H&E) stained sections of the cases were revised by experienced in gynecologic pathology to verify the diagnosis and differentiate the area most respresentating the tumor.

The histopathological grade of EEC was determined according to the International Federation of Gynaecology and Obstetrics by considering the non-squamous solid areas of the tumor. Grade 1 tumors comprised solid areas 5% or less, grade 2 tumors comprised solid areas between 5 and 50%, and grade 3 tumors comprised more than 50% solid areas[14].

Areas with no necrosis or hemorrhage were considered representative. A manual tissue conditioner was used to manually embed at least two core biopsies into new paraffin blocks from specified tumor regions (Thermo-Labvision, Fermont CA, USA). Each core was 2 mm in diameter. Sections of 5 µm thickness were taken from TMA paraffin blocks. Four slides were cut from all TMA blocks and 1 was used for immunohistochemical staining, and 1 for H&E, to confirm that the correct areas were selected.

The study protocol was been approved by the Ethics Committee of Süleyman Demirel University with the decision numbered 72867572-050.01.04-47478.

Immunohistochemical Staining

ER, PR, and STC-1 markers were immunohistochemically applied to the prepared TMA slides.

STC-1

Anti-STC-1 (rabbit polyclonal antibody, ab229477; Abcam) antibody: Five micrometer tissue sections were deparaffinized for an hour, rinsed with xylene for fifteen minutes, and rehydrated in an alcohol series for twenty minutes after being fixed with 10% formalin at 22 degrees for two days. Sections were blocked for 15 min at 37 °C with 10% goat serum, then incubated with anti-STC-1 primary antibody for 2 h at 37 °C (1: 100), providing endogenous peroxidase inactivation and antigen retrieval. Following this, the sections were incubated for an additional hour at 22 degrees with the kit's included secondary antibody rabbit immunoglobulin G conjugated to horseradish peroxidase. No further rarefaction was necessary.

After 15 min at 37 °C in horseradish enzyme-labeled chain avidin solution, the sections were washed. Later, the proteins were imaged using 3.3'-diaminobenzidine.

Pictures were taken under a microscope with x200 and x400 objectives. When a disagreement occurred between the observers, the final score was decided after a third observer was evaluated. The rate of positively stained cells and the staining intensity -measured as the number of positively stained cells per 100 cells- was used to calculate the IHC score. The rate of staining positive was calculated as follows: The percentage of cytoplasmic staining in the epithelium was evaluated as score 0: 0, score 1: 1-10%, score 2: 11-50%, score 3: 50-75%, score 4: 76% and above. Additionally, staining intensity was manually evaluated in the manner described below: Score 0: Negative/unstained, score 1: Yellow, score 2: Brown, and score 3: Dark brown.

It was calculated in the final quantification by multiplying two scores. The overall score was described as 0 being negative, 1-4 being weak, 5-8 being positive, and 9-12 being strong. The staining intensity and percentage were used to determine the final score. Low STC-1 expression was defined as an IHC value of 5 and below, and high STC-1 expression as a score more than 5 (Figure 1A-D)[15].

ER

ER alpha clone EP1 (rabbit monoclonal antibody, code GA084, Dako Omnis) antibody was ready to use and nuclear staining was considered positive. The evaluation was performed with respect to the method defined by Carcangiu et al.[16]. The evaluation was made according to the percentage of stained cells and the strength of the nuclear stain. The percentage of stained nuclei-positive cells was rated according to the following scale: Score 0: no staining/negative, score 1: 1-25%, score 2: 26-75%, and score 3: More than 76% were considered positive. This is how staining intensity was graded: Score 0: No staining, score 1: Poor; score 2: Strong and score 3: Compelling. The IHC score was calculated by adding both parameters. The IHC score was used to categorize tumors into three groups. Category 1: Corresponded to 2 points, Category 2: 3 or 4 points, and Category 3: 5 or 6 points[16]. Category 1 tumors were considered negative, Category 2 tumors were considered moderately positive, and Category 3 tumors were considered highly positive (Figure 1E-H).

PR

PR, clone PgR 1.294 (mouse monoclonal antibody, code GA090, Dako Omnis) antibody, ready to use, nuclear staining was considered positive. The evaluation was performed with respect to the method defined by Carcangiu et al.[16]. The evaluations was made according to the percentage of stained cells and the strength of the nuclear stain. The percentage of stained nuclei-positive cells was rated according to the following scale: Score 0: No staining/negative, score 1: 1-25%, score 2: 26-75%, and score 3: More than 76% were considered positive. This is how staining intensity was graded: score 0: No staining, score 1: Poor; score 2: Strong and score 3: Compelling. The IHC score was calculated by adding both parameters. The IHC score was used to categorize tumors into three groups.

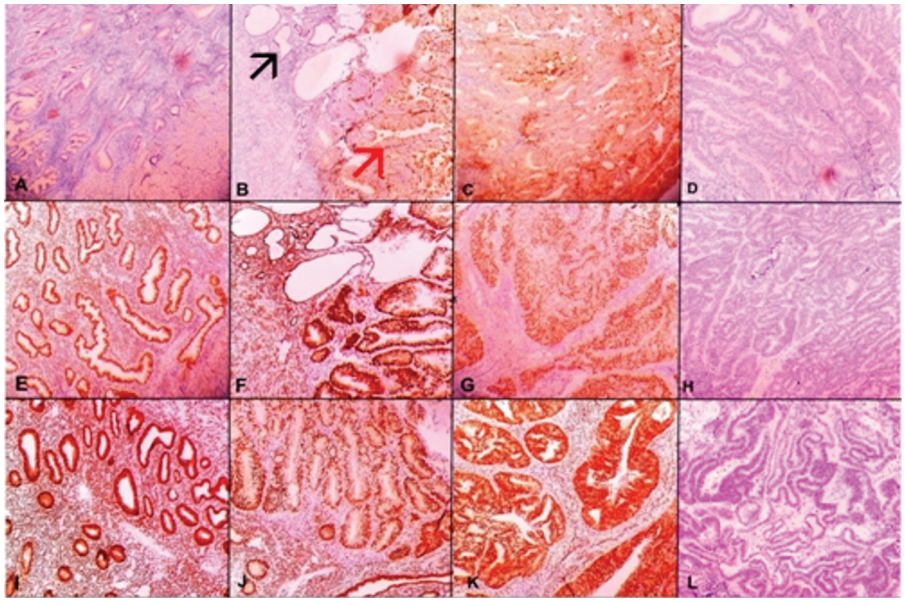

Figure 1. A-D) Staniocalcin-1 (STC-1) cytoplasmic expression [A- normal endometrium (NE) (low staining), B- Low staining was observed in NE (black arrow) foci, while high staining with STC-1 was noted in adjacent endometrial intraepithelial neoplasia (EIN) (red arrow) foci, C- Endometrioid endometrial cancer (EEC) (high staining), D- EEC (low staining), x100], E-H) Estrogen receptor nuclear expression [E- NE (highly positive staining), F- EIN (highly positive staining), G-EEC (highly positive staining), H-EEC (negative staining), x100], I-L) Progesterone receptor nuclear expression [I- NE (highly positive staining), J- EIN (highly positive staining), K- EEC (highly positive staining), L- EEC (negative staining), x100]

Table 1. Clinical and histopathological features of endometrioid endometrial cancer

	Mean ± SD
Age	56.6±9.1
Accompanying myoma/adenoma	n (%) (n=89)
No	53 (59.6)
Myoma	31 (34.8)
Adenoma	3 (3.4)
Myoma + adenoma	2 (2.2)
Tm grade	
Grade 1	47 (52.8)
Grade 2	30 (33.7)
Grade 3	12 (13.5)
Endocervical involvement	
Positive	12 (13.5)
Negative	77 (86.5)
Deep myometrial involvement	
Positive	20 (22.5)
Negative	60 (77.5)
Lymphovascular invasion	
Positive	6 (6.7)
Negative	83 (93.3)
Perineural invasion	
Positive	0 (0)
Negative	89 (100)
Metastatic lymph node	
Positive	3 (3.4)
Negative	86 (96.6)
STC-1 expressions	
Low	53 (59.6)
High	36 (40.4)
Progesterone expressions	
Negative	7 (7.9)
Moderately positive	23 (25.8)
Highly positive	59 (66.3)
Estrogene expressions	
Negative	6 (6.7)
Moderately positive	20 (22.5)
Highly positive	63 (70.8)

Tm: Tumor, STC-1: Stanniocalcin-1, SD: Standard deviation

Category 1: Corresponded to 2 points, Category 2: 3 or 4 points, and Category 3: 5 or 6 points[16]. Category 1 tumors were considered negative, Category 2 tumors were considered moderately positive, and Category 3 tumors were considered highly positive (Figure 1I-L).

As a control, the expression of STC-1, ER, and PR in NEs and cases with EIN and in malignant cases were compared.

Statistical Analysis

The difference between age, gender, STC-1, ER, and PR scores of patients with EEC were compared with the chi-square test. STC-1, ER, PR scores, and tumor grade of patients with EEC were analyzed by the Spearman correlation test. SPSS 21.0 (IBM, Chicago, IL, USA) software was used for statistical analysis, and p-value <0.05 was considered statistically significant.

Results

The mean age was 56.6 in the study population. In 31 (34.8%) cases accompanying leiomyoma was observed. Forty-seven (52.8%) EECs were grade 1, 30 (33.7%) grade 2, 12 (13.5%) grade 3 EECs. Endocervical involvement was observed in 12 (13.5%) patients, and deep myometrial invasion was observed in 20 (22.5%) patients, and 3 (3.4%) patients had metastatic lymph nodes (Table 1). In 89 EEC patients, 19 (21.3%) EINs and 2 (1.05%) endometrial polyps were observed at the time of diagnosis. The invasion to the bladder was detected in 1 (1.1%) patient with grade 3 EEC.

EIN and EECs showed increased ER expression compared to NE (p=0.044). High expression of STC-1 in EIN and EECs compared with NE was noted (p<0.001). Low staining was observed in the NE with STC-1 (Figure 1A), and staining was noted in EIN foci observed adjacent to the NE in Figure 1B, (Table 2). There was no significant difference between EIN and EEC expression of STC-1, ER, and PR (p=0.171, p=0.157 and, p=0.269).

STC-1 expression was significantly high in grade 1 and grade 2 EEC compared to grade 3 EEC (p=0.021) (Table 3). ER was statistically highly positive in grade 1 EEC (p=0.017) (Table 4). Grade 1 EECs have much less LVI than grade 3 tumors (p=0.005). As expected, grade 1 EECs exhibited considerably less myometrial invasion than grade 3 EEC (p=0.006) (Table 4). Patients with grade 2 EECs were statistically significantly older than the patients with grade 1 EEC (p=0.042). Tumor size was significantly higher in patients with grade 3 EEC than in grade 1 EC (p=0.034) (Table 4).

There was a negative association between tumor grade (r=-0.390; p<0.001) and myometrial invasion, but a positive correlation between ER and PR (r=0.559; p<0.001) (r=-0.281; p=0.008).

Discussion

In this study, STC-1, ER, and PR stains were evaluated immunohistochemically in the samples taken from patients

Table 2. Comparision of immunohistochemical findings in NE, EIN, EEC

		NE (n=21)	EIN (n=27)	EEC (n=89)	p*
ER expressions	Negative	0 (0)	1 (3.7)	6 (6.7)	0.044
	Moderately positive	9 (42.9)	2 (7.4)	20 (22.5)	
	Highly positive	12 (57.1)	24 (88.9)	63 (70.8)	
PR expressions	Negative	0 (0)	0 (0)	7 (7.9)	0.566
	Moderately positive	6 (28.6)	7 (25.9)	23 (25.8)	
	Highly positive	15 (71.4)	20 (74.1)	59 (66.3)	
STC-1 expressions	Low	21 (100)	20 (74.1)	53 (59.6)	<0.001
	High	0 (0)	7 (25.9)	36 (40.4)	

*Fisher's Exact test, NE: Normal endometrium, EIN: Endometrial intraepithelial neoplasia, EEC: Endometrioid Endometrial cancer, ER: Estrogen receptor, PR: Progesterone receptor, STC-1: Stanniocalcin-1

with EEC; clinical parameters, histopathological type, and prognostic factors were compared.

Morphological and molecular changes occur in endometrium with the different hormonal status, and physiology has been the target of extensive research to make the pathophysiology more understandable[17]. In our study, the expression of STC-1, ER, and PR evaluation in NE. EINand EEC was compared with the TMA. STC-1 expression in EIN and EECs was higher than NE. Secretory phase endometrium showed increased STC-1 expression in patients undergoing assisted reproductive techniques[18]. Patients with unexplained infertility showed decreased endometrial STC-1 expression according to a paper. Low STC-1 expression in the secretory endometrium period in a woman with endometriosis, and in endometrial pathologies were reported. It is yet unclear how STC-1 expresses itself in diseased and normal settings[17]. In our study, NE was taken as the control group, and additional disease information for the cases was not available. The low expression of STC-1 may also be due to additional diseases present in the cases or the presence of endometrial samples belonging to the similar phases.

EECs are typically observed in the peri-postmenopausal period[14]. Similarly, the mean age of all EECs in our study was 56.6±9.1. Patiens who have grade 1 tumors were younger than the patients that have grade 2 tumors.

EIN is predicted as the precursor of EEC; ER, PR positivity is common in EIN and EECs[14]. In our study, EIN in the different focuses accompanying EECs at the time of diagnosis was 21.3%. EIN and EECs showed significantly higher ER expression compared to the NE. However, PR expression was similar between the groups.

Prognostic factors for EC were reported as stage, tumor grade, histopathological type, myometrial invasion, age, and extrauterine spread in EC are among the criteria determined to predict prognosis[19]. In our study, we compared immunohistochemical markers with the mentioned parameters. Many ECs have been shown to express ER and PR[20]. Possible mechanisms for developing endometrial carcinogenesis include loss of ER and PR expression, and LN involvement are significantly poor prognostic indicators in patients with EEC, and their relationship with prognosis and survival has been qualitatively demonstrated[21,22]. Loss of ER and PR was correlated with more aggressive clinicopathological features[22]. In our study, ER was statistically highly positive in grade 1. Although PR was higher in grade 1 EECs, it was not statistically significant. Metastatic lymph nodes were observed in 3 of 89 patients, as expected in EECs, and since the group distribution was not balanced, comparison with immunohistochemical marker expression was not satisfactory.

The expression of STC-1 can vary between different tissues and in a given tissue section[23]. It is therefore possible that STC-1 functions differently among human tumors[24]. STC-1 is thought to be a promising biomarkers with various biological mechanisms in tumor progression due to increased mRNA levels in peripheral blood in cancer patients[25]. The expression of STC-1 and STC-2, evaluated in patients with laringeal squamous cell carcinoma, can be used for predicting recurrence and metastasis[24]. Another study showed that STC-1 and STC2 increase vascular endothelial growth factor (VEGF) prolonging the lifespan of multiple cancer patients in targeted therapy against angiogenesis mediators such as VEGF[26].

In the TMA study of STC-1 in EEC patients, LVI, deep myometrial invasion, and large tumor size were all associated with loss of STC-1 expression. Higher epithelial expression was observed in grade 1 EECs than in grade 3 EECs. Nuclear staining was not observed. No relationship was found between disease-specific survival and expression, and the effect of STC on prognosis could not be proven. The loss of expression in ECs was shown to be associated with increased recurrence[8]. Similarly in our study, STC-1 expression was significantly low in grade 3 tumors. Grade 1 EECs have much less LVI than grade 3 tumors. And no more relationship was found between other prognostic parameters and STC-1 expression.

In our study, cytoplasmic staining was observed in epithelial areas in tumor cells, and nuclear expression was not observed

Table 3. Comparison of STC-1 with clinical features of patients, histopathological features and ER, PR expression in EEC

	Low expression n (%) (n=53)	High expression n (%) (n=36)	p-value
Age (mean ± SD)	56.6±8.8	56.4±9.7	0.634[a]
Tm dimesions (mean ± SD)	4.9±3.6	4.3±3.5	0.279[a]
Accompanying myoma/adenoma			
No	31 (58.5)	22 (61.1)	0.396[b]
Myoma	20 (37.7)	11 (30.6)	
Adenoma	2 (3.8)	1 (2.8)	
Myoma + adenoma	0 (0)	2 (5.6)	
Tm grade			
Grade 1	28 (52.8)	19 (52.8)	0.021[b]
Grade 2	14 (26.4)	16 (44.4)	
Grade 3	11 (20.8)	1 (2.8)	
Endocervical involvement			
Positive	46 (86.8)	31 (86.1)	0.582[b]
Negative	7 (13.2)	5 (13.9)	
Deep myometrial involvement			
Positive	14 (26.4)	6 (16.7)	0.280[c]
Negative	39 (73.6)	30 (83.3)	
Lymphovascular invasion			
Positive	5 (9.4)	1 (2.8)	0.395[b]
Negative	48 (90.6)	35 (97.2)	
Perineural invasion			
Positive	0 (0)	0 (0)	-
Negative	53 (100)	36 (100)	
Metastatic lymph node			
Positive	1 (1.9)	2 (5.6)	0.563[b]
Negative	52 (98.1)	34 (94.4)	
PR expression			
Negative	6 (11.3)	1 (2.8)	0.211[b]
Moderately positive	11 (20.8)	12 (33.3)	
Highly positive	36 (67.9)	23 (63.9)	
ER expression			
Negative	5 (9.4)	1 (2.8)	0.194[b]
Moderately positive	9 (17)	11 (30.6)	
Highly positive	39 (73.6)	24 (66.7)	

[a] Mann-Whitney U test, [b] Fisher's Exact test, [c] chi-square analysis, Tm: Tumor, ER: Estrogen receptor, PR: Progesterone receptor, STC-1: Stanniocalcin-1, EEC: Endometrioid endometrial cancer, SD: Standard deviation

Table 4. Comparison of tumor grade with clinical histopathological and immunohistochemical expressions findings

	Grade 1 (n=40) n (%)	Grade 2 (n=37) n (%)	Grade 3 (n=12) n (%)	p-value
Age (mean ± SD)	54.4±9.9	58.7±6.3	59.6±2.9	0.042[a]
Tm dimesions (mean ± SD)	4.0±3.6	5.2±3.5	6.2±3.5	0.034[a]
Accompanying myoma/adenoma				
No	26 (55.3)	17 (56.7)	10 (83.3)	0.223[b]
Myoma	18 (38.3)	12 (40)	1 (8.3)	
Adenoma	1 (2.1)	1 (3.3)	1 (8.3)	
Myoma + adenoma	2 (4.3)	0 (0)	0 (0)	
Endocervical involvement				
Positive	7 (14.9)	4 (13.3)	1 (8.3)	0.824[b]
Negative	40 (85.1)	26 (86.7)	11 (91.7)	
Myometrial involvement				
Positive	5 (10.6)	9 (30)	6 (50)	0.006[b]
Negative	42 (89.4)	21 (70)	6 (50)	
Lymphovascular invasion				
Positive	0 (0)	3 (10)	3 (75)	0.005[b]
Negative	47 (100)	27 (90)	9 (75)	
Perineural invasion				
Positive	0 (0)	0 (0)	0 (0)	-
Negative	47 (100)	30 (100)	12 (100)	
Metastatic lymph node				
Positive	0 (0)	3 (10)	0 (0)	0.082[b]
Negative	47 (100)	27 (90)	12 (100)	
Progesterone expressions				
Negative	2 (4.3)	2 (6.7)	3 (25)	0.063[b]
Moderately positive	9 (19.1)	10 (33.3)	4 (33.3)	
Highly positive	36 (61)	18 (60)	5 (8.5)	
Estrogene expressions				
Negative	3 (6.4)	0 (0)	3 (25)	0.017[b]
Moderately positive	7 (14.9)	11 (36.7)	2 (16.7)	
Highly positive	37 (78.7)	19 (63.3)	7 (58.3)	
STC-1 expressions				
Low	28 (59.6)	14 (26.4)	11 (91.7)	0.027[c]
High	19 (40.4)	16 (53.3)	1 (8.3)	

[a] Kruskal-Wallis test, [b] Fisher's Exact test, [c] chi-square analysis, Tm: Tumor, ER: Estrogen receptor, PR: Progesterone receptor, STC-1: Stanniocalcin-1, SD: Standard deviation

for STC-1. No specific staining was observed in stromal cells, and the staining in the epithelium with STC-1 was consistent with other studies[17,27], showing that the main target of STC-1 is the epithelium.

Studies evaluating the expression of ovarian serous carcinoma and STC have shown that expression correlates with tumor grade[28]. In another study, it has been shown that STC plays a role in the aggressive course and metastasis by inducing cellular proliferation in tumors and reducing apoptosis[25]. In our study, STC-1 expression was significantly low in grade 3 EEC patients. The loss of expression in STC-1 was reported to be a poor prognostic factor in cervical cancer[11]. In another study, it was observed that high expression and tumor size were inversely correlated in hepatocellular carcinoma of the liver[29].

It has been shown that hyf-1alpha can participate in the proliferation of ccRCCs by inducing the accumulation of STC-1, down-regulating calcium. Distant organ metastasis, tumor diameter, and STC-1 expression were positively correlated with ccRCC[30].

The explanation on the effect of STC-1 on tumor proliferation may that tumor cells may use STC-1 for their growth.

Study Limitations

TMA is a common method used to predict prognosis in many cancers. In our study, tumor samples were taken from 2 different foci from each tumor and statistical analysis were performed by taking the average of the expressions. However, due to tumor heterogeneity, it may not represent the entire tumor.

Conclusion

STC-1 expression was positively correlated with low histologic grade in EECs. STC-1 can be used for discriminating low-grade EECs and high-grade EECs in curretage specimens. Since STC-1 is related to well-differantiated tumors, it can also be regarded as a good prognostic factor in EECs.

Ethics

Ethics Committee Approval: The study protocol was been approved by the Ethics Committee of Süleyman Demirel University with the decision numbered 72867572-050.01.04-47478.

Informed Consent: Retrospective study.

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Authorship Contributions

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