

Research Article

Clinical and pathologic predictors of survival in patients with endometrial stromal sarcoma

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ABSTRACT

Endometrial stromal sarcoma (ESS) is a rare uterine neoplasm and the clinical and pathologic factors that predict outcomes are poorly understood. We conducted an institutional retrospective review of patients with the diagnosis of ESS between January 1990 and April 2012. Demographic and clinical features, treatment data and outcomes were collected. Overall survival (OS) and progression free survival (PFS) were estimated using the Kaplan-Meier method. In 37 patients with ESS, 3 clinicopathologic factors were associated with OS in a multivariate model—age (hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.01-1.09, p=0.03), FIGO stage IV versus stage I disease (HR 4.05, 95% CI 1.11-14.8, p=0.03), and estrogen receptor status (HR 0.11, 0.02-0.69, p=0.02). Although the relationship between adjuvant therapy and OS was not significant, we demonstrate an association between adjuvant therapy and improved PFS in patients with ESS. Our observations suggest that advanced age and clinical stage are associated with worse OS and PFS in patients with ESS, while ER expression may be a marker of improved survival.

Keywords: sarcoma, endometrial sarcoma, gynecologic malignancy, outcomes, estrogen receptor

INTRODUCTION

Uterine sarcoma is a rare gynecologic tumor arising from the myometrium or connective tissue of the uterus and accounting for 3-7% of all uterine malignancies (1). Endometrial sarcoma is a subtype of uterine sarcoma that represents between 7-17% of uterine sarcomas (2, 3). Historically, endometrial sarcoma has been classified into 2 subtypes based on histological characteristics and mitotic rate—low grade endometrial stromal sarcoma (LGESS) and high grade endometrial stromal sarcoma (HGESS) (4). More recently, oncogenetic studies have demonstrated that the majority of LGESS contain the *JAZF1/JJAZ1* gene

fusion while this fusion is absent in the more aggressive HGESS (5). Based on differences in tumor genetics and natural history, the World Health Organization revised their classification of endometrial sarcoma into two categories—HGESS as undifferentiated endometrial sarcoma (UES) or high-grade undifferentiated uterine sarcomas (HGUS) with little or no evidence of endometrial stromal differentiation and LGESS as endometrial stromal sarcoma (ESS). The rarity of these tumors has led to difficulty in firmly establishing important prognostic factors and understanding the optimal treatment strategies, especially in those patients with advanced stage disease.

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ESS frequently expresses estrogen receptor (ER) and progesterone receptor (PR) with a pooled analysis demonstrating ER expression in 40-100% of cases and PR expression in 60-100% of cases. The relationship between hormone receptor status and outcomes is uncertain, but ER or PR expression makes these tumors potential targets for hormonal therapy (6). Pro-estrogen states including obesity and the use of hormone replacement therapy have been speculated to be harmful in patients with ESS, and obesity has been evaluated with varying results as a risk factor for carcinogenesis and prognosis for endometrial sarcoma (7, 8).

While hysterectomy is the treatment of choice for early stage EES, bilateral-oophorectomy (BSO) is also typically recommended for patients given the hormonally responsive nature of the tumor although whether this imparts a survival advantage remains unclear (9-11). The role of adjuvant therapy including radiation, hormonal, or chemotherapy remains controversial in ESS with two retrospective series showing that adjuvant radiotherapy has been shown to improve disease free survival but not overall survival (OS) in ESS while another study demonstrated the absence of recurrence in patients with ESS given adjuvant hormonal or radiation therapy (12-14).

Most of the data regarding the clinical and pathologic variables that may predict prognosis and the benefits of adjuvant therapy are based on small retrospective studies (12-16). In a population-based analysis from the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2003, Chan et al reported on the relationship between clinical and pathologic variables and disease-specific survival (DSS), demonstrating a relationship between older age, black race, advanced stage, higher grade, lack of primary surgery and nodal metastasis and poorer DSS (17). Yoon et al reported a multicenter study in which 114 patients with ESS in which stage, expression of ER and PR and nodal metastasis were significantly associated with overall survival (OS) (18). In this study we review our experience over the past 22 years treating ESS at Moffitt Cancer Center to add to the available literature regarding the role of adjuvant therapy, tumor hormone receptor status, and other clinical and pathologic variables and their relationship with OS and progression free survival (PFS) that may help to better understand management and prognostic markers in this rare disease.

MATERIAL AND METHODS

After Institutional Review Board (IRB) approval, all cases with the diagnosis of ESS from January 1990 through April 2012 were identified at Moffitt Cancer Center (Tampa, FL USA) through our institutional tumor registry. Hospital records including patient demographics, clinical information, operative notes, pathology reports, records of adjuvant treatments, and clinical outcomes were reviewed for each patient. Body mass index (BMI) was calculated with the earliest reported weight and height in the medical record, which corresponded to their initial referral for consultation to our institution. ER and PR status were documented according to status at the initial operation. Surgical staging based on operative reports and pathologic data at diagnosis was determined retrospectively according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system for uterine sarcomas. Final diagnosis of ESS was determined based on initial pathologic examination from referring institutions (when applicable) and expert review by dedicated sarcoma pathologists, or by expert review of final surgical pathology. Adjuvant therapy was recorded based on type as any combination of radiotherapy, chemotherapy, or hormonal therapy. The decision to give adjuvant therapy was made by the treating physician after discussion at a multidisciplinary tumor board.

Normally distributed continuous variable are summarized by mean and standard deviation. Non-normally distributed continuous variables are summarized by median and range. OS was calculated from the time of diagnosis to the date of death or to date of last follow up. Progression free survival (PFS) was calculated from the time of diagnosis and censored at either the date of recurrence, death or the date of last follow up. Vital status and follow up data was censored December 2014. Cox proportional hazard models were used for univariate and multivariate analyses. Kaplan-Meier survival curves and rates were estimated using the log-rank test. All tests were two-sided and a p value <0.05 was considered significant. Data were analyzed using R version 2.15.2. The study was approved by the Institutional Review Board (IRB).

RESULTS

A total of 64 patients were identified through the Moffitt Cancer Center tumor registry with a diagnosis code of ESS. Of these, 27 patients were excluded for incomplete records (n=7, incomplete clinical or staging

Table 1: Characteristics of 37 patients with endometrial stromal sarcoma

Characteristics	Value
Age (years); median (range)	51 (19-81)
Caucasian, n (%)	28 (76)
Current Smoker, n (%)	13 (35)
Median BMI (kg/m ²) (range)	27 (19-41)
PR positive tumor	14 (78)*
ER positive tumor	14 (78)*
Oophorectomy at or prior to diagnosis	31 (84)
Clinical Stage (FIGO)	
I	18 (49)
II	6 (16)
III	3 (8)
IV	9 (24)
Lymphadenectomy at initial Surgery**	3 (8)
Lymphovascular invasion	20 (54)
Pathologic lymph node positive or metastatic disease at diagnosis	10 (27)
Median Initial Size of Tumor (cm); median (range)	6 (2-23)

Notes: ESS=Endometrial Stromal Sarcoma; FIGO=International Federation of Gynecology and Obstetrics. * Hormone receptor status was available for 18 patients. **One ESS patient had lymph node positive disease at time of lymphadenectomy.

information, or no follow-up data) or a confirmed pathologic diagnosis other than ESS (n=20) resulting in 37 evaluable patients. The clinical and pathologic features of these patients are summarized in Table 1. The median age was 51 years (range 19-81) and the majority of patients (n=28, 76%) were of Caucasian race. Thirteen 13 (35%) patients had a smoking history and the median BMI was 27 kg/m² (19-41 kg/m²).

A cancer diagnosis was made at the time of total abdominal hysterectomy with bilateral salpingoophorectomy (TAH-BSO) in 23 (62%) patients, and 31 (84%) had BSO at or prior to diagnosis of ESS. Five (14%) patients were diagnosed at the time

of surgery due to a visceral or nodal metastasis on frozen section and 3 patients (8%) were diagnosed on final pathology after a TAH alone. Most patients had early stage disease with 18 patients (49%) having clinical FIGO stage I disease and 6 (16%) patients having FIGO stage II disease. Eighteen (49%) patients had available data regarding hormone receptor status—14 (78%) were estrogen receptor (ER) positive and 14 (78%) were progesterone receptor positive (PR). The median tumor size at the index operation was 6 cm (range 2-23 cm) and lymphovascular invasion was noted in 20 (54%) patients.

Table 2: Univariate analysis of Prognostic Factors in ESS (n=37)

Variables	Progression Free Survival			Overall Survival		
	H.R.	95% C.I.	P-value	H.R.	95% C.I.	P-value
Age at diagnosis (1 year increase)	1.01	0.97-1.04	0.73	1.05	1.01-1.09	0.03
Overweight (BMI >25kg/m ² vs ≤25kg/m ² *)	0.89	0.39-2.03	0.77	1.00	0.31-3.23	1.00
FIGO Stage II VS I*	1.31	0.41-4.20	0.65	1.80	0.40-8.16	0.45
FIGO Stage III VS I*	0.53	0.07-4.17	0.54	3.99	0.71-22.3	0.12
FIGO Stage IV VS I*	2.57	0.96-6.87	0.06	4.05	1.11-14.8	0.03
Smoking History (yes vs no*)	2.06	0.90-4.69	0.09	1.35	0.48-3.82	0.57
ER Positive Tumor (yes vs no*)	0.15	0.03-0.77	0.02	0.11	0.02-0.69	0.02
PR Positive Tumor (yes vs no*)	0.25	0.06-1.07	0.06	0.3	0.05-1.82	0.19
Initial Tumor Size (≥5cm vs <5cm*)	2.54	0.93-6.88	0.07	2.23	0.29-17.1	0.44

ESS: Endometrial Stromal Sarcoma, BMI: Body mass index, FIGO: International Federation of Gynecology and Obstetrics, ER: Estrogen Receptor, PR: Progesterone Receptor . *Indicates reference group.

Adjuvant treatment was given to 13 (35%) patients, primarily in patients with high risk or resected metastatic disease at diagnosis. Five patients received adjuvant radiotherapy, 2 adjuvant systemic chemotherapy, 4 adjuvant hormonal therapy, and 2 received combined adjuvant radiation and hormonal therapy. Adjuvant hormonal therapy included aromatase inhibitors or megestrol. Adjuvant chemotherapy included ifosfamide in one case and doxorubicin and a platinum agent in the other.

Median PFS was 49 months and median OS was 238 months. The results of the univariate analysis for PFS and OS with potential prognostic variables are summarized in Table 2. In 37 patients with ESS, 3 factors were associated with OS in a multivariate model—age (hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.01-1.09, $p=0.03$), FIGO stage IV versus stage I disease (HR 4.05, 95% CI 1.11-14.8, $p=0.03$), and estrogen receptor status (HR 0.11, 0.02-0.69, $p=0.02$). ER positive tumors had a trend towards improved OS in ESS even when adjusting for hormonal therapy use in these patients ($p=0.07$). Table 3 illustrates the univariate analysis of adjuvant treatments

and survival in ESS. There was a trend towards improvement in OS for those receiving any adjuvant therapy ($p=0.09$).

DISCUSSION

Uterine sarcomas are rare tumors with clinical heterogeneity making prospective or controlled trials difficult, and as such much of the data related to the diagnosis is derived from retrospective case series (12-14). We sought to add to the body of literature regarding this diagnosis by summarizing our experience with ESS over a 22-year period with particular attention to the clinical and pathologic features important for prognosis. We also sought to describe a potential role for adjuvant therapy in high-risk patients.

Our study supports previous observations demonstrating worse survival in older patients with ESS. In a large analysis of 831 women with ESS from the Surveillance, Epidemiology and End Results (SEER) database, Chan *et al* found that age over 52 years was associated with a worse disease-specific survival (DSS) ($P<0.001$) (17). Our study also

demonstrated a relationship between age and outcome with each year increase in age adversely impacting overall survival (OS). As with many age-related disease outcomes, advanced age likely serves as surrogate for comorbid conditions and functional status limitations that are related to outcome but cannot completely be accounted for in multivariate models. While containing fewer patients treated at a single institution than the data reported by Chan *et al*, our data adds to the available literature by demonstrated the relationship between age and both OS and PFS in a more contemporary series of patients.

Obesity is another a suspected risk factor for endometrial sarcoma given the elevated estrogen levels associated with obesity and the peripheral conversion of androgens to estrogens by adipose tissue. One case control study of patients with all subtypes of uterine sarcomas demonstrated an association with obesity and an increased risk of death, and a pooled analysis showed a significant risk endometrial sarcoma in obese patients (7, 8). The majority of the women diagnosed with ESS were overweight or obese with a median BMI 27 kg/m², but we did not detect a relationship between overweight and obesity and outcomes including PFS or OS. We are not able to draw definitive outcomes regarding obesity as a risk factor for ESS or worse outcomes, but given the small sample size it is possible that a true relationship was not detected. Large

multicenter collaborative studies are needed to further assess the relationship between obesity and disease incidence and outcomes in patients with ESS.

ESS can strongly express ER and PR, but some tumors are ER and PR negative (6, 19-21). The relationship between hormone receptor status and outcomes is unclear, but some data suggest that ER status is associated with improved outcomes. In one study of patients with all subtypes of uterine sarcoma, ER status correlated with improved median OS and was a strong prognostic factor (22). The mechanism by which ER and PR status may improve OS is unclear. There may be an intrinsic difference in tumor biology, or the difference may be related to the use of targeted hormonal therapy in the adjuvant or metastatic setting. Our results confirm previous observations suggesting that ER positive tumors may have unique tumor biology as the relationship between receptor status and outcomes remained significant after adjusting for the use of hormonal therapy. ER and PR status should be reported in future research of ESS and survival analysis should be stratified based on these two groups to further assess if ER expression may be a prognostic marker in ESS.

While total hysterectomy is considered standard of care for localized ESS, controversy remains over whether extending hysterectomy to include bilateral salpingoophorectomy impacts survival(9-11, 23-25). In

Table 3: Univariate analysis of adjuvant treatment in ESS (n=37)

Variables	N	Progression Free Survival			Overall Survival		
		H.R.	95% C.I.	P-value	H.R.	95% C.I.	P-value
Any Adjuvant therapy	13	0.30	0.11-0.78	0.01	0.33	0.09-1.19	0.09
Adjuvant Radiation	7	0.44	0.15-1.32	0.14	0.53	0.12-2.39	0.41
Adjuvant Hormonal therapy	6	0.53	0.16-1.81	0.31	0.97	0.21-4.4	0.97

H.R.=Hazard ratio, C.I.=Confidence interval, ESS=endometrial stromal sarcoma, *Sample size of patients receiving therapy too small for meaningful analysis, N=Number of patients who received type of therapy.

our analysis TAH-BSO was not associated with improved PFS or OS, possibly due to the small number of patients undergoing TAH alone. Since ESS may be an estrogen responsive malignancy TAH-BSO remains the recommendation for treatment of patients with ESS, but ovarian sparing surgery can be considered in younger patients (<35 years) with small tumors (2-3cm) (6).

Pelvic lymphadenectomy in the setting of clinically node negative is typically not recommended. A large multi-institutional review and National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) study both concluded that there was no benefit to complete surgical staging in both ESS and UES (26, 27). We describe an 8% incidence of nodal disease in patients with ESS. At our center therapeutic lymph node dissection remains the standard in patients with radiographic or clinical evidence of nodal disease, but elective lymph node dissection is not routinely performed.

In order to potentially improve outcomes in patients with ESS the use of adjuvant therapy has been explored. Options for adjuvant therapy include radiotherapy, chemotherapy, or hormonal therapy with these modalities being used alone or in combination. In a study of 22 patients, Kim *et al* concluded adjuvant therapy of any type had no benefit on disease-free survival in stage I ESS (9), while Diesing *et al* reported that survival was improved in six of eleven patients with UES and ESS who received adjuvant therapy (28). The only randomized clinical trial to study adjuvant radiotherapy for uterine sarcomas was completed by the European Organization for Research and Treatment of Cancer (29). In this study 28 patients with UES and ESS (of 224 uterine sarcomas total) were randomized to postoperative radiation or observation, and there was no survival benefit detected in any histological subtype, and no local control benefit in patients with UES and ESS (29). The results of these studies are limited by small sample sizes.

To date no randomized trial have been completed to determine the impact of adjuvant hormonal therapy on outcomes in hormone receptor positive UES or ESS, though retrospective studies have assessed the role of adjuvant hormonal therapy (10, 21, 30). In a multi institutional study of 43 patients with UES and ESS there was a decreased recurrence rate with post-operative progestin therapy while another study of 31 women with stage III to IV ESS and UES found that adjuvant progesterone therapy decreased the risk of

disease progression from 75% to 20% (6, 10). The role of adjuvant chemotherapy in ESS is questionable but treatment with doxorubicin or ifosfamide-based treatments have shown response rates in patients with ESS (31, 32). A study of 127 patients with advanced stage uterine sarcoma (37 patients had ESS or UES) there was a benefit from adjuvant chemotherapy though results specific to ESS were not reported (33).

Data from our series demonstrates a relationship between the use of any adjuvant therapy and improved PFS with a trend towards improved OS. These results must be interpreted within the context of the small patient numbers, and the inherent limitation selection bias given a nonrandomized study design with regards to adjuvant therapy. Another limitation of the study is that given the small sample size and very long study period, we cannot account for changes in outcomes due to time trends. Finally, it is uncertain whether or not the results of this single institution series are generalizable to other centers. We recommend that until a more definitive clinical trial on the role of adjuvant therapy in ESS is completed, that adjuvant therapy be used on a case-by-case basis in patients with high-risk ESS (i.e. those with suboptimal surgery, those with advanced age, or other risk factors for recurrence).

CONCLUSION

ESS is a rare disease that is difficult to study in a prospective manner at a single center. As with other rare tumors, collaborative multi-institutional and even international series and studies are needed to further define the natural history and optimal treatment strategy in ESS. In the absence of molecular pathologic data for analysis in this study, our observations suggest that factors such as hormone receptor status and age should be considered when discussing adjuvant therapy with ESS patients. These factors should best be studied in the context of clinical trials at institutions with experience in the management of ESS, and until more data is available adjuvant therapy should be considered in high-risk patients.

Abbreviations

ESS	endometrial stromal sarcoma
OS	overall survival
PFS	progression free survival
HR	hazard ratio
CI	confidence interval
LGESS	low grade endometrial stromal sarcoma

HGESS	high grade endometrial stromal sarcoma	DSS	disease specific survival
UES	undifferentiated endometrial sarcoma	IRB	Institutional Review Board
HUES	high grade undifferentiated sarcoma	BMI	body mass index
ER	estrogen receptor	FIGO	International Federation of Gynecology and Obstetrics
PR	progesterone receptor	TAH	total abdominal hysterectomy
SEER	Surveillance, Epidemiology and End Results	BSO	bilateral salpingoophorectomy

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