

Low Grade Endometrial Stromal Sarcoma of Uterine: Review of 17 Cases

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Received: 5 Nov. 2010; Received in revised form: 10 Dec. 2010; Accepted: 31 Dec. 2010

Abstract- Endometrial stromal sarcomas (ESS) are the second most common uterine sarcomas. Endometrial stromal sarcomas account for 0.25% of all uterine malignancies. Uterine sarcomas most often affect postmenopausal women. The aim of this retrospective study was to review the experience in the treatment and clinical outcome of low grade malignant endometrial stromal sarcoma. Seventeen patients with histologically proven low grade ESS in department of Gynecologic Oncology of the Vali-e-Asr Hospital, Tehran-Iran, between 1999 and 2008 were included in the analysis. Demographics, pathology, treatment, time to recurrence, salvage therapy and survival information was collected. The median age of our patients was 45.35±6.8 (range 36-61). The median parity of the patients was 5 (range 0-8). Most patients were diagnosed at FIGO stage I. The mean survival for patients with stage I and II was 73.5±35.09 and 57.6±5.37 months, respectively, with mortality rate of 5.9% through a median follow-up time of 68.82±30 months. Of 17 patients, seven cases (35.29%) were disease free at 6 years after hysterectomy. Radiotherapy was administered to four patients (23.53%). Only one patient recurred at 10th month after surgery. Surgeries not preserving ovarian function were helpful to decrease the risk of recurrence compared with those sparing ovarian function.

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Acta Medica Iranica, 2011; 49(9): 619-624.

Keywords: Sarcoma; Endometrial stromal; Outcome assessment; Surgery

Introduction

Endometrial stromal sarcomas (ESS) are the second most common uterine sarcomas (1). Endometrial stromal sarcoma is a rare entity of uterine malignancy, accounting for 0.2-1% of all uterine malignancies and 6-20% of all uterine sarcomas. The annual incidence of ESS is 1-2 per million women accounting for 400 to 700 patients each year in Europe (1-3). ESS can be mistaken for leiomyoma. Its clinical recognition may be difficult, and the diagnosis is often made postoperatively after histological examination (4,5).

The typical gross appearances of ESS are a single nodule, multiple solid-cystic masses, and a poorly demarcated lesion with occasional cystic degeneration or rarely cystic multilocular lesion (6). There are two types of endometrial stromal tumors. Low grade ESS (LGEES), and high grade endometrial sarcomas. The second group is without

recognizable evidence of a definite endometrial stromal phenotype (8).

LGEES have a fairly indolent course, but the second type is often fatal (1,8).

The pathogenesis of these lesions remains unknown, but exposure to tamoxifen and unopposed estrogens has been implicated in some cases (9). Endometrial stromal sarcomas may show a variety of morphologic appearances, including epithelial differentiation, a sex cord-like pattern, smooth muscle differentiation, and fibrous myxoid appearances (10).

ESS most often affect postmenopausal women (12). Women with LGEES are younger than women with other uterine sarcomas, with a median age between 45 and 57 years and generally do not have the usual risk factors for endometrial cancer. Patients usually present with abnormal vaginal bleeding, progressive menorrhagia, abdominal pain, and a pelvic mass (3,8).

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Most women with LGESS undergo bilateral salpingo-oophorectomy as part of primary treatment but estrogen can be produced by extra ovarian sources as well. Surgery is fundamental in LGESS as other sarcomas' management, and treatment generally consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) (3). Due to the high recurrence risk even with localized tumors, many clinicians advocate use of adjuvant chemotherapy, radiation therapy, and/or hormone therapy to suppress high grade, undifferentiated sarcomas that are relatively different even at stage I. The efficacy of chemotherapy in ESS is not clearly proven. The current role of chemotherapy in the treatment of ESS is the use of various different agents in patients with advanced or recurrent disease (13-15). Low-grade ESS, often containing a high level of progesterone receptors, is reported to respond to a hormonal therapy (11-15). Progestin therapy has been reported to reduce the risk of recurrence when used in the adjuvant setting (16).

Tumor size, mitotic count, tumor stage, histologic grade, involvement of surgical margins by tumor, menopausal status, and age have been reported to have prognostic significance in various studies. However, these findings are still discussed controversially (16,17).

These tumors typically have an indolent growth with a tendency for late recurrence (3,7). Pelvic or abdominal recurrence in stage I disease develop in one-third to one-half of patients (18). The prognosis for patients with low-grade ESS is more like that for patients with endometrial carcinomas (60%) while 5-year overall survival rate for patients with high grade lesions is reported less than 25% (1,16,19).

Due to its rarity, ESS has only been reported in a few studies, and these were limited to case reports or retrospective analysis based on a small number of patients (20,21).

The aim of this retrospective study was to review the experience in the treatment and clinical outcome of low grade malignant endometrial stromal sarcoma in 17 Iranian patients.

Patients and Methods

During a 9-year period from January 1999 to June 2008, 17 cases with ESS were treated in the Department of Gynecologic Oncology of the Vali-e-

Asr Hospital, Tehran University of Medical Sciences Tehran, Iran.

The study protocol was approved in research ethics committee of Tehran University of Medical Sciences.

Slides from each patients were reexamined to confirm the diagnosis. Patients with a diagnosis of high grade endometrial stromal (undifferentiated) sarcoma were excluded. Demographic data, pathologic findings, treatment information, time to recurrence, salvage therapy and survival were collected from the clinic and hospital records, which included data from other institutions if initial therapy was provided elsewhere.

Twelve patients had primary surgical management and underwent TAH-BSO, and four patients underwent subtotal hysterectomy and salpingo-oophorectomy.

In one patient, subtotal hysterectomy without salpingo-oophorectomy was performed.

Statistic analysis was performed using SPSS 12.0 software. Kaplan-Meier method with the log rank test were adopted.

Results

The data of 17 patients with low grade malignant endometrial stromal sarcoma treated between 1999 and 2008 were reviewed.

The mean age of our patients was 45.35 ± 6.8 (range 36-61) years. The median parity of the patients was $(4.53 \pm 2.13) \neq 5$ (range 0-8).

Of these 17 patients, 13 cases (76.47%) suffered from irregular vaginal bleeding, and 3 patients (17.65%) had been diagnosed to have leiomyoma before treatment.

Most patients (70.59%) were diagnosed at International Federation of Gynecology and Obstetrics (FIGO) stage I.

The median follow-up time was 68.82 ± 30 months. The mean survival of patients for stage I was 73.5 ± 35.09 months and for stage II was 57.6 ± 5.37 . Sixteen cases (94.1%) were still alive (Table 1). Only one patient died due to developing invasive ductal carcinoma of breast 3 years before death.

Recurrence occurred only in one patient at 10th month. Follow up of all of patients is shown in table 1. Radiotherapy was administered to four patients (23.53%).

Table 1. Characteristics of the 17 patients with ESS

Case	Age	Gravity	Referral cause	Tumor size (cm)	Stage of tumor	Treatment	Disease Free Survival (DSF)
1	52	6	Menometrorrhagia	4×3×1	I	Surgery	Up to now (4 years)
2	50	5	Menorrhagia	8	II	Surgery	Up to now (4 years)
3	41	5	Postmenopausal bleeding	9.5×5	I	Surgery	Up to now (3 years)
4	39	2	Vaginal bleeding	5×3×3	I	Surgery and letrozole	Up to now (3.5 years)
5	36	3	Vaginal bleeding	8×2.6	I	Surgery and tomoxifen	Up to now (2 years)
6	38	4	Vaginal bleeding	5×6.7	I	Surgery	Up to now (10 years)
7	52	5	Vaginal bleeding	7	I	Surgery	Up to now (10 years)
8	42	7	Vaginal bleeding	10×9×8	I	Surgery	Up to now (8 years)
9	43	9	Vaginal bleeding	2.5	I	Surgery	Up to now (6 years)
10	48	8	Vaginal bleeding	5	II	Surgery	Up to now (5 years)
11	49	0	Vaginal bleeding	8	II	Surgery	Up to now (10 years)
12	43	4	Vaginal bleeding	10	II	Surgery	expired at 2008 (DSF 6 years) due to invasive ductal carcinoma of breast
13	51	5	Menorrhagia	6	I	Surgery	Up to now (5 years)
14	37	3	Vaginal bleeding	4	I	Two Surgeries	Up to now (10 years)
15	40	5	Vaginal bleeding	6	II	Surgery	Up to now (5 years)
16	42	0	No symptom	5	I	Surgery	Up to now (3 years)
17	49	2	Menometrorrhagia	3	I	Surgery	Up to now (7 years)

Discussion

ESS is a rare form of uterine malignancies, and there is not abundant literature about it. ESSs are divided in low grade and high grade tumors according to cell morphology and mitotic count (7). However, there are controversies surrounding the separation of endometrial stromal sarcoma to low and high grade based on mitotic activity (22) Both types of them are often misdiagnosed as leiomyoma or other uterine benign disease before operation. In the report of sagae *et al.* 75% of 22 ESSs were preoperatively diagnosed as leiomyoma (9) Most early-stage patients have obvious symptoms such as abnormal vaginal bleeding, metrorrhagia and

uterine enlargement. These clinical signs however are not specific (23). Our findings supported this viewpoint.

The present study showed most of the patients were pre-menopause (76.47%). The median age at diagnosis was 45, slightly lower than those reported previously, 49 years for LGESS (24) and 44.35 years in study of Ganjoei *et al.* (3).

The treatment includes surgery and adjuvant radiation, with hormone therapy being a promising new approach (16,25) Consistent with previous reports, (3,7,26) we should treat ESS clinically in a different manner according to the grade and other prognostic factors such as depth of myometrial invasion (20). Diagnostic curettage or biopsy by

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hysteroscopy is useful in early detection (12). In our study, the results of diagnostic curettage suggested uterine malignancy in 29.4% of the patients.

Although the bulk of the tumor is almost always intramyometrial (18), most endometrial stromal sarcomas usually leads to diagnosis in uterine curettage (27). The diagnosis in five patients (29.4%) was ESS by curettage and other 12 patients were diagnosed after hysterectomy (70.58%) in our study.

The initial treatment for the patients with ESS is mainly based on surgery, generally TAH-BSO, which has definitive effect on the prognosis (20). Surgery is the primary treatment for recurrent endometrial stromal sarcoma when feasible (3). Surgery alone is generally not sufficient to treat ESS, especially high grade tumors, which have a more aggressive clinical behavior than low grade ones (28).

Chemotherapy is necessary for those patients with un differentiated tumors or deep myometrial invasion. The options of adjuvant therapy are hormonal therapy and observation either alone or in combination. The indicators and the roles of adjuvant therapies especially chemotherapy are still controversial. Most studies showed that the post-operative radiotherapy could decrease the risk of local recurrence (20).

Recurrent disease was treated with surgery alone (one case of 17 patients) (29). Radiotherapy administered to four patients (23.5%) as adjuvant therapy, although one of them recurred at 10th month.

Low grade ESS predicts an indolent behavior and a good prognosis. In the current study, the recurrence of the LGESS occurred only in one case with myometrial invasion at 10th month, but two recurrences occurred at 6 and 8 years, respectively.

Prolonged survival is common after surgical resection of recurrent or metastatic lesions (27). One patient was disease free three years after resection of vaginal metastasis and chemotherapy.

For the patients at stage I, overall 5 year survival was reported to be 94.7% (30).

Uterine sarcomas have a poor prognosis, with overall survival of less than 50% at 2 years, even presenting at an early stage is much worse than endometrial adenocarcinoma (31). In our study, five-year survival rate was 96%. The recurrence rate of the patients treated with postoperative adjuvant therapy had a low recurrence rate (30.3%) than those who did not (87.5%) (32). Complete cytoreduction is

important and adjuvant chemotherapy can improve the prognosis.

Advanced FIGO stage, deep myometrial invasion, and positive lymph-vascular space invasion (LVSI) were associated with poor prognosis in our patients with postmenopausal status confirming the results of park *et al.* (33).

A multivariate analysis revealed that FIGO stage ($P=0.025$), depth of myometrial invasion ($P=0.004$), and complete cytoreduction ($P=0.030$) were significantly associated with disease free survival, while menopausal status was not ($P=0.044$).

FIGO stage ($P=0.016$), depth of myometrial invasion ($P=0.029$) and LVSI ($P=0.020$) were significantly associated with overall survival (33). In our study the large size of tumor was associated with poor prognosis.

In conclusion, surgeries not preserving ovarian function compared with those sparing ovarian function were more helpful to decrease the risk of recurrence in low grade endometrial stromal sarcoma of uterine.

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