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ORIGINAL ARTICLE

Stanniocalcin-2 May Be a Potentially Valuable Prognostic Marker in Endometrial Cancer: a Preliminary Study

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Abstract

In the current study, we primarily aimed to investigate stanniocalcin-2 (STC_2) protein expression pattern in hysterectomy specimens from patients with endometrioid type endometrial cancer (EC) using immunohistochemistry. Secondly, in order to clarify its prognostic impact, we examined relationships of the expression levels of STC_2 with clinicopathologic features and outcome of patients. Histopathology slides of 49 patients were stained with the monoclonal mouse antibody targeting STC_2 protein. The expression levels of STC_2 were classified based on three-tiered semiquantitative scheme: negative expression, expression level of 0; low-expression, expression level of 1+; and high-expression, expression levels of 2+ and 3+. Recurrence-free survival (RFS) was used as the primary prognostic outcome. Immunohistochemical analysis revealed that 73.5% of tissue samples exhibited positive staining with STC_2. The intensity of staining with STC_2 was weak in 40.8%, moderate in 22.4%, and strong in 10.2%. Thirty-eight percent of samples showed negative expression; 18.4%, low-expression (1+); and 42.8%, high-expression (2 to 3+). High-expression of STC_2 was significantly associated with grade 2–3 tumors ($p = 0.026$) and disease recurrence ($p = 0.013$). Multivariate analysis revealed that both the tumor grade and STC_2 were independent predictors of disease recurrence. Kaplan-Meier analyses confirmed that patients with high-expression of STC_2 had a significantly poorer RFS than those with negative or low STC_2 expression ($p = 0.037$); although overall survival did not differ with respect to expression levels of STC_2 ($p = 0.148$). In conclusion, high-expression of STC_2 is a negative prognostic factor, associated with increased risk of recurrence in endometrioid EC.

Keywords Stanniocalcin-2 · Endometrial cancer · Prognostic factor · Recurrence

Introduction

Endometrial cancer (EC) is a hazard for the well-being of females, with newly diagnosed 320,000 cases worldwide annually. Totally, 76,000 cases ultimately die due to EC every year, making it the most common gynecological cancer and the 5th frequent malignancy in females [1]. Unfortunately, both the incidence and mortality rates of

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the disease are increasing [2]. Currently, the main challenge after diagnosing EC is identifying patients at risk for disease recurrence more precisely.

The well-established conventional risk factors for disease recurrence in EC include tumor histotype, stage, tumor grade, tumor size, age and lymphovascular space involvement [3]. However, patients with identical clinicopathologic features may exhibit different disease outcomes. The discrepancies in molecular phenotypes responsible for tumor invasion and metastasis are probably the main reasons of different tumor behaviors between similar tumors [4]. Therefore; it is obvious that there is a need for novel molecular markers to better predict the prognosis and to improve the outcomes.

Stanniocalcin-2 (STC_2) is a 56 kD homodimeric glycoprotein, encoded by STC_2 gene and expressed in almost all tissues [5]. Its main function is to regulate calcium and phosphate metabolism with its calcitonin-like activity. STC_2 accelerates inorganic phosphate-induced calcification, and inhibits ectopic calcification [6]. Recently, it has been shown that the STC_2 gene is a hypoxia-inducible factor 1 (HIF-1) target gene that promotes tumor-cell proliferation, invasion, migration, and epithelial-mesenchymal transition during hypoxia [5]. HIF-1 is a heterodimeric protein complex that is involved in homeostatic responses to low oxygen concentrations or hypoxia. It consists of a constitutively expressed β-subunit and an oxygen-regulated α-subunit [7]. In a study investigating the mechanism of action and biological function of STC_2, Kim et al. [8] demonstrated that, under oxidative stress conditions, transfection of adipose-derived stromal cells and umbilical cord blood-derived mesenchymal stem cells with STC_2 leads to activation of HIF1α-Akt and HIF1α-ERK 1/2 pathways. Activation of these signaling pathways consequently upregulates the expression of cell cycle regulators (cyclin A/D) and antiapoptotic proteins (Bcl-2), and thus increases cell survival upon oxidative stress. Although the role of HIF-1β protein in human cancers has been less investigated, it has been shown that HIF-1α and HIF-1β proteins share similar immunostaining and distribution patterns, and common signaling pathways in brain and prostate carcinogenesis [9, 10].

Previous studies [11–15] demonstrated that STC_2 overexpression is associated with disease progression and poor prognosis in various malignancies; however, the clinical significance of STC_2 in patients with EC has not been studied yet. In the current study, we primarily aimed to investigate STC_2 protein expression pattern in hysterectomy specimens from patients with endometrioid type EC using immunohistochemistry. Secondly, in order to clarify its prognostic impact, we examined relationships of the expression levels of STC_2 with clinicopathologic features and outcome of patients. To the best of our knowledge, this is the first study investigating STC_2 protein expression in EC patients.

Materials and Methods

Patients and Immunohistochemical Studies

Following the Institutional Review Board approval (No.: 547; Date: 20/09/2017), paraffin-embedded tissue samples of 49 patients with endometrioid type EC, who were treated at a single tertiary-care institution between 2007 and 2015, were selected randomly from the archives of Department of Gyneco-pathology.

Tissue sections of 5-μm thickness were cut from tissue blocks onto pre-coated slides. The samples were deparaffinized with xylene and rehydrated with ethanol. The slides were then incubated with the monoclonal mouse antibody targeting STC_2 protein (1:50 dilution; Abcam, United Kingdom) at 4 °C overnight. Finally, the stained tissue slides were assessed and scored by two sub-specialized gynecologic pathologists blinded to the clinicopathologic data.

Scoring the Immunoreactivity of STC_2

In the current study, a strong positive staining was defined as a brown signal, either on the cell membrane or within the cytoplasm; a moderate staining as a yellow-brown reaction; and a weak staining as a light yellow reaction [14]. Figure 1 shows microscopic views of the samples from each staining pattern.

The staining intensity was graded as follows: 0 = no staining; 1 = weak staining; 2 = moderate staining; and 3 = strong staining. The percentage of tumor cell staining was graded based on the following criteria: 0 = no staining; 1 = ≤10% of positive tumor cells; 2 = 11–50% of positive tumor cells; 3 = 51–80% of positive tumor cells; and 4 = ≥81% of positive tumor cells [11]. The staining score for STC_2 was calculated based on the sum of grades of staining intensity and percentage of staining, ranging from 0 to 7. A negative expression (0) was defined as no staining or ≤ 10% of cells stained regardless of intensity. A total grade of 3 was classified as 1+ expression; 4 to 5 as 2+ expression; and 6 to 7 as 3+ expression.

For the purpose of statistical evaluation, the expression levels of STC_2 were re-classified according to the three-tiered semiquantitative scheme: negative expression, expression level of 0; low-expression, expression level of 1+; and high-expression, expression levels of 2+ and 3 + .

Data Analysis

Following the completion of immunohistochemical studies, data regarding age at diagnosis, surgical procedures performed, stage of the disease, tumor grade, lymphovascular space invasion, myometrial invasion, cervical invasion, lymph node involvement, adjuvant therapy, disease recurrence, and disease status on the date of the last follow up were extracted from the institutional database.

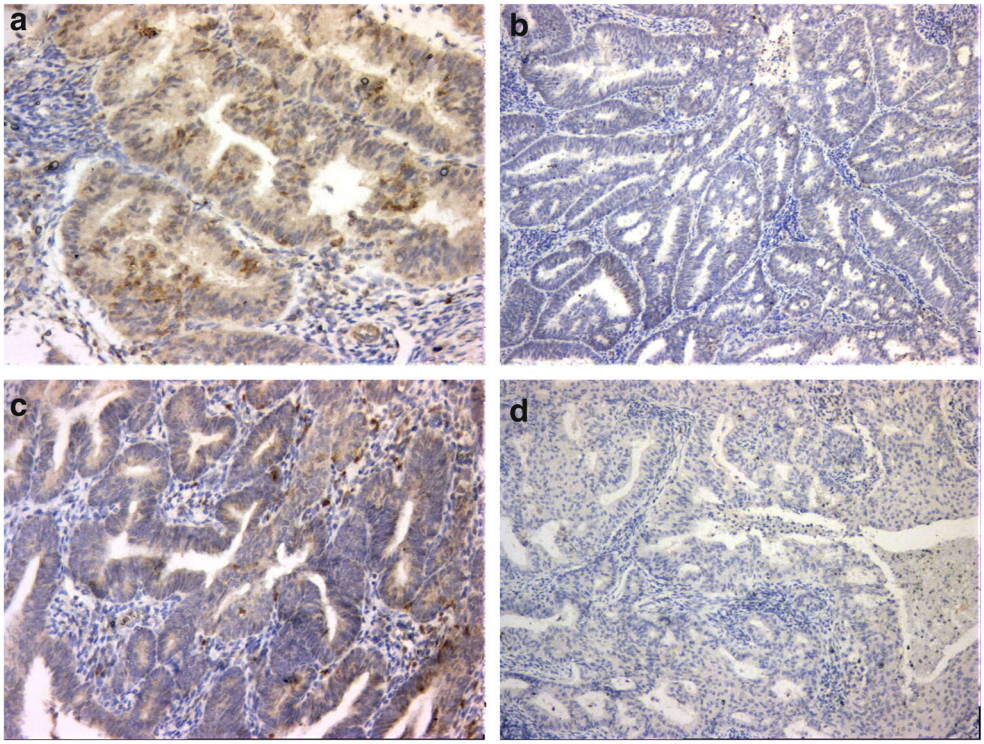

Fig. 1 Microscopic views of the samples from each STC_2 staining pattern. **a** Strong positive staining (×200) **b** Moderate staining (×200) **c** Weak staining (×100) **d** Negative staining (×100)

Binary variables were reported as counts and percentages. We expressed data as median and range for continuous variables. The relationships between STC_2 expression and clinicopathologic features were assessed using Mann-Whitney U test or chi square statistic, when appropriate.

Recurrence-free survival (RFS) was used as the primary prognostic outcome. First, prognostic roles of STC_2 and other clinicopathologic variables were assessed using logistic regression analysis. Variables with a p value <0.05 in univariate analysis were included into multivariate analysis. The effects of variables on disease recurrence were reported as adjusted odds ratios (OR) and 95% confidential intervals (CI). Then, the RFS and overall survival (OS) were estimated by the Kaplan-Meier method, and the log-rank test was performed to compare survival curves. RFS was measured from the date of surgery to the date of recurrence or death from any cause.

All analyses were performed using IBM-SPSS version 20.0 for Mac OS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results

Table 1 presents the clinicopathologic characteristics of 49 patients enrolled in the study. The median age at surgery was 57, ranging from 39 to 77. The majority of patients (63.3%) had FIGO (International Federation of Gynecology and Obstetrics) grade 1 tumor, 10.2% had grade 2, and 36.7% had grade 3. The distribution of stages based on $FIGO_{2009}$ classification was as follows: stage IA, 25 patients (51.0%); stage IB, 16 patients (32.6%); stage II, 5 patients (10.2%); and stage IIIC, 3 patients (6.1%). A total of twenty-three (46.9%) patients received adjuvant therapy. Of those, ten patients with stage IA disease who had adverse risk factors (ie, age, lymphovascular space involvement, tumor size, or lower uterine segment) received vaginal brachytherapy alone, five patients with stage IB and grade 2 to 3 disease received external beam radiotherapy (EBRT), five patients with stage II disease received EBRT followed by a brachytherapy boost, and three patients with stage IIIC disease received sequential chemo-irradiation which included two cycles of cisplatin 50 mg/m^2 in the first and fourth week of EBRT, followed by four cycles of paclitaxel 175 mg/m^2 and carboplatin area under the curve (AUC) 5 at 21-days intervals. A total of 7 patients (14.3%) experienced disease recurrence during a median follow up time of 63 months (range, 1 to 141 months).

STC_2 expression patterns of patients were summarized in Table 2. Immunohistochemical analysis revealed that 73.5% of tissue samples exhibited positive staining with STC_2. The intensity of staining with STC_2 was weak in 40.8%, moderate in 22.4%, and strong in 10.2%. According to the staining scoring analysis, 38.8% of samples showed negative expression (no staining or ≤ 10% of cells stained regardless of intensity); 18.4%, low-expression (1+); and 42.8%, high-expression (2 to 3+).

The relationships between the levels of STC_2 expression and clinicopathologic features were presented in Table 3.

Table 1 Characteristics of patients

Variables	Values
Age, median (range), years	57 (39–77)
Surgery, *n* (%)	
TH/BSO alone	8 (16.3)
TH/BSO plus lymphadenectomy	41 (83.7)
No. of lymph nodes removed, median (range)	25 (0–63)
FIGO grade, *n* (%)	
Grade 1	31 (63.3)
Grade 2	13 (10.2)
Grade 3	5 (36.7)
Lymphovascular space involvement, *n* (%)	5 (10.2)
Deep (≥50%) myometrial invasion, *n* (%)	21 (42.8)
Cervical invasion, *n* (%)	6 (12.2)
Lymph node involvement, *n* (%)	3/41 (7.3)
Stage, *n* (%)	
IA	25 (51.0)
IB	16 (32.6)
II	5 (10.2)
IIIC	3 (6.1)
Adjuvant therapy, *n* (%)	23 (46.9)
Brachytherapy alone	10 (20.4)
External beam pelvic radiotherapy ± brachytherapy	10 (20.4)
Sequential chemo-irradiation	3 (6.1)
Recurrence, *n* (%)	7 (14.3)
Median follow up time, (95% CI), months	63 (1–141)

TH/BSO, total hysterectomy bilateral salpingo-oophorectomy; *FIGO*, International Federation of Gynecology and Obstetrics; *CI*, confidential interval

High-expression of STC_2 was significantly related with FIGO grade 2–3 tumors ($p = 0.026$) and disease recurrence ($p = 0.013$). Multivariate analysis revealed that both the FIGO grade (OR, 2.772; 95% CI, 1.946–5.074; $p = 0.021$) and high-expression of STC_2 (OR, 2.455; 95% CI, 1.206–7.165; $p = 0.024$) were independent predictors of disease recurrence in endometrioid EC (Table 4). Kaplan-Meier analyses confirmed that patients with high-expression of STC_2 had a significantly poorer RFS than those with negative or low STC_2 expression ($p = 0.037$), (Fig. 2); although OS did not differ with respect to expression levels of STC_2 ($p = 0.148$).

Discussion

The current study investigated STC_2 protein expression in hysterectomy specimens from patients with endometrioid EC using immunohistochemistry. The study demonstrated that the rate of overall positive staining with STC_2 is high (73.5%), but its staining intensity is generally (40.8%) weak. The study also implied that high-expression of STC_2 is a negative prognostic factor, associated with increased risk of disease recurrence.

Growing evidences in the literature indicate that STC_2 protein displays crucial roles in the development and progression of several carcinomas. Dondeti et al. [16] identified STC_2 gene as a potential chromosome 5q oncogene; promoting carcinogenesis by inhibiting apoptosis in clear cell renal cell carcinomas. Law and Wong [17] reported that stable expression of exogenous STC_2 promotes epithelial-mesenchymal transition in hypoxic ovarian cancer cells, as revealed by the upregulation of N-cadherin/vimentin and downregulation of E-cadherin levels. STC_2 transfected ovarian cancer cells display high degree of motility with fibroblast morphology, which is correlated with a significant increase in the expression of matrix metalloproteinases 2 and 9, and with a higher invasive

Table 2 STC_2 expression features of patients

Variables	No. of patients	%
Staining of tumor cells with STC_2	36	73.5
Staining intensity		
No staining	13	26.5
Weak	20	40.8
Moderate	11	22.4
Strong	5	10.2
Percentage of tumor-cell staining		
No staining	13	26.5
≤10%	6	12.2
11–50%	16	32.7
51–80%	10	20.4
≥81%	4	8.2
Staining score		
0– Negative expression (no staining or ≤10% of cells stained regardless of intensity)	19	38.8
1+	9	18.4
2+	17	34.7
3+	4	8.2
Staining classification based on three-tiered semiquantitative scheme		
Negative expression (0)	19	38.8
Low–expression (1+)	9	18.4
High–expression (2–3+)	21	42.8

STC_2, stanniocalcin-2

Table 3 Relationships between the levels of STC_2 expression and clinicopathologic features

	Low-expression of STC_2		High-expression of STC_2	
	U/χ^2	p	U/χ^2	p
Age	252	0.497	233.5	0.220
FIGO grade 2–3	1.510	0.219	4.947	**0.026**
Lymphovascular space invasion	0.827	0.363	1.188	0.276
Deep myometrial invasion	0.258	0.612	0.340	0.560
Cervical invasion	0.363	0.547	1.915	0.166
Lymph node involvement	2.293	0.130	0.015	0.903
Stage ≥ II	0.987	0.320	2.219	0.528
Recurrence	1.161	0.281	6.125	**0.013**
Overall survival	1.161	0.281	2.722	0.099

STC_2, stanniocalcin-2; *U*, Mann-Whitney U test statistic; χ^2, chi square statistic; *FIGO*, International Federation of Gynecology and Obstetrics

Bold values indicate statistically significant ($p < 0.05$) values

potential [17]. Yang et al. [18] demonstrated that, in head and neck squamous cell carcinomas, STC_2 upregulates phosphorylation of AKT, a serine/threonine-specific protein kinase, and stimulates metastasis via Snail-mediated increase of vimentin and decrease of E-cadherin.

PTEN tumor suppressor gene, which normally acts to restrain phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway, is frequently inactivated in endometrioid ECs [19]. Mutated or deleted PTEN leads to increased activity of the PI3K, with resultant phosphorylation of AKT. Consequently, activated AKT upregulates the mammalian target of rapamycin (mTOR), a key regulator of apoptosis and cellular growth, and thus, triggers endometrial carcinogenesis [20]. It is possible that STC_2 protein may have a role in development of more aggressive endometrioid ECs via aggravating this pathway, as it has in head and neck carcinomas [18].

In line with molecular data, high levels of STC_2 expression have been reported as associated with poor clinical outcomes in all cancer types studied. Arigami et al. [11] examined STC_2 expression as a molecular blood marker in patients with gastric cancer. The authors found that STC_2 expression was significantly correlated with age, depth of invasion, venous invasion, lymph node metastasis, stage and poor survival. Zhang et al. [12] investigated STC_2 immunohistochemistry in hepatocellular carcinoma, and reported that STC_2 positive group exhibited a higher incidence of lymph node metastasis and a poorer OS compared with STC_2 negative group. Shen et al. [13] examined the expression of STC_2 protein by real time polymerase chain reaction (PCR) in cervical carcinoma patients who were treated with radiotherapy. The authors reported that cervical cancer patients had significantly increased expression of STC_2 at mRNA level compared with adjacent normal cervical tissues. They also noted that high-expression of STC_2 was correlated with lymph node metastasis and shorter OS. Similar findings were also reported from studies on laryngeal squamous cell carcinoma and colorectal carcinoma [14, 15].

In our study, a high level (2 to 3+) of STC_2 expression was significantly related with poor disease outcome, consistent with previous studies [11–15]. Patients with high STC_2 expression had significantly shorter RFS, although OS did not reach statistical significance. The main limitation of our study is its relatively small sample size. A small sample size is generally associated with higher type II statistical error and

Table 4 Clinicopathologic predictors of disease recurrence

	Unadjusted		Multivariate	
	U/χ^2	*P*	Coefficients (95% CI)	*P*
Age	215.6	0.348	–	–
FIGO grade 2–3	4.895	**0.032**	2.772 (1.946 to 5.074)	**0.021**
Lymphovascular space invasion	1.929	0.223	–	–
Deep myometrial invasion	2.385	0.186	–	–
High-expression of STC_2	6.125	**0.013**	2.455 (1.206 to 7.165)	**0.024**
Adjuvant therapy	2.348	**0.045**	1.735 (0.904 to 2.687)	0.086

U, Mann-Whitney U test statistic; χ^2, chi square statistic; *CI*, confidential interval; *FIGO*, International Federation of Gynecology and Obstetrics; *STC_2*, stanniocalcin-2

Bold values indicate statistically significant ($p < 0.05$) values

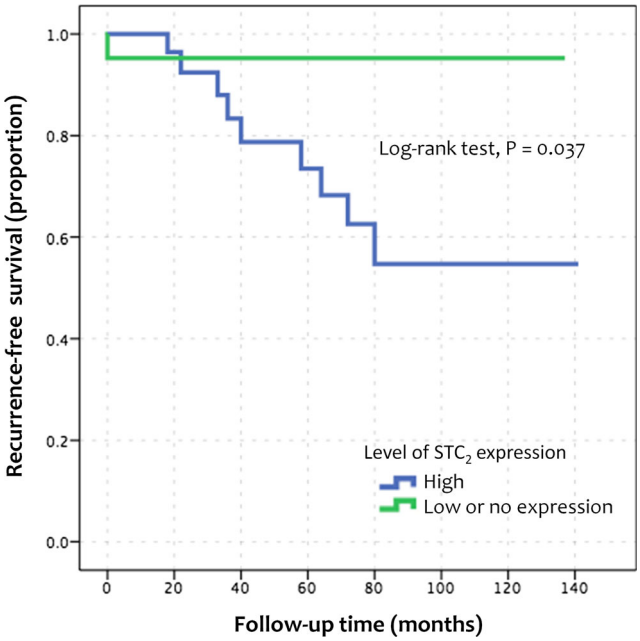

Fig. 2 Recurrence-free survival based on expression levels of STC_2

possibility of bias. In order to overcome type II error and to demonstrate the prognostic effect of STC_2 in 49 patients of our study group, we used a regression model based on 6 variables including 5 essential clinicopathologic covariates (age, FIGO grade, lymphovascular space invasion, myometrial invasion, and adjuvant therapy) along with the STC_2. Thus, by decreasing number of covariates, we increased the power of the analysis. Despite the limitations, there appears to be no study evaluating STC_2 expression pattern as well as its prognostic role in EC. Thus, the results should be considered preliminary and need to be validated in a larger sample.

In conclusion, high-expression of STC_2 detected by immunohistochemistry may be used as an adjunct prognostic marker in stratification of patients with EC into different risk of recurrence groups. In order to draw a definite conclusion, however, further studies are necessary.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare no conflicts of interest.

Ethical Approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study has been approved by Ethics Committee of the Akdeniz University School of Medicine. A written informed consent is not required for this type of retrospective study.

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