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Recurrence patterns and prognosis of endometrial stromal sarcoma and the potential of tyrosine kinase-inhibiting therapy

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ABSTRACT

Objective. Endometrial stromal sarcoma (ESS) is a rare uterine malignancy. The current treatment approaches yield unsatisfactory results, and potential therapeutic targets need exploration.

Methods. We reviewed the electronic medical records of 74 patients with low-grade ESS who had been evaluated at the University of Texas MD Anderson Cancer Center between 1995 and 2006. Using immunohistochemistry, we tested the expression of targets in paraffin-embedded tissue samples taken from 13 of the patients.

Results. Forty-seven patients (64%) had a recurrence, and 16 (22%) had died of their disease at last follow-up. The 10-year progression-free survival (PFS) rate was 43% (median PFS duration, 108 months), and the overall survival (OS) rate was 85% (median OS, 288 months). Patients who received hormonal therapy had an overall response rate of 27%; another 53% had stable disease, with a median time to progression of 24 months. No complete response or partial response was observed among patients who received radiotherapy or chemotherapy. In the paraffin-embedded specimens we tested, c-abl was expressed universally. Expression of PDGF-α, PDGF-β, VEGF, and c-Kit was detected in 33%, 36%, 54%, and 8%, of specimens, respectively. EGFR and HER-2 were not detectable in any specimens.

Conclusions. Our study suggests that ESS is a hormone-dependent malignancy, with hormonal therapy having activity in recurrent disease. Targeted therapy, specifically targeting c-abl may be a potential treatment for this disease.

Introduction

Uterine sarcomas are rare malignancies accounting for as few as 6% of malignant tumors of the uterine corpus [1]. Uterine sarcomas encompass a broad spectrum of neoplasms, from pure parenchymal tumors and endometrial stromal tumors (leiomyosarcoma and endometrial stromal sarcoma [ESS]) to mixed epithelial/stromal tumors. Low-grade ESS is characterized by fewer than 10 mitoses per 10 high-power fields and lack of significant atypia. Since low-grade ESS and high-grade ESS have vastly different prognostic factors and treatments, now ESS refers only to low-grade ESS and high-grade ESSs are grouped into undifferentiated endometrial sarcomas. Among the uterine sarcomas, ESS is very rare, representing around 0.2% of all uterine malignancies [2]. Most uterine sarcomas are generally aggressive, and in early reports, overall mortality rates approached 90%. However, ESS is generally a slow-growing tumor with an indolent clinical course [3]. Because of the rarity of the disease, no large-scale clinical study is available.

The mainstay of treatment of ESS is surgery. However, the surgical modality is controversial, with a lack of agreement on whether lymphadenectomy is necessary. Some gynecologic oncologists prefer that ESS be staged in the same careful fashion as endometrial adenocarcinoma, which requires complete lymphadenectomy. However, some studies have found that lymphadenectomy during surgery for ESS does not affect the prognosis and thus can be avoided [4,5].

In general, 30%–50% of ESS patients have late recurrence or metastasis after surgery. Because of the rarity of the disease, only a few clinical trials of chemotherapy for advanced or recurrent ESS have been reported, and most results were disappointing. Other reports have supported hormonal therapy for recurrent ESS, but these are limited to case reports and retrospective studies with small numbers of patients, and only about two-thirds of recurrent ESS is hormonally responsive [6,7]. It remains unclear what the optimal treatment is for patients with advanced stage or recurrent disease. ESS patients whose disease has a poor response to radiotherapy, chemotherapy, and hormonal therapy may find greater benefit from targeted therapy.

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In this study, we retrospectively assessed clinical histopathologic characteristics, recurrence patterns, therapeutic outcomes, and prognosis in a group of patients with low-grade ESS. By detecting the expression of hormone receptors (estrogen receptor [ER], progesterone receptor [PR]), kinases targeted by imatinib mesylate (platelet-derived growth factor receptor α and β [PDGF-α and -β], c-Kit, c-abl), vascular endothelial growth factor receptor (VEGF), epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor-2 (HER-2 or CerbB2), we hoped to identify potential therapeutic targets.

Materials and methods

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. Data were retrieved during a review of electronic medical records maintained in institutional databases. We only included patients diagnosed with low-grade ESS (now referred to as ESS) who had been histologically confirmed based on the uniform criteria and were reviewed by gynecological pathologists at MD Anderson from January 1995 through December 2006. For each patient included, we obtained demographic and clinical data, including age, ethnicity, symptoms, menopausal status, parity, oral contraceptive use, smoking history, alcohol use history, family history of cancer, surgical procedures, pathological diagnosis, tumor size, lymphatic vascular space invasion, recurrent/metastatic sites, chemotherapy history, radiotherapy history, hormonal therapy history, date of progression, and vital status or date of last follow-up. The patients' responses were assessed according to the results of serial radiographic evaluations using the Response Criteria in Solid Tumors (RECIST version 1.0).

For patients who had tumor samples preserved in paraffin blocks, we performed tissue microarray immunohistochemistry studies with three punches for each patient. Immunohistochemical expression of PDGF-α and -β, c-Kit, c-abl, ER, PR, VEGF, EGFR, and HER-2 were determined. Sections 4 micrometers thick were cut and deparaffinized in xylene. Sections were stained with a 1:50 dilution of polyclonal rabbit anti-PDGF-α antibody, a 1:50 dilution of polyclonal rabbit anti-PDGF-β antibody, a 1:100 dilution of polyclonal rabbit anti-human c-Kit antibody, a 1:100 dilution of polyclonal rabbit c-abl antibody, a 1:200 dilution of polyclonal goat ER antibody, a 1:100 dilution of polyclonal goat PR antibody, a 1:250 dilution of polyclonal goat VEGF antibody, a 1:200 dilution of polyclonal goat EGFR antibody, and a 1:50 dilution of polyclonal goat HER-2 antibody (Santa Cruz Biotechnology, Santa Cruz, CA). Detection of immunostaining was performed using a ChemMate kit (Santa Cruz Biotechnology) and diaminobenzidine as a chromogene. Positive control was provided by a prostate cancer specimen for PDGF-α and -β expression and a breast cancer specimen for c-Kit, c-abl, ER, PR, VEGF, EGFR, and HER-2 expression. For negative control, primary antibodies were replaced by another irrelevant antibody produced from the same species that produced the primary antibody.

The cellular immunohistochemical expression was scored by a single gynecologic pathologist (X.T.) blinded to clinical outcomes with a scoring system based on both the percentage of positive tumor cell nuclei and the staining intensity [8]. Staining intensity was graded 1+ to 3+, and distribution of the cellular staining was graded as 1+ (<10% of the cells), 2+ (10%–50% of the cells), or 3+ (≥50% of the cells). The combination of intensity and distribution was graded 0 (<1+), 1 (1+ to 2+), 2 (>2+ to 4+), or 3 (>4+ to 6+).

Progression-free survival (PFS) duration was calculated from the date of first surgery to the date of disease recurrence. Overall survival (OS) duration was calculated from the date of first surgery to the date of death or the last follow-up visit. Time to progression (TTP) was calculated from the date of treatment to the date of disease progression. Data analyses were performed with SPSS software for Windows (version 12.0; SPSS Inc., Chicago, IL). The rates of disease recurrences were compared using Pearson's chi-square and likelihood ratio methods. *P* values reported were two tailed, and a *P* value of <0.05 was considered statistically significant. PFS was determined by life table analysis. Survival curves were generated using the Kaplan–Meier method.

Results

Patient characteristics

We identified 84 patients with low-grade ESS who were evaluated at our institution from January 1995 through December 2006. Five patients were excluded because they experienced a recurrence of high-grade ESS, and five more patients were excluded because follow-

Table 1
Patients' clinical and histopathologic characteristics ($n=74$).

Characteristic	No. of patients (%)
Median age (years)	43.5 (range, 22–68)
Race/ethnicity	
White	30 (81)
Hispanic	3 (8)
Black	3 (8)
Asian	1 (3)
Unknown	37
Presenting symptom	
Heavy or irregular vaginal bleeding	29 (58)
Pelvic pain or pelvic pressure	12 (24)
Heavy bleeding and pelvic pain	4 (8)
Abnormal vaginal discharge	2 (4)
None	3 (6)
Unknown	24
Menopausal status	
Premenopausal	54 (82)
Postmenopausal	12 (18)
Unknown	8
Parity	
Nulliparous	15 (23)
Non-nulliparous	50 (77)
Unknown	9
Oral contraceptive use	
No	7 (18)
Yes	32 (82)
Unknown	35
Family history of cancer	
No	18 (30)
Yes	42 (70)
Unknown	14
Smoking history	
No	42 (74)
Yes	15 (26)
Unknown	17
Alcohol use history	
No	48 (96)
Yes	2 (4)
Unknown	24
Surgical procedure before recurrence	
Myomectomy/TAH/TAH + USO	18 (24)
TAH + BSO	38 (51)
TAH + BSO + lymphadenectomy ± omentectomy	18 (25)
Tumor size (cm)	8 (range, 2–18)
LVSI	
No	50 (68)
Yes	24 (32)
Postoperative therapy	
Pelvic radiation	6 (8)
Hormonal therapy	25 (34)
Chemotherapy and radiation therapy	2 (3)
Chemotherapy and hormonal therapy	1 (1)
Radiotherapy and hormonal therapy	1 (1)
No adjuvant therapy	39 (53)

FIGO, International Federation of Gynecology and Obstetrics; TAH, total abdominal hysterectomy; USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy; LVSI, lymphatic vascular space invasion.

Table 2
Responses to therapy in patients with recurrent endometrial stromal sarcoma ($n=35$*).

Treatment	CR	PR	SD	PD	Median TTP (months)
Radiotherapy	0	0	3 (100%)	0	31
Chemotherapy	0	0	4 (40%)	6 (60%)	6.5
Hormonal therapy	5 (17%)	3 (10%)	16 (53%)	6 (20%)	24

CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; TTP, time to progression.
* Twelve patients without measurable disease after surgery or radiographic data were not included.

up data were missing. The remaining 74 patients were included in the study.

Patients' clinical and histopathologic characteristics are summarized in Table 1. The median age at diagnosis was 43.5 years (range, 22–68 years), and 81% were Caucasian. The majority had presenting symptoms of heavy or irregular bleeding (33/50, 66%), and many had pelvic pain or pressure (16/50, 32%). Eighteen percent patients were postmenopausal at the time of diagnosis. Only four patients were preoperatively diagnosed with ESS by dilation and curettage; the remaining patients were diagnosed after surgery. The median tumor size was 8 cm (range, 2–18 cm). Among the eighteen patients who underwent lymphadenectomy, four (22%) had lymph node metastasis, of whom one patient had extrauterine spread at surgery. The median time from first surgery to last follow-up was 76 months (range, 2–444). After the primary surgery, 35 (47%) had adjuvant therapy, 6 with pelvic radiation of 50 Gy, 25 with hormonal therapy, 2 with chemotherapy and radiation therapy, 1 with chemotherapy and hormonal therapy, and 1 with radiotherapy and hormonal therapy (Table 1). Among the 9 patients who had adjuvant pelvic radiation therapy, 2 had in-field recurrences and 6 had distant metastasis. The median time to progression (TTP) of adjuvant radiation therapy, chemotherapy, and hormonal therapy was 168 months, 168 months, and 132 months, respectively.

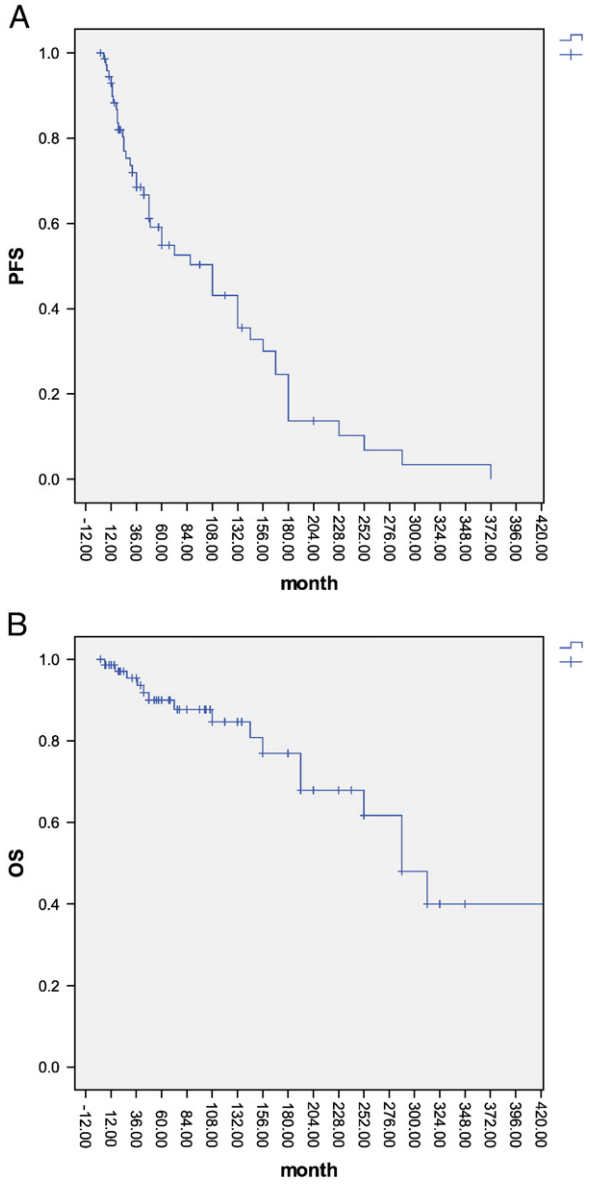

Fig. 1. Progression-free survival (PFS, A) and overall survival (OS, B) curves for 74 patients with ESS. For this cohort, median PFS was 108 months and median OS was 288 months.

Recurrences

Forty-seven (64%) of the seventy-four patients developed recurrent disease, and sixteen (22%) had died of disease at the time of last follow-up. The locations of recurrent disease were as follows: pelvic recurrence (20/47, 43%), extrapelvic recurrence (16/47, 34%), and both pelvic and extrapelvic recurrences (11/47, 23%). Extrapelvic recurrent sites included lung (13/47, 28%), intra-abdominal (11/47, 23%), liver (3/47, 6%), spleen (2/47, 4%), bone (2/47, 4%), retroperitoneum (1/47, 2%), abdominal wall (1/47, 2%), and pleural effusion (1/47, 2%).

Eighty-nine percent of patients (16/18) without bilateral salpingo-oophorectomy (BSO) had a recurrence, significantly higher than 55% (31/56) with BSO ($P<0.05$).

Among 47 patients with recurrent disease, 3 had radiotherapy (1 with radiation alone, 2 with radiation and hormonal therapy separately), 10 had chemotherapy (4 with chemotherapy alone, 6 with chemotherapy and hormonal therapy separately), 22 had hormonal therapy alone, and 12 without measurable disease after surgery or radiographic data were not evaluable. The response rates are shown in Table 2. Of patients who received hormonal therapy, 5 (17%) had a complete response (CR), 3 (10%) had a partial response (PR), 16 (53%) had stable disease, and 6 (20%) had disease progression. The median TTP of hormonal therapy was 24 months. The majority of hormonal therapy patients received megestrol acetate (28/30), and some received letrozole (2/30), arimidex (1/30), luprolide (3/30), or mifepristone (3/30) until their disease progressed. Some of these patients received more than one hormone. Only three patients received tamoxifen for a short period, switching later to megestrol acetate. No responses (CR or PR) were noted among the patients treated with radiotherapy or chemotherapy (Table 2).

Table 3
Expression of targets in endometrial stromal sarcoma as detected by immunohistochemistry ($n=13$).

Score	0	1	2	3
ER	3	1	1	8
PR	2	1	1	9
PDGF-α	8	3	1	0
PDGF-β	7	1	3	0
c-Kit	12	1	0	0
c-abl	0	0	1	12
VEGF	6	4	1	2
EGFR	13	0	0	0
HER-2	13	0	0	0

Three samples were missing for PDGF-α and PDGF-β.
The score was the combination of intensity and distribution and graded from 0 to 3.
ER, estrogen receptor; PR, progesterone receptor; PDGF-α and -β, platelet-derived growth factor receptor-α and -β; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor-2.

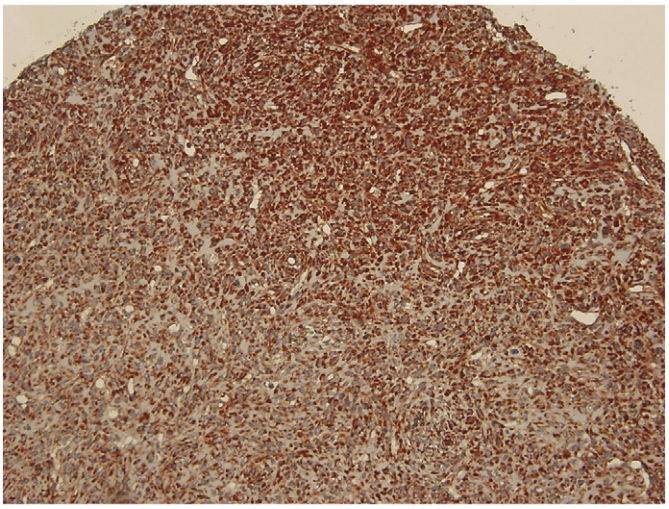

Fig. 2. Endometrial stromal sarcoma with overall high c-abl expression with strong diffuse cytoplasmic, nuclear staining and some membrane association. Magnification, 100×.

Survival

The 5-year PFS rate was 55%, and the 10-year PFS rate was 43%. The overall median PFS duration was 108 months. The 5-year overall survival (OS) rate was 90%, and the 10-year OS rate was 85%. The median OS duration was 288 months. PFS and OS curves are shown in Fig. 1.

Molecular studies

Thirteen patients had preserved tumor specimens available for testing. All samples were reviewed and confirmed as low-grade ESS by a gynecologic pathologist (J.L.). We then evaluated the specimens for expression of female hormone receptors (ER, PR), imatinib mesylate-targeted kinases (PDGF-α and -β, c-Kit, c-abl), VEGF, EGFR, and HER-2/CerbB2 (Table 3). C-Abl was expressed universally (12 samples with a strong positive result and one with moderate positive result) (Fig. 2). ER and PR expression was detected, respectively, in 10 (77%) of the 13 specimens and 11 (85%) of the 13 specimens. PDGF-α, PDGF-β, c-Kit, and VEGF expression was detected, respectively, in 4/12 (33%) with one sample missing, 4/11 (36%) with two samples missing, 1/13 (8%), and 7/13 (54%). EGFR and HER-2 were not detected in any specimens.

Discussion

The surgical modality for ESS is controversial. Some gynecologic oncologists prefer that ESS be staged as is endometrial adenocarcinoma, including exploratory laparotomy or minimal invasive procedure, total hysterectomy and BSO, omental biopsy, pelvic and para-aortic lymphadenectomy, and aspiration of abdominal fluid for cytologic evaluation [9]. However, some studies have found that including lymphadenectomy does not affect the prognosis [4,5], and thus some gynecologic oncologists prefer to exclude lymphadenectomy.

In our study, we found that ESS tumor cells extend through the myometrium into lymphatic and venous channels (32% patients had lymphatic vascular space invasion). Twenty-two percent of the patients who had lymphadenectomy had positive lymph nodes at the surgery. Further prospective study is needed to determine whether pelvic and para-aortic lymphadenectomy should be included in the surgical procedure for these patients.

Furthermore, in our study, most patients did not have a complete initial surgical procedure before being referred to our institution because the majority of patients we reviewed were premenopausal at the time of diagnosis and had few presenting symptoms. Many patients were incidentally diagnosed with ESS when undergoing surgery for uterine leiomyomata. In our cohort, eighty-nine percent of patients (16/18) without BSO had a recurrence, significantly higher than 55% (31/56) with BSO. This data confirmed the necessity of BSO in the procedure.

Adjuvant radiotherapy has been reported to reduce the incidence of pelvic recurrence without any survival benefit. We found that radiotherapy did control the progression of recurrent disease, with a median TTP of 31 months (Table 2). However, the benefit merits further evaluation with larger patient numbers and longer follow-up.

Many agents have been associated with minimal response rates in low-grade ESS [10]. However, the Gynecologic Oncology Group published a prospective phase II study of the effectiveness and toxicity of ifosfamide chemotherapy in patients with metastatic or recurrent ESS who were previously unexposed to chemotherapy [11]. In that study, 21 patients received ifosfamide (1.5 g/m^2) daily for 5 days every 3 weeks. The overall response rate was 33% with three patients (14%) having complete responses and four (19%) having partial responses. It is unclear how many patients had stable disease. In addition, 57% of all patients experienced grades 3–4 leukocytopenia [11]. In our study, no recurrent patients had complete or partial response after chemotherapy. Only 4 of 10 patients had stable disease after chemotherapy, with a medium TTP of 6.5 months (Table 2). Among the 10 patients, 6 patients underwent doxorubicin based chemotherapy (single dose or combination with cisplatinum, or ifosfamide, or paclitaxel). Six patients were administered taxane based chemotherapy (single dose or combination with gemcitabine, or carboplatin, or pegylated liposomal doxorubicin) and one with actinomycin D. Among the four patients with stable disease who received chemotherapy, two patients had gemcitabine plus taxotere, one patient had actinomycin D, and one patient had pegylated liposomal doxorubicin plus paclitaxel.

Compared with radiotherapy and chemotherapy, hormonal therapy was more effective for the recurrent patients in our cohort (27% overall response rate and 53% stable disease rate). Hormonal therapy was also associated with a relatively long response duration (median TTP of 24 months). ESS exhibits high levels of estrogen and progesterone receptors, as determined by this study and others [12,13]. Furthermore, studies have found that medroxyprogesterone acetate, megestrol acetate, aromatase inhibitors, and GnRH analogs have activity in ESS [6,7,14,15]. A recent study evaluated hormonal therapy for ESS with selective progesterone receptor modulators (mifepristone) [16]. Mifepristone's affinity for the progesterone receptor is five times greater than that of endogenous progesterone. As a result, mifepristone can produce a progesterone-like effect in the absence of progesterone. However, the phase II clinical study was discouraging, with an observed stable disease rate of 25% (3/12) and a median TTP of 48 days [16]. No partial or complete responses were observed. Thus, there remains a clear need to identify additional active agents for patients with recurrent ESS.

Targeted therapy may be an alternative for the treatment of recurrent ESS, with moderate side effects, long-term disease stabilization, and better responses than chemotherapy or radiotherapy in the other soft tissue sarcomas [17,18]. Tyrosine kinases (c-Kit, c-abl, and PDGF) play important roles in the regulation of cellular proliferation and differentiation and are strongly expressed in many cancers [19,20]. C-Kit is a proto-oncogene that codes for a transmembrane tyrosine kinase receptor (CD117). PDGF-β expression is also associated with tumor neoangiogenesis. The tyrosine kinase inhibitor imatinib mesylate is the first commercially available tyrosine kinase inhibitor which specifically targets c-Kit, abl, and PDGF. Imatinib mesylate has been approved for the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia (CML), which characteristically expressed a constitutively active abl tyrosine kinase. It is widely used for patients with gastrointestinal stromal tumors

(GIST) for its constitutively activated mutant c-Kit [21]. In the studies of ESS, the expression of c-Kit varied from 0% to 22% [22–24]. PDGF-α expression has been reported to occur in 59%–70% of ESS and PDGF-β expression in 0%–21.6% [23–25]. EGFR is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis, and angiogenesis. The high frequency of abnormalities in EGFR signaling in human cancers and laboratory studies showing that inhibition of EGFR can impair tumor growth means that EGFR is an attractive target for cancer treatment [26–30]. Monifar [31] reported that a majority of low-grade ESS patients tested positive for EGFR (70%, 14/20) but negative for HER-2–4. However, among samples we tested, only c-abl was expressed universally. PDGF-α, PDGF-β, and VEGF expression were much lower (33%, 36%, and 54%, respectively). EGFR and HER-2 expression were not detected in any samples we studied, while c-Kit was detected in only 8%. The difference of our EGFR expression as compared to Monifar's series may be different kits being utilized. Our small number of cases may also be the reason of not being able to detect the expression. It needs verification with more cases in the future.

Since one or more targets of imatinib are expressed in ESS, it may be opined that this agent may have clinical efficacy in this disease. However, it should be recalled that expression alone does not necessarily represent functionally "mission critical" mechanisms of pathogenesis. Indeed, a GOG phase II clinical trial of imatinib mesylate in the treatment of recurrent or persistent epithelial ovarian or primary peritoneal carcinoma demonstrated minimal clinical efficacy despite requiring expression of at least one target of imatinib (kit, PDGFR-alpha, or PDGFR-beta) [32]. Whether these kinases contribute to disease progression and whether imatinib mesylate is effective in the treatment of ESS should be explored in the future.

In conclusion, our study suggests that ESS is a hormone-dependent malignancy, with hormonal therapy having activity in recurrent disease. The universal expression of c-abl among the samples we tested suggests that c-abl may be therapeutically targeted in ESS with a tyrosine kinase inhibitor such as imatinib mesylate.

Conflict of interest statement
The authors declare no conflicts of interest.

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