Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Impact of oophorectomy and hormone suppression in low grade endometrial stromal sarcoma: A multicenter review

L.E. Stewart [a], T.L. Beck [a], N.V. Giannakopoulos [b], M.H. Rendi [b], C. Isacson [c], B.A. Goff [a,*]

[a] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Washington Medical Center, Seattle, WA, USA
[b] Department of Pathology, University of Washington Medical Center, Seattle, WA, USA
[c] CellNetix Pathology & Laboratories, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 28 December 2017
Received in revised form 5 March 2018
Accepted 7 March 2018
Available online xxxx

Keywords:
Endometrial stromal sarcoma
Progression free survival
Adjuvant therapy
Oophorectomy
Hormonal suppression

ABSTRACT

Objectives. Low grade endometrial stromal sarcoma (LG-ESS) is a rare cancer with an indolent course. We aimed to assess the effectiveness of adjuvant hormonal suppression (HT) with or without oophorectomy (BSO) in prolonging progression free survival (PFS) and overall survival (OS) in patients with LG-ESS.

Methods. We performed a multi-institutional retrospective review of patients treated for low grade LG-ESS from 1985 to 2014. Demographics, treatment and recurrence data were abstracted from medical records. Pathologic diagnosis was confirmed by a gynecologic pathologist. Long-term patient-reported outcomes were obtained via mailed survey.

Results. One-hundred-twelve patients underwent surgery for LG-ESS; 59 had postoperative data with a median follow-up of 55 months (1–325 months). The mean age at diagnosis was 48.5 years (22–82 years). Forty-nine (61%) had stage I disease. The most common presenting symptoms were abnormal uterine bleeding (38%) and pelvic mass (17%). Seventy-one (63%) patients had BSO at the time of diagnosis. Of the 59 patients with postoperative follow-up information, 49 (73%) underwent BSO, 26 (44%) received HT, 20 (33%) were expectantly managed, and 6 (10%) received chemotherapy, radiation or both. Median PFS for the entire group was 53 months and OS was 63 months. PFS for those who underwent BSO compared with those who retained their ovaries was 38 vs 11 months, $p = 0.071$. PFS for HT vs no HT was 28 vs 23 months, $p = 0.77$.

Conclusions. Consistent with prior series, our results support BSO to prolong PFS in LG-ESS but are limited by sample size. Larger studies with more complete follow-up are needed to determine the effect of adjuvant hormonal suppression.

1. Background

Low-Grade Endometrial stromal sarcoma (LG-ESS) is a rare, indolent uterine malignancy. It comprises only 0.2% of all uterine malignancies and roughly 20% of uterine sarcomas [1,2]. It is known to have an indolent clinical course with nearly 80% of patients presenting with stage I disease [3]. Regardless of stage at diagnosis, half of those diagnosed will recur, and recurrences are often delayed, occurring a median of 65 months from diagnosis and with recurrences reported >20 years after initial diagnosis [3–5]. These factors combine to make LG-ESS a difficult disease to study prospectively and therefore, the majority of treatment recommendations are based on small case series.

The classification of endometrial stromal sarcoma has varied significantly in the last decade. Historically, ESS was classified into low and high grade subtypes based on histopathologic features, namely mitotic index [6]. In 2008, the terms low-grade and high-grade were abandoned, such that those tumors with minimal nuclear atypia and fewer than 10 mitoses per high powered field were simply called endometrial stromal sarcomas whereas the diverse group of higher grade tumors was re-classified as undifferentiated uterine sarcomas (UES) [7]. More recently however, these diseases have been shown to have distinct mutational patterns linked with clinical behavior and prognosis, prompting a re-adoption of the original nomenclature [8].

Regardless of classification, LG-ESS is defined by a low mitotic index and is therefore poorly responsive to chemotherapy. Response to radiotherapy is not clear with some studies suggesting a survival benefit, although they included high-grade subtypes. Radiation has never been shown to provide a survival benefit in LG-ESS alone [9]. However, LG-ESS is thought to be hormonally responsive with near-universal expression of estrogen and progesterone receptors [10]. This has led many to postulate that estrogen deprivation via bilateral salpingo-oophorectomy (BSO), or suppressive hormone therapy (HT), or both together, may improve patient outcomes. Controversy has surrounded the

* Corresponding author at: University of Washington Medical Center, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, 1959 NE Pacific Street, Box 356460, Seattle, WA 98195, USA.
E-mail address: bgoff@uw.edu (B.A. Goff).

https://doi.org/10.1016/j.ygyno.2018.03.008
0090-8258/

widespread adoption of BSO in the upfront management of this disease which has a mean age at diagnosis of 48–50 years [11]. Data supporting any one management strategy is sparse largely due to the rarity of the disease. This has led to significant practice variation with regard to counseling and management of pre- and peri-menopausal women with this disease. We aimed to assess the effectiveness of HT with or without BSO in prolonging PFS and OS in a large group of women with ESS. We hypothesized that both HT and BSO would improve PFS in women with LG-ESS.

2. Materials and methods

We conducted a 30-year, multi-institutional, retrospective chart review which was augmented with long-term, patient-reported outcomes obtained via mailed survey. This study was approved by the Institutional Review Boards at the University of Washington/Fred Hutchinson Cancer Research Center and the Swedish Medical Centers. We included all patients diagnosed with endometrial stromal sarcoma at the University of Washington and Swedish Medical Centers in Seattle, WA between January 1985 and December 2014. Cases of endometrial stromal sarcoma were identified using diagnostic databases maintained by the departments of pathology. A total of 112 cases of LG-ESS were identified between the two institutions (97 from the University of Washington and 15 from Swedish Medical Centers). All pathologic specimens were reviewed by a gynecologic pathologist to confirm a diagnosis of low-grade endometrial stromal sarcoma. Any cases in which pathologic review resulted in a change in diagnosis (most commonly to high-grade ESS or UES), were excluded. All inpatient and outpatient records were reviewed and demographic data, operative technique, pathology reports, postoperative course, treatment and recurrence data were abstracted. Stage of disease was determined (when possible) from operative and pathology reports according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer. Adjuvant hormonal suppression was defined as any oral progestin, aromatase inhibitor, or injectable GnRH agonist. Study data were collected and managed using REDCap electronic data capture tools hosted at the Institute of Translational Health Science [12].

We developed a short, 14-item survey to gather long-term, patient reported outcomes. Items queried included vital status, disease recurrence, receipt of additional treatments, and long-term health outcomes such as dementia, secondary cancers, osteoporosis, and heart disease. The medical record and public records were searched for most current mailing address for each patient. Patients for whom a mailing address was available were sent a survey with a description of the study and a pre-paid return envelope.

Clinical characteristics were compared using Chi^2 test. Kaplan-Meier method was used for reporting PFS and OS. All survival analysis included data from both the medical record and survey follow-up. The log rank test was used to compare progression free and overall survival between groups with or without initial BSO, receipt of HT (yes/no), or expectant management following surgery.

3. Results

A total of 112 cases of LG-ESS were identified during the study period. The mean age at diagnosis was 48.5 years (22–82 years) and the mean BMI was 29.3 kg/m^2. Racial/ethnic information were available for 58 women, the majority of whom were Caucasian (87.9%). Six patients identified as Asian (10.34%) and one patient as Native Hawaiian/Pacific Islander (1.7%). Sixty-seven patients had available data on parity, among whom only 9 (11%) were nulliparous. Of the 80 patients (71%) for whom stage data were available, 49 had stage I disease (61%), 8 had stage II disease (10%), and 20 had stage III-IV disease (25%) (Table 1). The most common presenting symptoms were abnormal uterine bleeding (59%) and pelvic mass (29.5%). Only one patient was asymptomatic at diagnosis.

With respect to operative data, 71 (63.4%) patients underwent BSO at the time of initial surgery (Table 1). Of those who underwent BSO, 61 (85.9%) were aged 40 years or older and 29 (40.8%) were aged 50 years or older. Twenty-nine patients had undergone preoperative endometrial sampling of whom 8 (27%) had a benign finding, 1 (3%) was read as sarcoma NOS, 18 (62%) were ESS and 2 (6%) had missing or uninterpretable reports. Thirty-six patients (32.1%) underwent lymph node sampling, of which 5 (13.8%) were found to have pathologically-confirmed nodal involvement. Eight patients (25%) with advanced stage disease had operative reports which noted gross residual tumor.

Surveys were sent to 46 women who had a current mailing address in the medical record or in available public records. Twenty-nine were returned to sender and a second attempt at finding a valid address was unsuccessful. Of the 17 women who presumably received the survey, 16 were completed corresponding to a 94% response rate. No surveys were returned incomplete. Survey data added an additional 1–19 yrs of follow-up information for those patients who were reached. Four surveys provided long-term (10-19 yrs) follow-up data for patients who otherwise had no follow-up data available in the medical record.

Postoperative follow-up and management data were available for 59 patients, 49 (73%) of whom underwent BSO, 26 (44%) received HT, 20 (33%) were expectantly managed, and 6 (10%) received chemotherapy, radiation or both. Median follow-up was 55 months (1–325 months). Documented recurrences occurred in 42.8% of patients with median PFS of 53 months and OS of 63 months. Recurrences were predominantly located in the pelvis (60%) and the lung (13%)) (Table 2).

Table 1
Patient characteristics by surgical and adjuvant management.

	BSO N (%)	No BSO N (%)	HT N (%)	Expectant management N (%)
Mean age at diagnosis (range)	50 (27–82)	45 (22–73)	47 (22–74)	46 (24–62)
Mean BMI (range)	30 (18–45)	28 (20–38)	30 (18–45)	29 (20–43)
Race*				
Caucasian	32 (45)	16 (50)	22 (69)	14 (61)
Asian	6 (8)	0 (0)	3 (9)	3 (13)
Hawaiian/Pacific Islander	1 (1)	0 (0)	0 (0)	1 (4)
Unknown/not reported	32 (45)	16 (50)	7 (22)	5 (22)
Mean parity (range)	2.1 (0–7)	1.7 (0–5)	2.0 (0–7)	2.1 (0–5)
Stage**				
I	37 (52)	10 (31)	16 (50)	18 (78)
II–IV	22 (31)	8 (25)	14 (44)	2 (9)
Missing	12 (17)	14 (44)	2 (6)	3 (13)

Percentages may not total 100 due to missing data.
* Chi^2 $p < 0.001$ for HT vs expectant management groups.
** Chi^2 $p < 0.001$.

Please cite this article as: L.E. Stewart, et al., Impact of oophorectomy and hormone suppression in low grade endometrial stromal sarcoma: A multicenter review, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.03.008